

**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY**  
**WASHINGTON, D.C. 20460**OFFICE OF  
CHEMICAL SAFETY AND  
POLLUTION PREVENTION**MEMORANDUM**

Date: November 2, 2011

SUBJECT: Thiamethoxam – Human Health Risk Assessment for Crop Group 15 (including buckwheat, pearl millet, proso millet, oats, rye, teosinte, triticale) and Crop Group 16 Commodities (forage, fodder and straw of cereal grains group).

|                                                 |                                      |
|-------------------------------------------------|--------------------------------------|
| PC Code: 060109                                 | DP Barcodes: D384889                 |
| Decision Nos.: 441944                           | Registration Nos.: 100-941           |
| Petition No.: 0F7805                            | Regulatory Action: Amended Section 3 |
| Risk Assessment Type: Single Chemical Aggregate | Case No.: 7614                       |
| TXR No.: None                                   | CAS No.: 153719-23-4                 |
| MRID No.: None                                  | 40 CFR: 180.565                      |

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## 1.0 Executive Summary

Thiamethoxam is a broad spectrum nitroguanidine insecticide which belongs to the pesticidal class of compounds known as the neonicotinoids (Group 4A; Insecticide Resistance Action Committee). It has activity against sucking and chewing insects on a wide variety of crops. Thiamethoxam appears to interfere with the nicotinic acetylcholine receptors of the insect's nervous system, but the specific receptor site is unknown at this time. It does not inhibit cholinesterase or interfere with sodium channels and, therefore, has a different mode of action than organophosphate, carbamate, and pyrethroid insecticides.

This risk assessment addresses the requested new use of thiamethoxam for seed treatment of Crop Group 15, cereal grains and Crop Group 16, forage, fodder and straw of cereal grains group. In conjunction with the proposed new uses, Syngenta has requested the establishment of permanent tolerances for residues of thiamethoxam and its metabolite, CGA-322704 (clothianidin), in or on the cereal grain commodities listed in Table 2.2.3 below.

Databases for toxicology, residue chemistry, and occupational/residential exposure are complete for the purpose of this human health risk assessment. An immunotoxicity study, a new requirement under 40 CFR Part 158 as a part of the data requirements for registration of a pesticide (food and non-food uses), has recently been received and was screened.

In mammals, thiamethoxam shows toxicological effects primarily in the liver, kidney, testes, and hematopoietic system (blood cellular system). In addition, developmental neurological effects were observed in rats. The developmental effect is being used to assess risks associated with acute exposures to thiamethoxam, and the liver and testicular effects are the basis for assessing longer term exposures. It is classified as "not likely to be carcinogenic to humans." The selected endpoints and points of departure for risk assessment from the available data are protective of all toxicological effects, including potential immunotoxic effects, observed in the database for all population groups. In addition, the dietary and residential exposures are not likely to be underestimated. Therefore, the Health Effects Division (HED) has reduced the FQPA Safety Factor to account for sensitivity of infants and children from 10X to 1X.

Based on the available toxicity database and the Agency's current practices, short- and intermediate-term inhalation risks for thiamethoxam were assessed using an oral toxicity study. The Agency is in the process of evaluating a March, 2010 Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) report and may, as appropriate, re-examine and develop new policies and procedures for conducting inhalation risk assessments, including route-to-route extrapolation of toxicity data. If any new policies or procedures are developed, the Agency may revisit the need for an inhalation toxicity study for thiamethoxam and/or a re-examination of the inhalation toxicity risk assessment.

HED has examined the residue chemistry database for thiamethoxam. There are no residue chemistry issues that would preclude granting Section 3 registration for the requested uses of

thiamethoxam (as Cruiser PD or Cruiser 5FS) and establishing permanent tolerances for combined residues of thiamethoxam and CGA-322704 in/on cereal grain commodities, as specified below.

The dietary exposure estimates are based on highly conservative, health-protective assumptions regarding residue levels in food and water as well as the extent to which crops are treated with thiamethoxam. Risk estimates associated with dietary exposure are below HED's level of concern for all population subgroups, including those of infants and children.

There are no new residential exposure scenarios associated with this action. Exposures in a residential setting may occur following application of thiamethoxam to turf and/or indoor crack and crevice treatment and were previously assessed. Residential uses which result in MOEs less than 100 are of concern. Since the turf and indoor labels indicated that products would be applied by commercial applicators only, a residential handler assessment was not performed. HED is examining its policy regarding residential handler exposure and may require assessments in the future during registration review of thiamethoxam unless the product is "restricted". A residential postapplication dermal and oral exposure assessment was performed resulting in MOEs greater than 100, and are not of concern for the assessed population subgroups.

HED has assessed dietary (food + drinking water) as well as various non-dietary "residential" exposures for purposes of performing an aggregate risk assessment. The acute aggregate risk is composed of exposures to thiamethoxam residues in food and drinking water and is equivalent to the acute dietary risk and is well below HED's level of concern for all population subgroups.

The short- and intermediate-term aggregate risk is composed of residential exposures plus background (chronic) exposures to thiamethoxam residues in food and drinking water. All such risks are well below HED's level of concern for all population subgroups.

Chronic aggregate risk is composed of exposures to thiamethoxam residues in food and drinking water and is equivalent to the chronic dietary risk. The chronic risk estimates are below HED's level of concern for all population subgroups.

Given the existing and proposed use patterns for thiamethoxam as well as the health-protective assumptions throughout this risk assessment, it is unlikely that any geographic, ethnic, or socioeconomic population will have increased exposure relative to the standard population subgroups assessed by OPP.

All occupational handler scenarios for **cereal grains excluding corn** (using HED seed treatment SOPs) resulted in MOEs greater than 100 and therefore were not of concern, with one exception. The multiple activity scenario for cereal grain resulted in a risk of concern (MOE = 72) even with use of double layers and gloves. However, the exposure assessment based on the current Cruiser® label restriction, limiting the amount of product used per day (38 gals/day) utilizing an open system, resulted in MOEs greater than 100 using PPE (i.e. gloves) and are not of concern.

All occupational handler scenarios for **corn** (using HED seed treatment SOPs) resulted in MOEs significantly below the level of concern (LOC =  $\text{MOE} \geq 100$ ) even with the use of personal protective equipment (PPE) consisting of gloves and coveralls. An exposure assessment based on the current Cruiser® label restriction limiting the amount of product used per day (**38 gals/day**) utilizing an open system resulted in MOEs greater than or equal to 100 using PPE (i.e. gloves) and are not of concern. However, HED concludes that high acreage crops such as corn are typically treated using closed systems. Furthermore, the amount of 21,591 lbs of corn seed treated per day does not represent typical practice and appears to significantly underestimate the actual amount of corn seed treated in most commercial facilities. Therefore, **HED recommends that the Cruiser label specify that in the case of corn, only closed systems can be used. The 215 gals/day restriction for closed systems is considered to be practical. The 38 gallon restriction for open system use for corn seed is not considered to be practical.**

Because exposures for workers whose sole task is to clean commercial seed treatment equipment are assumed to be independent of application rate or the amount of seed treated, HED conducted a separate short-term risk assessment using the maximum exposure value measured in Syngenta's proprietary Helix® seed treatment study. The exposure data were separated into cleaners who conduct a "total clean-out" and those who conduct a "partial clean-out." The MOEs ranged from 160 (total clean-out) to 790 (partial clean-out) and were not of concern.

Secondary handler exposures during planting activities were estimated using information provided in the Science Advisory Council for Exposure SOP #14. All secondary handler scenarios for seed planters resulted in MOEs greater than 100 and are not of concern.

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment.

This exposure/risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide to determine their dermal and inhalation exposure. These studies comprise the Seed Treatment SOPs 14 and 15 and the Helix 289 Seed Treatment Study on Canola. EPA has reviewed all the studies in these multi-pesticide generic exposure databases, and on the basis of available evidence has found them to have been neither fundamentally unethical nor significantly deficient relative to standards of ethical research conduct prevailing when they were conducted. There is no regulatory barrier to continued reliance on these studies, and all applicable requirements of EPA's Rule for the Protection of Human Subjects of Research (40 CFR Part 26) have been satisfied.

## **2.0 HED Recommendations**

HED has no objection to the establishment of permanent tolerances as shown in Table 2.2.3.

HED notes that label restrictions (see section 2.3.2), assumed in HED's ORE risk assessment and appearing on the draft label, should remain on the label. In addition, a revised Section F should be submitted as discussed in section 2.2.3.

## **2.1 Data Deficiencies/Conditions of Registration**

None.

## **2.2 Tolerance Considerations**

### **2.2.1 Enforcement Analytical Method**

References: Residue Chemistry Memo D252021; G.J. Herndon; 30 March 2000  
Residue Chemistry Memo D265079; G.J. Herndon; 8 May 2000  
Residue Chemistry Memo D271516; M. Doherty; 29 May 2001  
Residue Chemistry Memo D281702; M. Doherty; 17 April 2007  
Residue Chemistry Memo D367065; W. Drew; 3 May 2010

The HPLC Method AG-675 with UV or MS detection was previously submitted in conjunction with thiamethoxam petitions. Method AG-675 has been determined to be adequate for enforcing tolerances for residues of thiamethoxam and CGA-322704 in crop and livestock commodities. Syngenta has submitted a revised Method AG-675, i.e., Method GRM.009.04A. The full extraction steps for plant and livestock commodities, including the microwave extraction step for liver, have been incorporated. The limits of quantitation (LOQs) of Method GRM.009.04A have been established at 0.01 ppm each for residues of thiamethoxam, CGA-322704 and CGA-265307. Method validation data are available for Method GRM.009.04A.

### **2.2.2 International Harmonization**

Codex maximum residue limits (MRLs) are established for residues of thiamethoxam in commodities of barley, maize, sweet corn, and wheat. There are no CODEX MRLs corresponding to the new tolerances being recommended for in this review. Canada has established an MRL of 0.02 mg/kg for residues of thiamethoxam and CGA-322704 in all food crops, and is transitioning to specific commodity MRLs (all at 0.02 mg/kg) on a variety of crops including various cereal grains, peas and beans, soybeans, sweet corn, and sunflower.

HED is recommending increasing the barley grain tolerance to 0.4 ppm in order to harmonize with the Codex MRL of 0.4 ppm. (Note: the MRL expressions continue to remain different, as the Codex MRL is for the parent compound only.)

### **2.2.3 Recommended Tolerances**

HED has examined the residue chemistry database for thiamethoxam. There are no residue chemistry issues that would preclude granting Section 3 registration for the requested uses of

thiamethoxam (as Cruiser PD or Cruiser 5FS) and establishing permanent tolerances for combined residues of thiamethoxam and CGA-322704 in/on grain commodities, as specified in Table 2.2.3.

The available data for barley, corn, rice, sorghum, and wheat support tolerances for thiamethoxam, including its metabolites and degradates, in or on the following commodities, at the levels listed below. Compliance with the tolerance levels specified below is to be determined by measuring only the sum of thiamethoxam and CGA-322704 (calculated as the stoichiometric equivalent of thiamethoxam).

| <b>Table 2.2.3. HED-Recommended Food Tolerances for Thiamethoxam's Proposed Uses in/on Crop Group 15/16 Commodities.</b> |                          |                             |                                                                                                                                          |
|--------------------------------------------------------------------------------------------------------------------------|--------------------------|-----------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Commodity                                                                                                                | Proposed Tolerance (ppm) | Recommended Tolerance (ppm) | Comments; <i>Correct Commodity Definition</i>                                                                                            |
| <b>Tolerances Proposed under 180.565(a)</b>                                                                              |                          |                             |                                                                                                                                          |
| Crop Group 15, grains (except barley)                                                                                    |                          | 0.02                        | Grain, cereal, group 15, except barley                                                                                                   |
| Barley, grain                                                                                                            |                          | 0.4                         | HED suggests increasing the tolerance from 0.3 ppm to 0.4 ppm to match the Codex MRL level (tolerance/MRL expressions remain different). |
| Buckwheat, grain                                                                                                         | 0.02                     | --                          | Tolerance for grain is covered under Crop Group 15, grains (except barley)                                                               |
| Buckwheat, forage                                                                                                        | 0.50                     | 0.50                        |                                                                                                                                          |
| Buckwheat, hay                                                                                                           | 0.02                     | 0.02                        |                                                                                                                                          |
| Buckwheat, straw                                                                                                         | 0.02                     | 0.02                        |                                                                                                                                          |
| Oat, grain                                                                                                               | 0.02                     | --                          | Tolerance for grain is covered under Crop Group 15, grains (except barley)                                                               |
| Oat, forage                                                                                                              | 0.50                     | 0.50                        |                                                                                                                                          |
| Oat, hay                                                                                                                 | 0.02                     | 0.02                        |                                                                                                                                          |
| Oat, straw                                                                                                               | 0.02                     | 0.02                        |                                                                                                                                          |
| Pearl, grain                                                                                                             | 0.02                     | --                          | Tolerance for grain is covered under Crop Group 15, grains (except barley)                                                               |
| Pearl millet, forage                                                                                                     | 0.02                     | 0.02                        |                                                                                                                                          |
| Pearl millet, stover                                                                                                     | 0.02                     | 0.02                        |                                                                                                                                          |
| Proso millet, grain                                                                                                      | 0.02                     | --                          | Tolerance for grain is covered under Crop Group 15, grains (except barley)                                                               |
| Proso millet, forage                                                                                                     | 0.02                     | 0.02                        |                                                                                                                                          |
| Proso millet, stover                                                                                                     | 0.02                     | 0.02                        |                                                                                                                                          |
| Proso millet, straw                                                                                                      | 0.02                     | 0.02                        |                                                                                                                                          |
| Rye, grain                                                                                                               | 0.02                     | --                          | Tolerance for grain is covered under Crop Group 15, grains (except barley)                                                               |
| Rye, forage                                                                                                              | 0.50                     | 0.50                        |                                                                                                                                          |
| Rye, straw                                                                                                               | 0.02                     | 0.02                        |                                                                                                                                          |

**Table 2.2.3. HED-Recommended Food Tolerances for Thiamethoxam's Proposed Uses in/on Crop Group 15/16 Commodities.**

| Commodity         | Proposed Tolerance (ppm) | Recommended Tolerance (ppm) | Comments; <i>Correct Commodity Definition</i>                              |
|-------------------|--------------------------|-----------------------------|----------------------------------------------------------------------------|
| Teosinte, grain   | 0.02                     | --                          | Tolerance for grain is covered under Crop Group 15, grains (except barley) |
| Teosinte, forage  | 0.10                     | 0.10                        |                                                                            |
| Teosinte, stover  | 0.05                     | 0.05                        |                                                                            |
| Triticale, grain  | 0.02                     | --                          | Tolerances for wheat covered under triticale, see 40CFR§180.1.             |
| Triticale, forage | 0.05                     | --                          |                                                                            |
| Triticale, hay    | 0.02                     | --                          |                                                                            |
| Triticale, straw  | 0.02                     | --                          |                                                                            |
| Wild rice, grain  | 0.02                     | --                          | Tolerance for grain is covered under Crop Group 15, grains (except barley) |

(Note: When the tolerance for Crop Group 15 grains is established, the existing individual commodity tolerances for specific Crop Group 15 grain commodities should all be removed, with the exception of barley which is also being revised.)

#### 2.2.4 Revisions to Petitioned-For Tolerances

A tolerance for either Crop Group 15 or Crop Group 16 commodities is not appropriate except for Crop Group 15 grains (except barley), because the use pattern is not the same for all Crop Group 15 commodities. Specifically, there is a foliar use on barley and there are much higher tolerances for barley hay and straw associated with this foliar use. It is for similar reasons that a Crop Group 16 tolerance would not be appropriate. In addition, there are also significant differences in the tolerances for the different cereal forages, i.e., wheat forage at 0.5 ppm, corn forage at 0.10 ppm, and sorghum forage at 0.02 ppm. Therefore, tolerances for each individual commodity should be established by translating residue data from the most appropriate representative commodity, except for grains which all have the same tolerance (excluding barley). Tolerances are not required for triticale and wild rice because these commodities are covered by the wheat and rice tolerances, as specified in 40 CFR §180.1.

### 2.3 Label Recommendations

#### 2.3.1 Recommendations from Residue Reviews

None.

#### 2.3.2 Recommendations from Occupational Assessment

HED recommends that label specify that in the case of corn, only the closed system 215 gals/day restriction applies (i.e., no open system use).

**NOTE:** In addition, HED provided an exposure assessment based on the current Cruiser® label restriction limiting the amount product used per day (8 hours) for seed treatment facilities utilizing a closed system to 215 gals/day or more than 38 gallons of Cruiser per 8-hour day for seed treatments utilizing an open system.

### 2.3.3 Recommendations from Residential Assessment

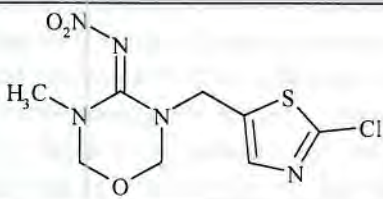
None.

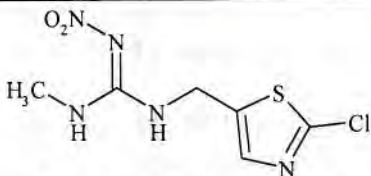
## 3.0 Introduction

Thiamethoxam is a broad spectrum nitroguanidine insecticide which belongs to the pesticidal class of compounds known as the neonicotinoids. It has activity against sucking and chewing insects on a wide variety of crops. It appears to interfere with the nicotinic acetylcholine receptors of the insect's nervous system, but the specific receptor site is unknown at this time. It does not inhibit cholinesterase or interfere with sodium channels and, therefore, has a different mode of action than organophosphate, carbamate, and pyrethroid insecticides.

The chemical structure and nomenclature of thiamethoxam and its regulated metabolite, CGA-322704, are presented in Table 3.1. The physicochemical properties of the technical grade of thiamethoxam are presented in Table 3.2. The metabolite CGA-322704 is the active ingredient clothianidin (PC Code 044309).

### 3.1 Chemical Identity

| Table 3.1. Nomenclature.  |                                                                                                                                         |
|---------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| Chemical structure        |                                                     |
| Empirical Formula         | C <sub>8</sub> H <sub>10</sub> ClN <sub>5</sub> O <sub>3</sub> S                                                                        |
| Common name               | Thiamethoxam                                                                                                                            |
| Company experimental name | CGA 293343                                                                                                                              |
| IUPAC name                | 3-(2-chloro-1,3-thiazol-5-ylmethyl)-5-methyl-1,3,5-oxadiazinan-4-ylidene(nitro)amine                                                    |
| CAS name                  | 3-[(2-chloro-5-thiazolyl)methyl]tetrahydro-5-methyl-N-nitro-4H-1,3,5-oxadiazin-4-imine                                                  |
| CAS registry number       | 153719-23-4                                                                                                                             |
| End-use products (EP)     | 25% WG formulation (Actara® Insecticide; EPA Reg. No. 100-938)<br>47.6% liquid formulation (Cruiser® Insecticide; EPA Reg. No. 100-941) |
| Chemical Class            | Neonicotinoid, Group 4A                                                                                                                 |

| Table 3.1. Nomenclature.                    |                                                                                                                                                        |
|---------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| Known Impurities of Concern                 | None                                                                                                                                                   |
| Chemical structure of CGA-322704 metabolite |  <p>N-[(2-chloro-5-thiazoyl)methyl]-N'-methyl-N''-nitroguanidine</p> |
| Common Name                                 | Clothianidin                                                                                                                                           |

### 3.2 Physical/Chemical Characteristics

| Table 3.2. Physicochemical Properties of Thiamethoxam.     |                                                                      |                         |                                                           |
|------------------------------------------------------------|----------------------------------------------------------------------|-------------------------|-----------------------------------------------------------|
| Parameter                                                  | Value                                                                |                         | Reference                                                 |
| Melting point/range                                        | 139.1°C                                                              |                         | PMRA Regulatory Note (REG2001-03) on Thiamethoxam, 2/9/01 |
| pH                                                         | 4.7 (1% solution in water)                                           |                         |                                                           |
| Density                                                    | 1.57 g/cm <sup>3</sup>                                               |                         |                                                           |
| Water solubility                                           | 4.1 g/L (25°C)                                                       |                         |                                                           |
| Solvent solubility                                         | <u>Solvent</u>                                                       | <u>Solubility (g/L)</u> |                                                           |
|                                                            | acetone                                                              | 48                      |                                                           |
|                                                            | dichloromethane                                                      | 110                     |                                                           |
|                                                            | ethyl acetate                                                        | 7.0                     |                                                           |
|                                                            | hexane                                                               | <1 mg/L                 |                                                           |
|                                                            | methanol                                                             | 13                      |                                                           |
|                                                            | octanol                                                              | 0.62                    |                                                           |
| toluene                                                    | 0.68                                                                 |                         |                                                           |
| Vapor pressure                                             | 2.7 x 10 <sup>-9</sup> Pa (20°C)<br>6.6 x 10 <sup>-9</sup> Pa (25°C) |                         |                                                           |
| Dissociation constant, pK <sub>a</sub>                     | No dissociation within the pH range 2–12                             |                         |                                                           |
| Octanol/water partition coefficient, Log(K <sub>ow</sub> ) | 0.13 (25°C)                                                          |                         |                                                           |
| UV/visible absorption spectrum                             | Not available                                                        |                         |                                                           |

Thiamethoxam is a solid under ambient conditions and has a low volatility. The compound has relatively low solubility in nonpolar organic solvents and its octanol/water partition coefficient suggests that accumulation of thiamethoxam in fatty tissues is unlikely to occur.

### 3.3 Pesticide Use Pattern

Syngenta has submitted a draft label for Cruiser® Insecticide (EPA Reg. No. 100-941), a 5 lb/gal FIC formulation. The proposed use directions on buckwheat; millet, pearl; millet, proso; oats; rye; teosinte, triticale; and wild rice are presented in Table 3.3 below. HED notes that Actara® Insecticide (EPA Reg. No. 100-938), a 25% WG formulation of thiamethoxam, is currently registered for both seed treatment and foliar treatment of barley.

Cruiser is intended to provide early season protection of seedlings against injury by bird cherry-oat aphids, English grain aphid, Greenbug, Hessian fly, Russian wheat aphid, and wireworm, and to reduce potential spread of barley yellow dwarf virus due to aphid vectors.

Use Restrictions: Cruiser may be applied by closed or open system seed treatment application processes. Do not apply more than 215 gallons of Cruiser per 8-hour day for seed treatment utilizing a closed system. Do not apply more than 38 gallons of Cruiser per 8-hour day for seed treatments utilizing an open system. There is a 120-day plant back restriction on the label.

| TABLE 3.3. Summary of Proposed Use Directions on Buckwheat, Pearl Millet, Proso Millet, Oats, Teosinte, Triticale, and Wild Rice. |                                              |                                                      |                         |                           |                 |                                                                                                                                                                                                       |
|-----------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|------------------------------------------------------|-------------------------|---------------------------|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Use Timing; Type; and Equipment                                                                                                   | Product [File Symbol or Registration Number] | Single Use Rate                                      | Maximum Uses per Season | Maximum Seasonal Use Rate | PHI (Days)      | Use Directions and Limitations                                                                                                                                                                        |
| <b>Proposed Uses -<br/>Buckwheat, Pearl Millet, Proso Millet, Oats, Teosinte, Triticale, and Wild Rice</b>                        |                                              |                                                      |                         |                           |                 |                                                                                                                                                                                                       |
| Seed treatment.                                                                                                                   | Cruiser 5FS [100-941]                        | 0.052 lbs a.i./100 lb. of seed                       | 1 (Implied)             | NS <sup>1</sup>           | NS <sup>1</sup> | Do not use at a rate that will result in the use of more than 0.266 lb. thiamethoxam per acre per season. Minimum plant back interval is 120 days from the date the Cruiser treated seed was planted. |
| <b>Existing Uses -<br/>Barley</b>                                                                                                 |                                              |                                                      |                         |                           |                 |                                                                                                                                                                                                       |
| Seed treatment.                                                                                                                   | Cruiser 5FS [100-941]                        | 0.052 lbs a.i./ 100 lb. of seed (0.001 mg ai/seed)   | 1 (Implied)             | NS                        | NS              | 120-Day Plant back interval.                                                                                                                                                                          |
| Foliar spray; ground/aerial                                                                                                       | Actara® [100-938]                            | 0.0625 lb ai/A                                       | 2                       | 0.125 lb ai/A             | 21              | Use ground (minimum spray volume of 10 GPA) or aerial (5 GPA) equipment. Minimum retreatment interval (RTI) is 7 days.                                                                                |
| <b>Corn</b>                                                                                                                       |                                              |                                                      |                         |                           |                 |                                                                                                                                                                                                       |
| Seed treatment                                                                                                                    | Cruiser 5FS [100-941]                        | 0.05-0.35 lb ai/100 lb seed (max. of 0.8 mg/ kernel) | 1 (implied)             | NS                        | NS              | Application to the corn seeds is to be made as a slurry at a maximum rate of 9 fl. oz./100 lbs seed, equivalent to 0.35 lb ai/100 lb seed.                                                            |

| <b>TABLE 3.3. Summary of Proposed Use Directions on Buckwheat, Pearl Millet, Proso Millet, Oats, Teosinte, Triticale, and Wild Rice.</b> |                                                     |                                |                                |                                  |                   |                                                                                                                                                                                                                                                                     |
|------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|--------------------------------|--------------------------------|----------------------------------|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Use Timing; Type; and Equipment</b>                                                                                                   | <b>Product [File Symbol or Registration Number]</b> | <b>Single Use Rate</b>         | <b>Maximum Uses per Season</b> | <b>Maximum Seasonal Use Rate</b> | <b>PHI (Days)</b> | <b>Use Directions and Limitations</b>                                                                                                                                                                                                                               |
| <b>Rice</b>                                                                                                                              |                                                     |                                |                                |                                  |                   |                                                                                                                                                                                                                                                                     |
| Seed treatment                                                                                                                           | Cruiser 5FS [100-941]                               | 0.03 mg ai/seed                | 1 (implied)                    | NS                               | NS                | Not for use on water-seeded rice production. Do not use treated rice for the aquaculture of edible fish and crustaceans. Treated rice should not be sown by aerial application equipment. Not to exceed 120 lb. seed/acre seeding rate. Equivalent to 0.17 lb ai/A. |
| <b>Sorghum</b>                                                                                                                           |                                                     |                                |                                |                                  |                   |                                                                                                                                                                                                                                                                     |
| Seed treatment                                                                                                                           | Cruiser 5FS [100-941]                               | 0.3 lbs a.i./100 lb. of seed   | 1 (implied)                    | NS                               | NS                | Closed system must be used for commercial treatment of sorghum.                                                                                                                                                                                                     |
| <b>Wheat</b>                                                                                                                             |                                                     |                                |                                |                                  |                   |                                                                                                                                                                                                                                                                     |
| Seed treatment                                                                                                                           | Cruiser 5FS [100-941]                               | 0.052 lbs a.i./100 lb. of seed | 1 (implied)                    | NS                               | NS                |                                                                                                                                                                                                                                                                     |

1. NS = Not Specified.

### Conclusions

The submitted use directions for treatment of buckwheat, pearl millet, proso millet, oats, teosinte, triticale, and wild rice are sufficient to allow for evaluation of the available residue data relative to the proposed use patterns.

### 3.4 Anticipated Exposure Pathways

The Registration Division has requested an assessment of human health risk to support the proposed new use of thiamethoxam on Crop Group 15 commodities. HED determined that Crop Group 16 commodities needed to be evaluated as well. Humans may be exposed to thiamethoxam in food and drinking water, since thiamethoxam may be applied directly to growing crops and application may result in thiamethoxam reaching surface and ground water

sources of drinking water. Application of thiamethoxam to crop group 15 commodities crop could also result in residues in crop group 16 Commodities (forage, fodder and straw of cereal grains group), which are animal feed items. There are also residential uses of thiamethoxam, i.e., turf and indoor crack and crevice treatments, so there is likely to be exposure in residential or non-occupational settings. In an occupational setting, applicators may be exposed while handling the pesticide prior to application, as well as during application. There is a potential for post-application exposure for workers re-entering treated fields.

Risk assessments have been previously prepared for the existing uses of thiamethoxam. This risk assessment considers all of the aforementioned exposure pathways based on the proposed new uses of thiamethoxam, but also considers the existing uses as well, particularly for the dietary exposure assessment.

### **3.5 Consideration of Environmental Justice**

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (<http://www.eh.doe.gov/oeqa/guidance/justice/eo12898.pdf>). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

### **4.0 Hazard Characterization and Dose-Response Assessment**

Thiamethoxam has activity against sucking and chewing insects. It is a broad spectrum insecticide which belongs to the neonicotinoid class of compounds. While laboratory data indicate that thiamethoxam interferes with the nicotinic acetyl choline receptors of the insect's nervous system, the specific binding site/receptor(s) is unknown at this time. Although imidacloprid, also a neonicotinoid insecticide, is also known to interfere with nicotinic acetyl

choline receptors, thiamethoxam appears to function at a different location. Thiamethoxam does not inhibit cholinesterase or interfere with sodium channels and, therefore, has a different mode of action than organophosphate, carbamate and pyrethroid insecticides. Thiamethoxam is reported to have excellent acropetal translocation in the xylem and no basipetal movement in the phloem.

In an *in vitro* nicotinic receptor binding study, thiamethoxam had essentially no affinity for either mammalian nicotinic acetyl choline receptor subtype and was considered inactive. This thiamethoxam binding affinity study to rat forebrain  $\alpha_4\beta_2$  and  $\alpha_7$ -type nicotinic receptors was considered Acceptable/Non-Guideline.

#### 4.1 Toxicology Studies Available for Analysis

The toxicological database for thiamethoxam is sufficient for purposes of human health risk assessment. The scientific quality is relatively high and the toxicity profile of thiamethoxam can be characterized for most effects, including potential carcinogenic, mutagenic, developmental, and neurotoxic. The doses and endpoints for use in human health risk assessments are summarized in Tables 4.5.4a and 4.5.4b, below. Recent changes to 40 CFR Part 158 make immunotoxicity testing (870.7800) required for pesticide registration. The study was required in conjunction with a previous risk assessment for proposed uses of thiamethoxam (9/25/2008), and was recently submitted and screened. The screen of the immunotoxicity study indicates that the doses and endpoints used for this for risk assessment are protective of potential immunotoxicity.

The following studies were submitted in support of thiamethoxam registration: acute and subchronic neurotoxicity; subchronic feeding studies in rats, mice and dogs; a subchronic dermal study in rats; chronic/carcinogenicity in rats; carcinogenicity in mice; a chronic study in dogs; developmental studies in rats and rabbits; developmental neurotoxicity; two reproduction studies in rats; mutagenicity battery; and metabolism. In addition, in conjunction with the update of the cancer classification in 2005, a number of studies were submitted to support the mode of action for carcinogenicity.

#### 4.2 Absorption, Distribution, Metabolism, & Elimination (ADME)

In rats, thiamethoxam is rapidly and extensively absorbed, widely distributed, and very rapidly eliminated, mostly in urine. The highest tissue concentrations are in skeletal muscle (10-15% of administered dose). The half-life times from tissues ranged from 2-6 hours. Very low tissue residues were reported after 7 days. Within 24 hours, approximately 84-95% of the administered dose was excreted in urine, while 2.5-6% was excreted in the feces. Most was excreted as unchanged parent (70-80% of dose). The major biotransformation reaction is cleavage of the oxadiazine ring to form the corresponding nitroguanidine compound (CGA-322704). Enterohepatic circulation is negligible.

In mice, approximately 72% of the administered dose was excreted in the urine and 19% was excreted in feces. Small but measurable amounts were detected in expired air (approximately 0.2% of dose). Parent (33-41% of administered dose) and 2 predominant metabolites: 8-12% and 9-18% of administered dose were found. These are the same structures that were most commonly observed in rat excreta; however, the proportions are quite different in mouse excreta. One additional significant metabolite (mouse R6) was isolated from feces samples. Between 30-60% of the administered dose was excreted as metabolites.

#### 4.2.1 Dermal Absorption

HED recommends use of a 5% dermal absorption factor based on an evaluation of *in vivo* dermal absorption data for two formulated products containing thiamethoxam and an *in vivo* dermal absorption study in the rat using technical thiamethoxam. The 5% dermal absorption value represents the maximum amount absorbed for all dose groups for either formulation tested in the most recent study.

#### 4.3 Toxicological Effects

The database on thiamethoxam indicates that the primary targets for this chemical are the liver, testes, kidney, and hematopoietic system. In addition, effects on the thyroid (rats and dogs) and the adrenal gland (rats) are seen in the short-term studies.

The **liver** effects occur across species, sexes and routes of administration. In the rat, inflammatory cell infiltration and necrosis of single hepatocytes are observed in the 28-day dermal study and hepatocellular hypertrophy and lymphohistiocytic infiltration of the liver are observed in the subchronic oral studies. Chronic oral exposure induces an increase in the incidence of foci of cellular alteration in females. In rats, there was no evidence of liver tumors at the dose levels tested. Females appear to be more sensitive than males for liver effects in rats. In the mouse, the following effects were observed in oral studies: hepatocellular hypertrophy, necrosis of single hepatocytes, lymphocytic infiltration (subchronic and chronic), apoptosis, induction of microsomal enzymes, Kupffer cell pigmentation (subchronic), Kupffer cell hyperplasia, increased incidence of foci of cellular alteration, and increased mitotic activity (chronic). Male mice are more sensitive to the liver pathology than are females. Chronic dosing also results in the development of benign and malignant liver tumors in both sexes of mice. An increase in the number of animals with multiple tumors is also observed; however, treatment does not affect the latency to tumor formation nor lethality resulting from the observed tumors. The incidence of non-neoplastic and neoplastic pathology is increased at the same dose level, i.e., there is no clear departure point between doses that induce tumors and other systemic toxic effects. In both rats and mice, there appears to be increasing severity of effects with increasing dose. In rats, the lowest dose at which an effect is observed in the liver does not appear to decrease significantly with increasing length of exposure to the test material. Due to dose spacing, it is not possible to determine if this is the case in the mouse, which appears to be the most sensitive species.

**Testicular effects** are observed in the rat and dog. They consist of decreased testes weights, increased incidence and severity of seminiferous tubular atrophy and sperm abnormalities at low dose levels in the rat; decreased testes weights associated with microscopic evidence of reduction in spermatogenesis and occurrence of spermatid giant cells in the testes at toxic dose levels in the subchronic dog study; and atrophy of the seminiferous tubules at minimally to moderately toxic dose levels in the chronic dog study. Testicular effects were noted in both of the 2-generation reproduction studies. The effects in the rat are only observed in the F<sub>1</sub> males in the two-generation reproduction study and are not observed at any other time. In both studies, there is evidence of increased quantitative susceptibility for male pups. Reproductive effects in males appear in the F<sub>1</sub> generation in the form of increased incidence and severity of testicular tubular atrophy in one study and sperm abnormalities in the other study. While the testicular effects observed in the two studies differ, the findings of the two studies support each other and are consistent relative to observed thiamethoxam toxicity. These effects are being used as the basis for risk assessment because they are observed at very low dose levels. It is anticipated that they may be observed after either intermediate-term or chronic exposure, particularly when exposure occurs *in utero*.

The **kidney** effects occur in both sexes of the rat but are found primarily in the male. They are observed following either oral or dermal exposure. The majority of the kidney effects (hyaline changes in the renal tubules) have been attributed by the study authors to accumulation of  $\alpha_{2u}$ -globulin, a protein that is unique to male rats, in the proximal convoluted tubules. The observed pathology is consistent with  $\alpha_{2u}$ -globulin mediated kidney toxicity. Collectively, special studies submitted demonstrate an increase in accumulation of  $\alpha_{2u}$ -globulin in conjunction with the observance of hyaline droplets in some dose groups as compared to lower levels observed in controls.

**Hematological** effects are observed in the rat, dog and mouse with the dog being the most sensitive species. Both sexes appear to be affected; although the male appears to be more affected in the rodent and the female more affected in the dog. In the rat, increased spleen weights, increases in the incidence and severity of hemosiderosis and/or extramedullary hematopoiesis are observed in both the subchronic and chronic studies. In the mouse, a slight reduction in erythrocytes, hemoglobin and hematocrit, accompanied by increased mean corpuscular volume and mean corpuscular hemoglobin are observed in the subchronic feeding study at very high dose levels. In the dog, leukopenia and slight microcytic anemia are observed in the subchronic oral study.

**Thyroid** effects in the rat (thyroid follicular cell hypertrophy) and dog (increase in thyroid weight) may be due to induction of microsomal enzymes in the liver, which in turn affect the hypothalamus-pituitary-thyroid-liver homeostatic process for regulation of thyroid hormones. Evidence of this is the presence of hepatocellular hypertrophy in several species. The **adrenal** effects observed in the subchronic rat studies generally consist of fatty change and inflammatory cell infiltration of the adrenal cortex.

**Alanine aminotransferase (ALT)** levels are significantly decreased in the dog and companion animal studies. While the toxicological significance of this observation is unclear, there is no doubt regarding its association to treatment with thiamethoxam. It has been proposed that the decreases in ALT activity may be caused by either interference with or suppression of *in vivo* concentrations of pyridoxal phosphate (vitamin B6, a cofactor necessary for ALT activity) or by direct suppression of ALT synthesis. If thiamethoxam interferes with vitamin B6, it could have significant implications regarding potential adverse developmental effects.

**Developmental/Reproductive Effects:** In the developmental studies, there is no quantitative or qualitative evidence of increased susceptibility of rat or rabbit fetuses to *in utero* exposure to thiamethoxam. The developmental NOAELs are either higher than or equal to the maternal NOAELs. The toxicological effects in fetuses do not appear to be any more severe than those in the dams or does. In the rat developmental neurotoxicity study, there was no quantitative evidence of increased susceptibility.

Two reproduction studies are available. In both studies, there is evidence of increased quantitative susceptibility for male pups. Reproductive effects in males appear in the F<sub>1</sub> generation in the form of increased incidence and severity of testicular tubular atrophy in one study and sperm abnormalities in the other study. While the testicular effects observed in the two studies differ, the findings of the two studies support each other and are consistent relative to observed thiamethoxam toxicity.

**Carcinogenicity and Mutagenicity:** Thiamethoxam induces hepatocellular adenomas and carcinomas in male and female Tif:MAGf (SPF) mice. The HED Cancer Assessment Review Committee (June 13, 2005) concluded that the mouse liver tumors arise through a non-genotoxic mode of action characterized by a series of key events that include: perturbation of cholesterol biosynthesis, hepatotoxicity, cell death (both as single cell necrosis and apoptosis) and a sustained increase in cell replication rates. The mouse appears to be uniquely sensitive to this mode of action. Because of the threshold nature of the mode of action and the unique sensitivity of the mouse, it is concluded that humans are unlikely to be at risk for developing tumors following exposures to thiamethoxam. The CARC classified Thiamethoxam as “**Not Likely to be Carcinogenic to Humans**” based on convincing evidence that a non-genotoxic mode of action for liver tumors was established in the mouse and that the carcinogenic effects are a result of a mode of action dependent on sufficient amounts of a hepatotoxic metabolite produced persistently. Quantification of carcinogenic potential is not required. The submitted mutagenicity studies are adequate and indicate that thiamethoxam is not mutagenic.

Acutely, technical thiamethoxam is slightly toxic to rats and moderately toxic to mice via the oral route (Toxicity Category III); it is of low toxicity to rats via the dermal (Toxicity Category III) and inhalation routes (Toxicity Category IV). It is not irritating to the skin and minimally irritating to the eye, and is not a dermal sensitizer.

#### 4.4 Safety Factor for Infants and Children (FQPA Safety Factor)

HED further recommends that the 10X FQPA safety factor for the protection of infants and children be reduced to 1X. There is no quantitative or qualitative evidence of increased susceptibility of rat or rabbit fetuses to *in utero* exposure to thiamethoxam in the developmental toxicity studies. The developmental NOAELs are either higher than or equal to the maternal NOAELs. There was no evidence of increased quantitative susceptibility in the DNT study in rats.

Although there is evidence of increased quantitative susceptibility for male pups of both two-generation reproductive studies, NOAELs and LOAELs were established in these studies, and HED selected the NOAEL for testicular effects in F<sub>1</sub> pups as the basis for risk assessment. HED has confidence that the NOAEL selected for risk assessment is protective of the most sensitive effect (testicular) for the most sensitive subgroup (pups) observed in the toxicological database. In addition, the NOAELs selected for risk assessment are protective of all toxicological effects observed in the database including treatment-related changes in the adrenal gland, thyroid, testes and ovaries. Thus, HED believes the FQPA safety factor should be reduced to 1X.

The toxicity database for thiamethoxam is complete, although the immunotoxicity study has not been completely reviewed. The available data for thiamethoxam show the potential for immunotoxic effects, including changes in spleen weight and leukopenia. However, HED concluded that the leukopenia was associated with an anemic response as opposed to direct immunotoxicity. In addition, the reduced spleen weights were observed at high doses, and were not statistically significant. Based on these considerations and a screen of the immunotoxicity study recently submitted, HED previously concluded that an additional database uncertainty factor (UFDB) was not needed to account for the lack of the immunotoxicity study.

The dietary food exposure assessment is not likely to underestimate exposure/risk. The dietary drinking water assessment utilizes water concentration values generated by models and associated modeling parameters that are designed to provide conservative, health protective, high-end estimates of water concentrations which will not likely be exceeded. The residential exposure assessment was conducted using standard, health-protective assumptions.

##### 4.4.1 Completeness of the Toxicology Database

The database for evaluating *in utero* or postnatal susceptibility is adequate for the purpose of the current risk assessment, and for evaluating the need for an FQPA safety factor. However, the database is not complete because the required immunotoxicity study has recently been submitted and not yet reviewed. The following acceptable studies are available:

- Developmental toxicity studies in rats and rabbits
- Two two-generation reproduction studies in rats
- Developmental neurotoxicity study in rats

The available data for thiamethoxam show the potential for immunotoxic effects, including changes in spleen weight and leukopenia. However, as explained in the previous section, HED previously concluded that an additional database uncertainty factor (UFDB) was not needed to account for the lack of the immunotoxicity study. While the immunotoxicity has not been completely reviewed, it has been screened by HED, and the screen indicates that its final review would not impact the point of departure used in this assessment.

#### **4.4.2 Evidence of Neurotoxicity**

Thiamethoxam was tested in acute, 90-day and developmental neurotoxicity studies. In the acute neurotoxicity study, drooped palpebral closure, lower rectal temperature, increased forelimb grip strength (males only) and decreased locomotor activity were observed 2-3 hours after dosing. Effects at a higher dose included abnormal body tone, ptosis, impaired respiration, tremors, longer latency to first step in the open field, crouched-over posture, gait impairment, hypo-arousal, decreased number of rears, uncoordinated landing during the righting reflex test, slight lacrimation (females only) and higher mean average input stimulus value in the auditory startle response test (males only). These effects were no longer evident at the 1 week and 2 week post-dosing examinations. In addition to these findings, 3 females were found dead within the first 2 days after treatment. There were no treatment-related histopathological findings noted in the central or peripheral nervous system at any dose level tested.

In the 90-day neurotoxicity study, there were no treatment-related systemic or neurotoxicological effects observed at any dose level tested up to 95 mg/kg bw/day in males and 216.4 mg/kg bw/day in females. In addition, no treatment-related histopathological findings were noted in the central or peripheral nervous systems. The subchronic mammalian neurotoxicity study was not tested at sufficiently high dose levels; however, a new study is not required at this time because no neuropathology was observed at the dose levels tested, and the weight of the evidence from the other toxicity studies indicates that there is no reason for concern.

In the developmental neurotoxicity study, there was no evidence of neurotoxicity in the dams exposed up to 298.7 mg/kg/day; a dose that was associated with decreases in body weight gain and food consumption. In pups exposed to 298.7 mg/kg/day, there were significant reductions in absolute brain weight and size (i.e., length and width of the cerebellum was less in males on day 12, and there were significant decreases in Level 3-5 measurements in males and in Level 4-5 measurements in females on day 63).

The following evidence of neurotoxicity was observed in other oral studies. In the 28-day dog study there was a decrease in absolute but not relative brain weight in females at 43 mg/kg/day. This does not appear in either the 90-day study (up to 50 mg/kg/day) or the chronic dog study (up to 45 mg/kg/day). In the mouse carcinogenicity study, there was an increase in relative brain weight in high dose males that was attributed to reduction in body weight gain. In the rat chronic/carcinogenicity study, there was a slight increase in incidence of brain effects in high dose males. Microscopically, this increase was associated with hydrocephalus and pressure

atrophy which was secondary to pituitary adenomas. The increased incidence of brain effects is not likely due to a neuronal tissue malformation but, rather, secondary to a pituitary adenoma.

#### 4.4.3 Evidence of Sensitivity/Susceptibility in the Developing/Young Animal

In the developmental studies, there is no evidence of increased quantitative or qualitative susceptibility of rat or rabbit fetuses to *in utero* exposure to thiamethoxam. The developmental NOAELs are either higher than or equal to the maternal NOAELs. The toxicological effects in fetuses do not appear to be any more severe than those in the dams or does. In the rat developmental neurotoxicity study, there was no quantitative evidence of increased susceptibility; however, there was increased qualitative susceptibility because the effects in the pups (reduced brain weight and significant changes in brain morphometric measurements) were considered to be more severe than findings in the dams (decreased body weight gain and food consumption).

There is evidence of increased quantitative susceptibility for male pups in both two-generation reproductive studies. In one study, there are no toxicological effects in the dams; whereas, for the pups, reduced bodyweights are observed at the highest dose level, starting on day 14 of lactation. This contributes to an overall decrease in bodyweight gain during the entire lactation period. The reproductive effects in males appear in the F<sub>1</sub> generation in the form of increased incidence and severity of testicular tubular atrophy (see developmental/reproductive section). These data are considered to be evidence of increased quantitative susceptibility for male pups (increased incidence of testicular tubular atrophy at 1.8 mg/kg/day) when compared to the parents (hyaline changes in renal tubules at 61 mg/kg/day; NOAEL is 1.8 mg/kg/day). In a more recent two-generation reproduction study, the most sensitive effect was sperm abnormalities at 3 mg/kg/day (the NOAEL is 1.2 mg/kg/day) in the F<sub>1</sub> males. This study also indicates increased susceptibility for the offspring for this effect.

Although there is evidence of increased quantitative susceptibility for male pups in both reproductive studies, NOAELs and LOAELs were established in these studies and the Agency selected the NOAEL for testicular effects in F<sub>1</sub> pups as the basis for risk assessment. The Agency has confidence that the NOAEL selected for risk assessment is protective of the most sensitive effect (testicular) for the most sensitive subgroup (pups) observed in the toxicological database.

#### 4.4.4 Residual Uncertainty in the Exposure Database

There is low concern for an increase in quantitative susceptibility in the rats or rabbits since developmental and offspring toxicity occurred at dose levels equal to or higher than the doses where parental toxicity was observed in three studies (rat developmental, rabbit developmental and rat developmental neurotoxicity). There is also low concern for the increased qualitative susceptibility observed in the DNT study because the doses and endpoints selected for risk assessment are protective of the effects in the offspring. As noted previously, the Agency

selected the NOAEL for testicular effects in F<sub>1</sub> pups based on two reproductive toxicity studies for risk assessment to be protective of all sensitive subpopulations.

There is evidence of neurotoxicity after acute exposure to thiamethoxam at doses of 500 mg/kg/day including drooped palpebral closure, decrease in rectal temperature and locomotor activity and an increase in forelimb grip strength. However, no evidence of neuropathology was observed. These effects occurred at doses at least 14-fold and 416-fold higher than the doses used for the acute, and chronic risk assessments, respectively; thus, there is low concern for these effects since it is expected that the doses used for regulatory purposes would be protective of the effects noted at much higher doses.

#### **4.5 Toxicity Endpoint and Point of Departure Selections**

##### **4.5.1 Dose-Response Assessment**

The database on thiamethoxam indicates the primary targets for this chemical are the liver, testes, kidney, and hematopoietic system. The testicular effects are considered to be toxicologically significant and occur at low doses, and therefore most of the endpoints for risk assessment are based on these effects.

In the liver, enzyme induction and hepatocellular hypertrophy in and of themselves are not necessarily considered adverse effects. However, other effects were associated with these observations that are considered to be toxicologically significant. These include necrosis of single hepatocytes, foci of cellular alteration, apoptosis, Kupffer cell infiltration, pigmentation and hyperplasia, and benign and malignant liver tumors. The majority of the kidney effects may be attributed to accumulation of  $\alpha_2\mu$ -globulin, a protein that is unique to male rats, and, therefore, these kidney effects are not relevant to humans. The hematological effects are observed in three species. These include increased spleen weights, increases in the incidence and severity of hemosiderosis and/or extramedullary hematopoiesis and a slight reduction in erythrocytes, hemoglobin and hematocrit. In the dog, leukopenia and slight microcytic anemia have been observed. While these effects could be potential indication of immunotoxicity, HED concluded that the leukopenia was associated with an anemic response, as opposed to direct immunotoxicity. The decreases in spleen weight occurred at very high doses, and were not statistically significant. These effects are not considered to be as significant as the testicular, liver, and kidney effects. They often appear at very high dose levels and the changes are not dramatic.

##### **Acute Reference Dose (aRfD) - Females age 13-49**

A separate aRfD is not being used for females age 13-49. Females in this age group will be assessed using the aRfD for the general population.

##### **Acute Reference Dose (aRfD) - General Population**

Study Selected: Developmental Neurotoxicity Study—rat (OPPTS 870.6300)

MRID No.: 46028202, 46028201

Dose and Endpoint for Establishing aRfD: Developmental NOAEL = 34.5 mg/kg/day based on delayed sexual maturation in male pups, and reduced brain morphometric measurements LOAEL = 298.7 mg/kg/day.

Comments on Study/Endpoint/Uncertainty Factors: The endpoint chosen was presumed to occur following a single exposure and could be relevant for all populations, including children. The endpoint is based on the most sensitive effect in the most sensitive subpopulation (pups). Although the toxicological effects occurred in pups, it is not known if these effects resulted from pre- or post-natal dosing, and therefore the endpoint is relevant to all populations, and is considered to be protective. An UF of 100 was applied to account for inter-species extrapolation (10x) and intra-species variation (10x).

$$\text{Acute RfD} = \frac{34.5 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}} = 0.35 \text{ mg/kg/day}$$

### **Chronic Reference Dose (cRfD)**

Study Selected: Two 2-Generation Reproduction Toxicity Studies—rat (OPPTS 870.3800)

MRID No.: 44718707; 46402902, 46402904, 46402906

Dose and Endpoint for Establishing the cRfD: The Agency selected both two-generation reproductive studies as co-critical. The NOAEL of 1.2 mg/kg/day is based on sperm abnormalities in the F<sub>1</sub> males observed after *in utero* and post-natal exposure in the rat reproduction study at 3 mg/kg/day. In the other two-generation reproduction study, the NOAEL of 0.6 mg/kg/day and LOAEL of 1.8 mg/kg/day are based on testicular atrophy in F<sub>1</sub> males. The higher NOAEL was selected from these two studies based on the rationale detailed below in “Comments on Study/Endpoints/Uncertainty Factors.” While the testicular effects observed in the two reproductive studies differ, the findings support each other and are consistent relative to observed thiamethoxam toxicity. Although histopathological effects (tubular atrophy) were not observed in the more recent 2004 study at low dose levels, the observation of reduced sperm production would be expected to co-occur with the tubular atrophy that was observed in the 1998 study.

Uncertainty Factor(s): An UF of 100 was applied to account for inter-species extrapolation (10x) and intra-species variation (10x).

Comments on Study/Endpoint/Uncertainty Factors: The endpoint is based on the most sensitive effect observed in offspring. The endpoint is appropriate because effects were observed after subchronic exposure and are thus likely to be observed after chronic exposure.

Although the NOAEL of 1.2 mg/kg/day is very close to the LOAEL of 1.8 mg/kg/day for testicular effects, the Agency has confidence that the NOAEL is protective. The NOAEL of 1.2 mg/kg/day is based on the 2004 study for significant reductions in the number of sperm in the right testes of F<sub>1</sub> males at 3 mg/kg/day. This endpoint is considered conservative and protective because there was no dose-response relationship and these findings were not observed in the F<sub>0</sub> males. Most of the other sperm parameters were not significantly altered until much higher dose levels of 155 mg/kg/day. Although some sperm abnormalities were noted in the 1998 study, such as decreased sperm motility, even at 0.6 mg/kg/day, there was no dose-response relationship, there was high variability among all groups and there were no treatment-related effects on sperm count or sperm morphology. Based on a special complementary study conducted to evaluate this finding, HED concluded the sperm effects in this study were likely due to technical error and not treatment-related. However, based on consideration of both reproductive studies, the Agency believes that it is appropriate to select a NOAEL of 1.2 mg/kg/day for these sperm effects for use in risk assessment.

The LOAEL of 1.8 mg/kg/day is based on testicular atrophy in F<sub>1</sub> generation males. In the 2004 study, testicular lesions were marginal even at much higher dose levels of 155 mg/kg/day where there was an increase in incidence but not severity of testicular lesions. The difference in the two studies may possibly be due to different grading criteria, and also differences in histopathological evaluation protocols. The 1998 study only evaluated one slice per testis. The 2004 study evaluated 4 slices per testis, calculated an average numerical grade and reported only marginal testicular lesions at 155 mg/kg/day. Therefore, HED believes the LOAEL of 1.8 mg/kg/day for testicular atrophy is likely to be conservative and protective because of the findings of the 2004 study.

Although there are no indications of effects on other reproductive parameters (i.e. mating, gestation, fertility and viability), similar effects were observed in a second species (dog) after subchronic exposure. Due to the high fecundity of rats, the lack of effects on other reproductive parameters is not necessarily an indication that the testicular effects would not be a problem in humans. Since no data are available to indicate how the testicular effects occur or whether or not they can definitively be considered adverse, the testicular effects were selected to provide a conservative approach for assessment of risk to humans. In addition, it is not known whether the observed effects are due to exposure to either the male or female or both parents in the study. Therefore, the endpoint will be applied to the general population.

The Agency recognizes that this endpoint may not be relevant for young children that are sexually immature. However, this endpoint was determined to be conservative and health-protective for use in risk assessment.

$$\text{Chronic RfD} = \frac{1.2 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}} = 0.012 \text{ mg/kg/day}$$

**Incidental Oral Exposure (Short- and Intermediate-Term)**

Study Selected: 90-day Oral Toxicity —dog (OPPTS 870.3150)

MRID No.: 44718702

Dose and Endpoint for Risk Assessment: The incidental oral endpoint (all durations) of 8.23 mg/kg/day is based on slightly prolonged prothrombin times and decreased plasma albumin and A/G ratio (both sexes); decreased calcium levels and ovary weights and delayed maturation in the ovaries; decreased cholesterol and phospholipid levels, testis weights, spermatogenesis, and spermatogenic giant cells in testes (males) that occurred at 32 mg/kg/day in males and 33.9 mg/kg/day in females.

Comments on Study/Endpoint: The Agency recognizes that some of the observed effects in this study (i.e., testicular and ovarian effects) may not be relevant for young children that are sexually immature. However, these effects occurred along with other more toxicologically relevant findings for children, and thus this endpoint was determined to be conservative and health-protective for use in risk assessment.

The Agency also considered the rat and mouse 90 day toxicity studies for endpoint selection that reported LOAELs of 17.64 mg/kg/day and 14.3 mg/kg/day, respectively. The dog NOAEL of 8.23 mg/kg/day is protective of the effects noted in rats and mice. In addition, the renal effects in the rat study are most likely attributed to accumulation of  $\alpha_2$ -globulin, and thus are not relevant to humans.

**Dermal Exposure (Short-, Intermediate- and Long-Term) Adults**

Study Selected: Two 2-Generation Reproduction Toxicity Studies—rat (OPPTS 870.3800)

MRID No.: 44718707; 46402902, 46402904, 46402906

Dose and Endpoint for Risk Assessment: The dermal endpoint for adults, all durations (1.2 mg/kg/day) is based on sperm abnormalities and testicular effects observed after *in utero* and post-natal exposure in the rat reproduction studies (see comments from the chronic dietary section above).

Comments on Study/Endpoint: Although a 28-day dermal toxicity study in rats is available, HED selected a reproductive NOAEL because the reproductive parameters are not evaluated in the dermal toxicity study and thus the consequences of these effects cannot be ascertained for the

dermal route of exposure. Since an oral toxicity study was selected, a 5% dermal absorption factor is recommended.

### **Dermal Exposure (Short-, Intermediate- and Long-Term) Children Age 1 to 6 Years**

Study Selected: 28-Day Dermal Toxicity Study—rat (OPPTS 870.3200)

MRID No.: 44710402

Dose and Endpoint for Risk Assessment: The dermal endpoint (children 1-6, all durations) of 60 mg/kg/day is based on increased plasma glucose, triglyceride levels, and alkaline phosphatase activity as well as inflammatory cell infiltration in the liver and necrosis of single hepatocytes in females at 250 mg/kg/day.

Comments on Study/Endpoint: The Agency selected the dermal toxicity study to assess young children because the testicular effects observed in the two-generation rat reproduction study are not relevant for young children that are sexually immature. Because a route-specific toxicity study was selected, a dermal absorption factor is not necessary when assessing dermal exposure to children.

### **Inhalation Exposure (Short-, Intermediate- and Long-Term)**

Based on the available toxicity database and the Agency's current practices, short- and intermediate-term inhalation risks for thiamethoxam were assessed using an oral toxicity study. The Agency sought expert advice and input on issues related to this route to route extrapolation approach (i.e. the use of oral toxicity studies for inhalation risk assessment) from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009. The Agency received the SAP's final report on March 2, 2010 (<http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html>). The Agency is in the process of evaluating the SAP report and may, as appropriate, re-examine and develop new policies and procedures for conducting inhalation risk assessments, including route to route extrapolation of toxicity data. If any new policies or procedures are developed, the Agency may revisit the need for an inhalation toxicity study for thiamethoxam and/or a re-examination of the inhalation toxicity risk assessment.

Study Selected: Two 2-Generation Reproduction Toxicity Studies—rat (OPPTS 870.3800)

MRID No.: 44718707, 46402902, 46402904, 46402906

Dose and Endpoint for Risk Assessment: NOAEL of 1.2 mg/kg/day is based on sperm abnormalities and testicular effects observed after *in utero* and post-natal exposure in the rat reproduction studies (see comments from the chronic dietary endpoint section above).

Comments about the Study/Endpoint: Since no data are available to indicate how much exposure will induce the effects, the effects are considered to be appropriate for all exposure durations. Other than acute toxicity, no inhalation studies are available. Therefore, the reproductive endpoint is selected for inhalation exposure. Inhalation absorption is assumed to be 100% of oral absorption. The Agency recognizes that this endpoint may not be relevant for young children that are sexually immature. However, based on the use pattern and physical-chemical characteristics, the Agency does not anticipate inhalation exposure to young children.

### Level of Concern for Margin of Exposure

| Table 4.5.1 Summary of Levels of Concern for Risk Assessment. |                             |                                     |                           |
|---------------------------------------------------------------|-----------------------------|-------------------------------------|---------------------------|
| Route                                                         | Short-Term<br>(1 - 30 Days) | Intermediate-Term<br>(1 - 6 Months) | Long-Term<br>(> 6 Months) |
| Occupational (Worker) Exposure                                |                             |                                     |                           |
| Dermal                                                        | 100                         | 100                                 | 100                       |
| Inhalation                                                    | 100                         | 100                                 | 100                       |
| Residential Exposure                                          |                             |                                     |                           |
| Dermal                                                        | 100                         | 100                                 | 100                       |
| Inhalation                                                    | 100                         | 100                                 | 100                       |
| Incidental Oral                                               | 100                         | 100                                 | 100                       |

#### 4.5.2 Recommendation for Combining Routes of Exposures for Risk Assessment

According to FQPA (1996), when there are potential residual exposures to a pesticide, an aggregate risk assessment must consider exposures from 3 major routes: oral, dermal, and inhalation.

Similar endpoints were selected for short-, intermediate- and long-term exposures via oral, dermal and inhalation routes, so they may be aggregated. The endpoints are protective of adverse testicular, liver and hematological effects, which appear to be the most sensitive effects of thiamethoxam exposure via oral and dermal routes.

#### 4.5.3 Cancer Classification and Risk Assessment Recommendation

Thiamethoxam induces hepatocellular adenomas and carcinomas in male and female mice. These findings served as the basis for HED's initial conclusion that thiamethoxam was likely to

be carcinogenic to humans; furthermore, HED recommended using a linear low dose extrapolation for assessing cancer risk. The registrant subsequently conducted a number of studies to support a mode of action for carcinogenicity in mice. These studies were evaluated, and the Cancer Assessment Review Committee (CARC) agreed with the registrant that a plausible mode of action has been established for the development of liver tumors in a mouse bioassay with thiamethoxam. The liver tumors in the mouse arise through a non-genotoxic mode of action characterized by a series of key events that include: perturbation of cholesterol biosynthesis, hepatotoxicity, cell death (both as single cell necrosis and apoptosis) and a sustained increase in cell replication rates. Neither the key events nor an increase in liver tumors are seen in rats fed on diets containing up to 3000 ppm thiamethoxam. The key metabolites, CGA330050 and CGA265307, responsible for the key events in the mouse are not formed in sufficient quantities in the rat and explain the lack of a carcinogenic response in this species.

A sufficient amount of active metabolite must be produced along with persistent exposure to the active metabolite to lead to the hepatotoxic/regenerative proliferative/neoplastic response in the mouse. Limited human *in vitro* metabolism studies suggest that humans are more similar to the rat compared to the mouse in producing the active metabolite. The rat does not develop tumors following treatment with thiamethoxam. Thus, the mouse appears to be uniquely sensitive to this mode of action. Because of the threshold nature of the mode of action and the unique sensitivity of the mouse, it is concluded that humans are unlikely to be at risk for developing tumors following exposures to thiamethoxam.

In accordance with the EPA's *Final Guidelines for Carcinogen Risk Assessment* (March, 2005), the CARC re-classified thiamethoxam as **"Not Likely to be Carcinogenic to Humans"** based on convincing evidence that a non-genotoxic mode of action for liver tumors was established in the mouse and that the carcinogenic effects are a result of a mode of action dependent on sufficient amounts of a hepatotoxic metabolite produced persistently. Although humans are qualitatively capable of producing the active metabolite, thiamethoxam is unlikely to pose a cancer risk to humans unless sufficient amounts of metabolites are persistently formed to drive a carcinogenic response. Lastly, the non-cancer assessment is sufficiently protective of the key events (perturbation of liver metabolism, hepatotoxicity/regenerative proliferation) in the animal mode of action and, thus, cancer is not an issue. Thus, quantification of carcinogenic potential is not required.

#### 4.5.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

| Table 4.5.4a. Toxicological Doses and Endpoints for Thiamethoxam for Use in Dietary and Residential Human Health Risk Assessments. |                       |                                    |                                         |                                 |
|------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------|-----------------------------------------|---------------------------------|
| Exposure/<br>Scenario                                                                                                              | Point of<br>Departure | Uncertainty/FQPA<br>Safety Factors | Level of Concern<br>for Risk Assessment | Study and Toxicological Effects |

**Table 4.5.4a. Toxicological Doses and Endpoints for Thiamethoxam for Use in Dietary and Residential Human Health Risk Assessments.**

| Exposure/<br>Scenario                                                          | Point of<br>Departure                                                         | Uncertainty/FQPA<br>Safety Factors                                       | Level of Concern<br>for Risk Assessment                | Study and Toxicological Effects                                                                                                                                                                                                                                                                                                                                                                        |
|--------------------------------------------------------------------------------|-------------------------------------------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Acute Dietary<br><u>All populations</u><br>including infants<br>and children   | NOAEL = 34.5<br>mg/kg/day                                                     | UF <sub>A</sub> = 10x<br>UF <sub>H</sub> = 10x<br>SF <sub>FQPA</sub> = 1 | aRfD = 0.35<br>mg/kg/day<br>aPAD = 0.35<br>mg/kg/day   | <b>Rat Developmental Neurotoxicity study</b><br>LOAEL = 298.7 mg/kg/day based on delayed sexual maturation in male pups, and reduced brain morphometric measurements.                                                                                                                                                                                                                                  |
| Chronic Dietary<br><u>All populations</u><br>including infants<br>and children | NOAEL = 1.2<br>mg/kg/day<br>(MRID<br>46402904)                                | UF <sub>A</sub> = 10x<br>UF <sub>H</sub> = 10x<br>SF <sub>FQPA</sub> = 1 | cRfD = 0.012<br>mg/kg/day<br>cPAD = 0.012<br>mg/kg/day | <b>2-Generation reproduction study</b><br>LOAEL = 1.8 mg/kg/day based on increased incidence and severity of tubular atrophy in testes of F <sub>1</sub> generation males.<br><b>2-Generation reproduction study</b><br>LOAEL = 3 (males), not determined (females) mg/kg/day based on sperm abnormalities in F <sub>1</sub> males.                                                                    |
| Incidental Oral (all<br>durations)                                             | NOAEL = 8.23<br>mg/kg/day                                                     | UF <sub>A</sub> = 10x<br>UF <sub>H</sub> = 10x<br>SF <sub>FQPA</sub> = 1 | MOE = 100<br>(residential)                             | <b>90-day Dog study</b><br>LOAEL = 32 (males) 33.9 (females) mg/kg/day based on slightly prolonged prothrombin times and decreased plasma albumin and A/G ratio (both sexes); decreased calcium levels and ovary weights and delayed maturation in the ovaries (females); decreased cholesterol and phospholipid levels, testis weights, spermatogenesis, and spermatid giant cells in testes (males). |
| Dermal (all<br>durations) (Adults)                                             | Oral study<br>NOAEL = 1.2<br>mg/kg/day<br>(dermal<br>absorption rate<br>= 5%) | UF <sub>A</sub> = 10x<br>UF <sub>H</sub> = 10x<br>SF <sub>FQPA</sub> = 1 | MOE = 100<br>(residential)                             | <b>2-Generation reproduction study</b><br>LOAEL = 1.8 mg/kg/day based on increased incidence and severity of tubular atrophy in testes of F <sub>1</sub> generation males.<br><b>2-Generation reproduction study</b><br>LOAEL = 3 (males), not determined (females) mg/kg/day based on sperm abnormalities in F <sub>1</sub> males.                                                                    |
| Dermal (all<br>durations) (infants/<br>children 1-6 yrs)                       | Dermal Study<br>NOAEL = 60<br>mg/kg/day                                       | UF <sub>A</sub> = 10x<br>UF <sub>H</sub> = 10x<br>SF <sub>FQPA</sub> = 1 | MOE = 100<br>(residential)                             | <b>Rat 28-Day Dermal Toxicity Study</b><br>LOAEL = 250 (females) mg/kg/day based on increased plasma glucose, triglyceride levels, and alkaline phosphatase activity and inflammatory cell infiltration in the liver and necrosis of single hepatocytes in females.                                                                                                                                    |
| Inhalation (all<br>durations)                                                  | Oral study<br>NOAEL = 1.2<br>mg/kg/day<br>(inhalation                         | UF <sub>A</sub> = 10x<br>UF <sub>H</sub> = 10x<br>SF <sub>FQPA</sub> = 1 | MOE = 100<br>(residential)                             | <b>2-Generation reproduction study</b><br>LOAEL = 1.8 mg/kg/day based on increased incidence and severity of tubular atrophy in testes of F <sub>1</sub>                                                                                                                                                                                                                                               |

**Table 4.5.4a. Toxicological Doses and Endpoints for Thiamethoxam for Use in Dietary and Residential Human Health Risk Assessments.**

| Exposure/Scenario                 | Point of Departure                                                                                                                                                                                                     | Uncertainty/FQPA Safety Factors | Level of Concern for Risk Assessment | Study and Toxicological Effects                                                                                                                                            |
|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|--------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                   | absorption rate = 100% of oral absorption)                                                                                                                                                                             |                                 |                                      | generation males.<br><b>2-Generation reproduction study</b><br>LOAEL = 3 (males), not determined (females) mg/kg/day based on sperm abnormalities in F <sub>1</sub> males. |
| Cancer (oral, dermal, inhalation) | <b>"Not Likely to be Carcinogenic to Humans"</b> based on convincing evidence that a non-genotoxic mode of action for liver tumors was established in the mouse. Quantification of cancer risk is <u>not</u> required. |                                 |                                      |                                                                                                                                                                            |

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF<sub>A</sub> = extrapolation from animal to human (interspecies). UF<sub>H</sub> = potential variation in sensitivity among members of the human population (intraspecies). UF<sub>L</sub> = use of a LOAEL to extrapolate a NOAEL. UF<sub>S</sub> = use of a short-term study for long-term risk assessment. UF<sub>DB</sub> = to account for the absence of key data (i.e., lack of a critical study). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

**Table 4.5.4b. Summary of Toxicological Doses and Endpoints for Thiamethoxam for Use in Occupational Human Health Risk Assessments.**

| Exposure/Scenario                                                    | Point of Departure                                                     | Uncertainty Factors                            | Level of Concern for Risk Assessment | Study and Toxicological Effects                                                                                                                                                                                                                                                                                                     |
|----------------------------------------------------------------------|------------------------------------------------------------------------|------------------------------------------------|--------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Dermal Short-term (1-30 days) and Intermediate-term (1-6 months)     | Oral study NOAEL = 1.2 mg/kg/day (dermal absorption rate = 5%)         | UF <sub>A</sub> = 10x<br>UF <sub>H</sub> = 10x | MOE = 100 (occupational)             | <b>2-Generation reproduction study</b><br>LOAEL = 1.8 mg/kg/day based on increased incidence and severity of tubular atrophy in testes of F <sub>1</sub> generation males.<br><b>2-Generation reproduction study</b><br>LOAEL = 3 (males), not determined (females) mg/kg/day based on sperm abnormalities in F <sub>1</sub> males. |
| Inhalation Short-term (1-30 days) and Intermediate-term (1-6 months) | Oral study NOAEL = 1.2 mg/kg/day (inhalation absorption factor = 100%) | UF <sub>A</sub> = 10x<br>UF <sub>H</sub> = 10x | MOE = 100 (occupational)             | <b>2-Generation reproduction study</b><br>LOAEL = 1.8 mg/kg/day based on increased incidence and severity of tubular atrophy in testes of F <sub>1</sub> generation males.<br><b>2-Generation reproduction study</b><br>LOAEL = 3 (males), not determined (females) mg/kg/day based on sperm abnormalities in F <sub>1</sub> males. |

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF<sub>A</sub> = extrapolation from animal to human (interspecies). UF<sub>H</sub> = potential variation in sensitivity among members of the human population (intraspecies). UF<sub>L</sub> = use of a LOAEL to extrapolate a NOAEL. UF<sub>S</sub> = use of a short-term study for long-term risk assessment. UF<sub>DB</sub> = to account for the absence of key data (i.e., lack of a critical study). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

## **4.6 Endocrine Disruption**

As required under FFDCA section 408(p), EPA has developed the Endocrine Disruptor Screening Program (EDSP) to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a “naturally occurring estrogen, or other such endocrine effects as the Administrator may designate.” The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. This list of chemicals was selected based on the potential for human exposure through pathways such as food and water, residential activity, and certain postapplication agricultural scenarios. This list should not be construed as a list of known or likely endocrine disruptors.

Thiamethoxam is not among the group of 58 pesticide active ingredients on the initial list to be screened under the EDSP. Under FFDCA sec. 408(p) the Agency must screen all pesticide chemicals. Accordingly, EPA anticipates issuing future EDSP test orders/data call-ins for all pesticide active ingredients.

For further information on the status of the EDSP, the policies and procedures, the list of 67 chemicals, the test guidelines and the Tier 1 screening battery, please visit our website: <http://www.epa.gov/endo/>.

## **5.0 Dietary Exposure and Risk Assessment**

### **5.1 Metabolite/Degradate Residue Profile**

Data have been submitted and reviewed depicting the metabolism of thiamethoxam in numerous crops and the environment. HED has determined that the plant and livestock residues of concern for purposes of tolerance enforcement and risk assessment are the combined residues of thiamethoxam and clothianidin (CGA-322704). For a complete discussion of metabolism in crops and livestock, including chemical names and structures, see the Residue Chemistry Summary Document (M. Doherty, D281702, March 2007).

#### **5.1.1 Summary of Plant and Animal Metabolism Studies**

References: 44939802.der.doc (Cucumber)  
45093709.der.doc (Tobacco)  
45093711.der.doc (Tobacco)  
45093713.der.doc (Potato)  
45093714.der.doc (Lettuce)  
MARC Decision Memo: D258614, 8/31/99, G.J. Herndon  
Residue Chemistry Memo D252021, 3/30/00, G.J. Herndon (PP#9F5046)  
Residue Chemistry Memo D265079, 5/8/00, G.J. Herndon (PP#9F5051)

The metabolism of thiamethoxam in crops generally involves: (i) opening of the oxadiazine ring by hydrolysis; (ii) loss of the nitro group; (iii) hydrolysis of the guanidine moiety to urea derivatives; (iv) cleavage of the N-C bridge between the two ring systems; and (v) N-demethylation of the oxadiazine ring or its derivatives. Initial hydrolysis of the oxadiazine ring of thiamethoxam yields CGA-322704, which is a major metabolite in corn, pears, rice and wheat. CGA-322704 can then either: (i) lose its nitro group to form NOA-421275 (a major metabolite in corn); (ii) undergo N-demethylation to yield CGA-265307; or (iii) be cleaved at the N-C bridge to form NOA-405217 and the thiazole ring metabolites CGA-359683 and CGA-349208. Alternatively, thiamethoxam may initially lose its nitro group to form NOA-407475, and then undergo hydrolysis of the oxadiazine ring to form NOA-421275, or oxidation of the oxadiazine ring to form CGA-355190.

The nature of the residue in livestock is adequately understood based on acceptable goat and hen metabolism studies. The metabolism of thiamethoxam in ruminants and poultry is similar. The major metabolic pathway involves hydrolysis of the oxadiazine ring to form CGA-322704 and subsequent demethylation to produce CGA-265307; loss of the nitro group from these two metabolites also yields NOA-421275 and NOA-421276. Several major metabolites (MU3, L14, and MU12) in both ruminants and poultry also result from the reduction of the nitro group in thiamethoxam or CGA-265307 to a hydrazine, and subsequent conjugation with acetic or 2-oxo-propionic acids. Separation of the thiazole and oxadiazine rings was only a minor pathway in ruminants and poultry.

### 5.1.2 Summary of Environmental Degradation

Thiamethoxam is expected to be persistent and mobile in terrestrial and aquatic environments. These fate properties suggest that thiamethoxam has the potential to move into surface water and shallow ground water.

### 5.1.3 Comparison of Metabolic Pathways

Metabolism studies with thiamethoxam have been submitted on corn, cucumber, lettuce, pear, potato, rice, tobacco, and wheat. The studies on cucumber, lettuce, pear, and rice reflected foliar applications, and the studies on corn, potato, and wheat reflected seed treatment and/or soil drench applications. The tobacco studies included soil and foliar treatments. HED previously determined (and continues to support the decision) that the residues of concern for purposes of

tolerance enforcement and risk assessment are the combined residues of thiamethoxam and CGA-322704. The metabolic pathways were similar for the different plants.

Thiamethoxam metabolism in rats is similar to that observed in the goat and in poultry. In rats, thiamethoxam is absorbed rapidly and extensively, and is widely distributed, followed by very rapid elimination, mostly in the urine (84-95%). The half-life times from tissues ranged from 2-6 hours. The major biotransformation reaction is cleavage of the oxadiazine ring to form the corresponding nitroguanidine compound (*i.e.*, clothianidin, the regulated metabolite in plants and livestock). In mice, approximately 72% of the administered dose is excreted in the urine, while 19% is excreted in the feces. The predominant components are unchanged parent (33-41% of administered dose) and two other metabolites (8-12% and 9-18% of administered dose). These are the same structures that were most commonly observed in rat excreta; however, the proportions are quite different in mouse excreta.

#### 5.1.4 Residues of Concern Summary and Rationale

MARC Decision Memo: D258614, 8/31/99, G.J. Herndon  
Residue Chemistry Memo D252021, 3/30/00, G.J. Herndon  
Residue Chemistry Memo D265079, 5/8/00, G.J. Herndon  
Residue Chemistry Memo D281702, 4/17/07, M. Doherty

HED's Metabolism Assessment Review Committee (MARC) concluded that the majority of any toxicity associated with thiamethoxam and its metabolites was due to the presence of the N-nitro group. The MARC concluded that metabolites that did not contain this N-nitro group (including those that contain only the chlorothiazole ring) would exhibit less toxicity and therefore would not need to be regulated.

In target crops, ruminant muscle and milk the parent and the CGA-322704 metabolite (*i.e.*, clothianidin) accounted for a high percentage of the identified radioactivity. Other metabolites occurring at significant levels did not contain the N-nitro group. The situations in poultry and rotational crops were similar with the exception that the MARC recommended the additional metabolite CGA-265307 be analyzed in any laying hen feeding study or field rotational crop studies.

With respect to drinking water, the fate data indicated that the parent molecule is stable in water at neutral and acidic pHs, but at elevated pHs was likely to be hydrolyzed. Major metabolites (> 10% of applied parent compound) included CGA-355190, CGA-353968, and NOA-405217. The parent is also quite stable in soil (half lives of about 300 - 350 days). The Committee was not concerned with the relative levels of the metabolites CGA-355190 and CGA-353968 due to the absence of the N-nitro group. NOA-405217 contained the N-nitro group, but was only a significant metabolite under hydrolysis at pH 9. The MARC concluded that the residue of concern in drinking water is the parent thiamethoxam considering its stability in water and soil. However, EFED should inform the Committee in the future if additional data show levels of other nitro-containing compounds (*e.g.*, CGA-322704, CGA-282149, CGA-265307, NOA-

405217, NOA-404617) comparable to that of the parent. For example, in areas where soil pH is 8 or higher, EFED should consult with the Committee if they conclude that levels of NOA-405217 in water approach those of parent thiamethoxam.

Based on the above rationale, HED concludes that the residues of concern for thiamethoxam are as outlined in the table below. In the case of rotational crops, tolerances are not needed with the plantback intervals on current labels and residues on these crops do not need to be considered in dietary risk assessment.

| Table 5.1.4. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression |                 |                                      |                                                                     |
|-------------------------------------------------------------------------------------------------------------------|-----------------|--------------------------------------|---------------------------------------------------------------------|
| Matrix                                                                                                            |                 | Residues included in Risk Assessment | Residues included in Tolerance Expression for Compliance Monitoring |
| Plants                                                                                                            | Primary Crop    | Thiamethoxam + chlothianidin         | Thiamethoxam + clothianidin                                         |
|                                                                                                                   | Rotational Crop | Not Applicable                       | Not Applicable                                                      |
| Livestock                                                                                                         | Ruminant        | Thiamethoxam + chlothianidin         | Thiamethoxam + clothianidin                                         |
|                                                                                                                   | Poultry         | Thiamethoxam + chlothianidin         | Thiamethoxam + clothianidin                                         |
| Drinking Water                                                                                                    |                 | Thiamethoxam                         | Not Applicable                                                      |

## 5.2 Food Residue Profile

Syngenta had previously submitted a proposal that ChemSAC approve the use of wheat and barley residue data for oats. The ChemSAC concluded (Nov. 25, 2009 ChemSAC Minutes, Extrapolation of Residue Data from Barley and Wheat to Oats) that it was acceptable to set a tolerance on oats translating wheat and barley residue data provided that the timing of applications to these crops is similar.

A tolerance for either Crop Group 15 or Crop Group 16 commodities is not appropriate except for Crop Group 15 grains (except barley), because the use pattern is not the same for all Crop Group 15 commodities. Specifically, there is a foliar use on barley and there are much higher tolerances for barley hay and straw associated with this foliar use. It is for similar reasons that a Crop Group 16 tolerance would not be appropriate. In addition, there are also significant differences in the tolerances for the different cereal forages, i.e., wheat forage at 0.5 ppm, corn forage at 0.10 ppm, and sorghum forage at 0.02 ppm. Therefore, tolerances for each individual commodity should be established by translating residue data from the most appropriate representative commodity, except for grains which all have the same tolerance (excluding barley).

HED's policy document for conducting such data translation is contained in "*Guidance for Translation of Field Trial Data from Representative Commodities in the Crop Group Regulation to Other Commodities in Each Crop Group/Subgroup, HED Standard Operating Procedure 2000.1*", Margaret Stasikowski, 9/12/2000. The following data translations are allowed for Crop Group 15 and Crop Group 16 commodities.

**Crop Group 15: Cereal Grains,** Representative Commodities: Corn, sweet and corn, field; rice; sorghum, grain; and wheat.

| CROP GROUP COMMODITY | REPRESENTATIVE COMMODITY                 |
|----------------------|------------------------------------------|
| Barley               | Wheat                                    |
| Buckwheat            | Wheat                                    |
| Corn, field          | Corn, field                              |
| Corn, sweet          | Corn, sweet                              |
| Millet, pearl        | Sorghum, grain                           |
| Millet, proso        | Sorghum, grain                           |
| Oat                  | Wheat                                    |
| Popcorn              | Corn, field                              |
| Rice                 | Rice                                     |
| Rye                  | Wheat                                    |
| Sorghum, grain       | Sorghum, grain                           |
| Teosinte             | Wheat (corn now recommended – see below) |
| Triticale            | Wheat                                    |
| Wheat                | Wheat                                    |
| Wild rice            | Rice                                     |

**Crop Group 16: Forage, Fodder and Straw of Cereal Grains,** Representative Commodities: Corn, wheat, and any other cereal grain crop. The commodities in this crop group consist of the forage, stover, and straw of all commodities included in the cereal grains group as applicable. All cereal grains are livestock feed items.

There are existing residue data for all of the representative commodities for Crop Group 15, i.e., corn (sweet and field), rice, sorghum and wheat. In addition data are available for barley seed treatment and foliar use on barley. The proposed seed treatment use on buckwheat, pearl millet, proso millet, oats, rye, teosinte, triticale, and wild rice is the same or very similar to the existing seed treatment uses on corn (sweet and field), rice, sorghum, and wheat.

Wheat is the appropriate representative commodity for many of the small grains like oats, rye, triticale, and buckwheat. 40 CFR §180.1 states that when a tolerance is established for wheat, that tolerance or exemption from a tolerance also applies to triticale. The use on wheat is identical to that for all of the proposed commodities. Pearl millet and proso millet are more closely related to sorghum than wheat. In addition, the registered use rate for sorghum is higher than the proposed use rate on millet, and would not underestimate potential residue levels in or on millet. Teosinte is a plant closely related to corn, and translating corn residue data to teosinte is the appropriate choice for data translation (Bernard Schneider, Ph.D., 6/2/2011 email communication). The use rate for corn is higher than the proposed use rate on teosinte; however,

both uses are for seed treatment and translating corn data to teosinte would be conservative. Rice and wild rice have similar use patterns, cultural practices and translating rice data to wild rice is the most appropriate residue data translation. (Note: A tolerance for wild rice, bran is not needed.)

HED concludes that the following data translations are appropriate. A revised Section F should be submitted to reflect the tolerances specified above (see “Recommended Tolerances” in section 2.2.3), including the Crop Group 16 commodities, which were not included in the petition or Notice of Filing.

| Commodity    | Data Translation Commodity | Comments                                          |
|--------------|----------------------------|---------------------------------------------------|
| Buckwheat    | Wheat                      |                                                   |
| Oats         | Wheat                      |                                                   |
| Pearl millet | Sorghum                    | Straw tolerances are not needed for pearl millet. |
| Proso millet | Sorghum                    |                                                   |
| Rye          | Wheat                      |                                                   |
| Teosinte     | Corn, field                |                                                   |
| Triticale    | Wheat                      | See 40 CFR §180.1.                                |
| Wild rice    | Rice                       |                                                   |

### 5.3 Water Residue Profile

Reference: EFED Memo D373378, C. Koper, 20 May 2010  
EFED Memo D391528, C. Koper, 28 July 2011

Thiamethoxam is expected to be persistent and mobile in terrestrial and aquatic environments. These fate properties suggest that thiamethoxam has a potential to move into surface water and shallow groundwater.

The drinking water residues used in these dietary risk assessments were provided by EFED (D391528, C. Koper, 28 July 2011; and D373378, C. Koper, 20 May 2010), and incorporated directly into the dietary assessments. Water residues were incorporated in DEEM-FCID via entry into the food categories “water, direct, all sources” and “water, indirect, all sources.” The estimated drinking water concentrations (EDWCs) in surface water are 0.13177 ppm and 0.01131 ppm for acute and chronic scenarios, respectively. Typically, HED uses the higher of the surface or groundwater estimates for each duration when assessing dietary risk.

The EDWCs were incorporated into the acute and chronic thiamethoxam assessments. Clothianidin, a major metabolite of thiamethoxam in plants and livestock, is not a significant degradate of thiamethoxam in surface or groundwater sources of drinking water.

For surface water, the EDWCs for the crops modeled in this assessment did not exceed the previous EDWCs for rice reported in the previous drinking water assessment (D363202) dated 07 April 2009. The reported acute concentration of 131.77 µg/L, annual mean (chronic) concentration of 11.31 µg/L and the highest 30 year annual average concentration of 11.31 µg/L from the rice model are higher than the calculated EDWCs (see Table 5.3) for the various uses on other crops. Therefore, the current EDWCs for surface water do not supersede the drinking water concentrations previously estimated for this chemical (D363202, F. Khan, 7 April 2009).

For groundwater, based on the proposed highest annual use rate for dry bulb onions and the proposed use rates for peanut and alfalfa seed treatment, the SCI-GROW model concentration of thiamethoxam was 4.66 µg/L, 1.24 µg/L and 0.34 µg/L, respectively. This value was compared to 4.14 µg/L reported for grapes in the previous drinking water assessment (D329467) dated 10 January 2007. The predicted value for grapes is a corrected value described in detail in a previous drinking water assessment (D368072) dated 2 Feb 2010. Since 4.66 µg/L is greater than 4.14 µg/L, the current EDWC supersedes the previously recommended EDWC for groundwater.

The acute and chronic scenario EDWCs in surface water (0.13177 and 0.01131 ppm, respectively) were obtained via exposure modeling which utilized a modified Tier I Rice Model and the Provisional Cranberry Model. This model and its description are available at the EPA internet website via the web link, <http://www.epa.gov/oppefed1/models/water/>.

| <b>Table 5.3. Tier II Estimated Drinking Water Concentrations (EDWCs) resulting from applications of Thiamethoxam.</b> |                                                         |                                  |                                    |                                |
|------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|----------------------------------|------------------------------------|--------------------------------|
| <b>Drinking Water Source (model)</b>                                                                                   | <b>Use Scenario (modeled rate)</b>                      | <b>1-in-10 year acute (µg/L)</b> | <b>1-in-10 year chronic (µg/L)</b> | <b>30- year average (µg/L)</b> |
| Surface Water (PRZM/EXAMS)                                                                                             | NC Peanuts:<br>(1 app. <sup>1</sup> X 0.08 lbs ai/acre) | 1.51                             | 0.16                               | 0.05                           |
|                                                                                                                        | CA Alfalfa<br>(January 9)                               | 0.37                             | 0.07                               | 0.03                           |
|                                                                                                                        | MN Alfalfa<br>(May 25)                                  | 0.27                             | 0.03                               | 0.02                           |
|                                                                                                                        | NC Alfalfa<br>(March 25)                                | 0.55                             | 0.08                               | 0.03                           |
|                                                                                                                        | PA Alfalfa<br>(March 9)                                 | 0.37                             | 0.05                               | 0.03                           |
|                                                                                                                        | TX Alfalfa<br>(August 25)                               | 0.89                             | 0.10                               | 0.05                           |
|                                                                                                                        | IL Alfalfa<br>(May 25)                                  | 0.58                             | 0.06                               | 0.03                           |
|                                                                                                                        | (all were 1 app. X 0.022<br>lbs. ai/acre)               |                                  |                                    |                                |

**Table 5.3. Tier II Estimated Drinking Water Concentrations (EDWCs) resulting from applications of Thiamethoxam.**

| Drinking Water Source (model)                                                                 | Use Scenario (modeled rate)                                                     | 1-in-10 year acute (µg/L)   | 1-in-10 year chronic (µg/L) | 30- year average (µg/L) |
|-----------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|-----------------------------|-----------------------------|-------------------------|
|                                                                                               | <u>Dry Bulb Onions:</u><br>CA Onion<br>GA Onion<br>(1 app. X 0.3 lbs ai/acre)   | 1.57<br>20.45               | 0.25<br>1.54                | 0.06<br>0.44            |
|                                                                                               | <u>Leafy Vegetables:</u><br>CA Lettuce (1 run)<br>(1 app. X 0.266 lbs. ai/acre) | 23.78                       | 3.68                        | 1.29                    |
| Tail water                                                                                    | Rice<br>(0.173 lbs ai/A/year)                                                   | <b>131.77<sup>1,2</sup></b> | <b>11.31<sup>1,3</sup></b>  | 11.31 <sup>1,3</sup>    |
|                                                                                               | Cranberry<br>(0.188 lbs ai/A/year)                                              | 54.75 <sup>2</sup>          | 4.50 <sup>3</sup>           | 4.50 <sup>3</sup>       |
| Groundwater (SCI-GROW)                                                                        | <u>Peanuts:</u><br>(1 app. X 0.08 lbs ai/acre)                                  | 1.24                        | 1.24                        | 1.24                    |
|                                                                                               | <u>Alfalfa:</u><br>(1 app. X 0.022 lbs. ai/acre)                                | 0.34                        | 0.34                        | 0.34                    |
|                                                                                               | <u>Dry bulb onions:</u><br>(1 app. X 0.30 lbs. ai/acre)                         | 4.66                        | 4.66                        | 4.66                    |
| Bold text denotes maximum estimated EDWC values. All values adjusted with PCA factor of 0.87. |                                                                                 |                             |                             |                         |

1 Recommended EDWCs for surface water.

2 EDWCs based on day 1.

3 EDWCs based on average of 365 days.

### Monitoring Data

Only very limited monitoring data are available for thiamethoxam and these data are discussed below; due to this limitation HED used modeling data for the drinking water residue estimate for both the acute and chronic dietary risk assessments.

The registrant has conducted small-scale prospective groundwater studies in several locations in the US to investigate the mobility of thiamethoxam in a vulnerable hydrogeological setting. A review of those data (Amer Al-Mudallal, D339099, 4/18/06) shows that generally residues of thiamethoxam (as well as CGA-322704) are below the limit of quantitation (0.05 ppb). When quantifiable residues are found, they are sporadic and at low levels. The maximum observed residue levels from any monitoring well were 1.0 ppb for thiamethoxam and 0.73 ppb for CGA-322704. These values are well below the modeled estimates summarized above, indicating that the modeled estimates are, in fact, protective of what actual exposures are likely to be.

### 5.4 Dietary Risk Assessment

Reference: Dennis McNeilly, 29 Sept 2011, D392489.

Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 2.03) which uses food consumption data from the U.S. Department of Agriculture's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. These analyses were performed to support the Section 3 request for thiamethoxam use and tolerances for Crop Group 15 (the Cereal grains group) and Crop Group 16 commodities (the Forage, Fodder, and Straw of the Cereal Grains Group). Thiamethoxam is currently registered for use on barley, field corn, sweet corn, pop corn, rice, sorghum, and wheat. This action expands the use and establishes a tolerance for the remaining commodities in these two crop groups.

A separate risk assessment that addresses risks from clothianidin residues resulting from the direct application of clothianidin, as well as risks from residues of clothianidin coming from thiamethoxam uses was conducted (D384145, Michael Doherty) concurrently to support the new uses that are the subject of this action.

There is available information indicating that thiamethoxam and clothianidin have different toxicological effects in mammals and should be assessed separately; however, in conducting these assessments, residues of clothianidin coming from thiamethoxam were combined with residues of thiamethoxam. The total residue was then used to estimate dietary exposure and risk. Clothianidin, a major metabolite of thiamethoxam in plants and livestock, is not a significant degradate of thiamethoxam in surface or groundwater sources of drinking water.

These assumptions result in conservative, health-protective estimates of exposure (Table 5.4.6). Risk estimates for acute and chronic dietary exposure for all assessed population subgroups are below HED's level of concern, which is generally 100% of the acute or chronic adjusted dose (aPAD or cPAD).

#### **5.4.1 Description of Residue Data Used in Dietary Assessment**

Reference: Dennis McNeilly, 29 Sept 2011, D392489.

The acute assessment is based on tolerance level residues of thiamethoxam/clothianidin (the tolerance is for combined residues). The chronic analysis is based on tolerance level/proposed tolerance levels and/or average field trial (D391723, D. McNeilly, July 23, 2011) residues and assumes 100% crop treated for all commodities.

The drinking water residues used in these dietary risk assessments were provided by EFED (D391528, C. Koper, 28 July 2011; and D373378, C. Koper, 20 May 2010), and incorporated directly into the dietary assessments. Water residues were incorporated in DEEM-FCID via entry into the food categories "water, direct, all sources" and "water, indirect, all sources." The estimated drinking water concentrations (EDWCs) in surface water are 0.13177 ppm and 0.01131 ppm for acute and chronic scenarios, respectively. Typically, HED uses the higher of

the surface or groundwater estimates for each duration when assessing dietary risk, with the surface water (rice tail water) having higher values in this case.

#### **5.4.2 Percent Crop Treated Used in Dietary Assessment**

The dietary assessment is a screening-level assessment using tolerance level residues for the acute analysis. Tolerance levels and anticipated residues (calculated from field trial data) for selected commodities (discussed in detail in D376368, D. McNeilly, 23 Nov 2010) were used in the chronic assessment. The chronic assessment anticipated residues were average residues from crop field trial data. **For both the acute and chronic analyses, 100% crop treated was assumed.**

#### **5.4.3 Acute Dietary Risk Assessment**

The DEEM-FCID™ analyses estimate the dietary exposure of the US population and various population subgroups. The results reported in Table 5 are for the general U.S. population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, females 13-49, adults 20-49, and adults 50+ years. The acute results summarized in Table 5.4.6 are for the 95<sup>th</sup> percentile of exposure.

Based on highly conservative assumptions, acute dietary (food and water) risk estimates at the 95<sup>th</sup> percentile of exposure are less than or equal to 9.5% of the acute population-adjusted dose (aPAD) for all population subgroups. Generally, HED is concerned when risk estimates exceed 100% of the PAD; therefore, all acute dietary risk estimates are below HED's level of concern (LOC).

#### **5.4.4 Chronic Dietary Risk Assessment**

Chronic dietary (food and water) risk estimates are less than or equal to 43% of the chronic population-adjusted dose (cPAD) for all population subgroups. Generally, HED is concerned when risk estimates exceed 100% of the PAD; therefore, all acute and chronic dietary risk estimates are below HED's level of concern (LOC).

Generally, HED is concerned when risk estimates exceed 100% of the PAD; therefore, all chronic dietary risk estimates are below HED's level of concern (LOC).

#### **5.4.5 Cancer Dietary Risk Assessment**

Thiamethoxam has been classified as "not likely to be carcinogenic to humans." As such, the risk of cancer from thiamethoxam is not of concern. The chronic risk assessment would be protective for any potential cancer effects.

#### **5.4.6 Summary Table**

As previously stated, for acute and chronic assessments, HED is concerned when dietary risk exceeds 100% of the PAD. The DEEM-FCID™ analyses estimate the dietary exposure of the US population and various population subgroups. The results of the assessments are shown in Table 5.4.6, below.

**Table 5.4.6 Summary of Estimated Dietary (Food + Drinking Water) Exposures and Risk for Thiamethoxam.**

| Population Subgroup                          | aPAD, mg/kg/day | Acute Estimates (95 <sup>th</sup> Percentile) |              | cPAD, mg/kg/day | Chronic Estimates   |              |
|----------------------------------------------|-----------------|-----------------------------------------------|--------------|-----------------|---------------------|--------------|
|                                              |                 | Exposure, mg/kg/day                           | Risk, % aPAD |                 | Exposure, mg/kg/day | Risk, % cPAD |
| U.S. Population                              | 0.35            | 0.018076                                      | 5.2          | 0.012           | 0.002823            | 24           |
| <b>All infants (&lt; 1 year)<sup>1</sup></b> | <b>0.35</b>     | <b>0.033162</b>                               | <b>9.5</b>   | 0.012           | 0.003024            | 25           |
| <b>Children 1-2 yrs</b>                      | 0.35            | 0.032986                                      | 9.4          | <b>0.012</b>    | <b>0.005141</b>     | <b>43</b>    |
| Children 3-5 yrs                             | 0.35            | 0.026594                                      | 7.6          | 0.012           | 0.004522            | 38           |
| Children 6-12 yrs                            | 0.35            | 0.018835                                      | 5.4          | 0.012           | 0.003243            | 27           |
| Youth 13-19 yrs                              | 0.35            | 0.014313                                      | 4.1          | 0.012           | 0.002334            | 20           |
| Adults 20-49 yrs                             | 0.35            | 0.016270                                      | 4.7          | 0.012           | 0.002589            | 22           |
| Adults 50+ yrs                               | 0.35            | 0.016611                                      | 4.8          | 0.012           | 0.002644            | 22           |
| Females 13-49 yrs                            | 0.35            | 0.016124                                      | 4.6          | 0.012           | 0.002615            | 22           |

1 - The population subgroup with the highest estimated exposure/risk is bolded.

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

### 6.1 Residential Handler Exposure

Reference: Thiamethoxam: Occupational and Residential Exposure Assessment for Section 3 Registration, M. Collantes; July 24, 2009; D359207

There are no new residential uses associated with this action. Residential turf and indoor crack and crevice uses for thiamethoxam were assessed previously (M. Collantes; March 2007; D332064 and M. Collantes; July 2009; D359462). Thiamethoxam is applied by commercial applicators only; therefore, an assessment for homeowner applicators exposure was not performed.

HED is examining its policy regarding residential handler exposure and may require assessments in the future during registration review of thiamethoxam unless the product is “restricted”.

### 6.2 Postapplication Exposure

There is a potential for exposure from entering areas previously treated with thiamethoxam that could lead to exposures for adults and children. Postapplication residential scenarios were assessed using the HED Draft Standard Operating Procedures (SOPs) for Residential Exposure Assessments (12/18/97), and the Revisions to the Standard Operating Procedures (SOPs) for Residential Exposure Assessment (Science Advisory Council for Exposure Policy 12, Revised February 22, 2001). The level of concern (LOC) for the margin of exposure (MOE) is 100 for all residential uses. All post-application dermal and oral scenarios associated with turf and indoor crack and crevice uses resulted in MOEs greater than 100 and are not of concern.

A summary of the dermal postapplication exposure and risks is included in Table 6.2a.

| Table 6.2a.: Postapplication Dermal Exposure for Children and Adults for 0.1% and 0.05% Sprays for Crack and Crevice |                     |                                           |       |                                          |                          |                                  |            |                                         |                      |                  |
|----------------------------------------------------------------------------------------------------------------------|---------------------|-------------------------------------------|-------|------------------------------------------|--------------------------|----------------------------------|------------|-----------------------------------------|----------------------|------------------|
| Surface                                                                                                              | Population Subgroup | ISR <sup>1</sup><br>(µg/cm <sup>2</sup> ) | CF    | TC <sup>2</sup><br>(cm <sup>2</sup> /hr) | ED <sup>3</sup><br>(hrs) | Dermal Absorption<br>(mg/kg/day) | BW<br>(kg) | Dermal Dose <sup>4</sup><br>(mg/kg/day) | NOAEL<br>(mg/kg/day) | MOE <sup>5</sup> |
| Carpet                                                                                                               | adult               | 0.025                                     | 0.001 | 16,700                                   | 8                        | 0.05                             | 60         | 0.00278                                 | 1.2                  | 430              |
|                                                                                                                      | child               |                                           |       | 6,000                                    |                          | 1                                | 15         | 0.08                                    | 60                   | 750              |
| Vinyl                                                                                                                | adult               | 0.05                                      |       | 16,700                                   | 4                        | 0.05                             | 60         | 0.00278                                 | 1.2                  | 430              |
|                                                                                                                      | child               |                                           |       | 6,000                                    |                          | 1                                | 15         | 0.08                                    | 60                   | 750              |

1. ISR = indoor surface transferable residues = deposition residue (0.5 µg/cm<sup>2</sup>) x fraction of residue available for transfer from carpet vs. hard surface (0.05/0.1)

2. Tc = transfer coefficient based on HED Residential SOPs

3. ED = exposure duration based on HED Residential SOPs

4. Dose =  $\text{ISR (}\mu\text{g/cm}^2\text{)} \times 0.001 \text{ (mg/}\mu\text{g)} \times \text{Tc (cm}^2\text{/hr)} \times \text{ED (hrs/day)} \times \text{dermal absorption for adults only (mg/kg/day)}$   
BW (kg)

5. Adult MOE =  $\frac{\text{NOAEL (1.2 mg/kg/day)}}{\text{Dermal Dose}}$  Child MOE =  $\frac{\text{NOAEL (60 mg/kg/day)}}{\text{Dermal Dose}}$

Table 6.2b summarizes the MOEs for hand-to-mouth transfer of pesticide residues from indoor crack and crevice use.

| Table 6.2b.: Postapplication Oral Exposure for Children for 0.1% and 0.05% Sprays for Crack and Crevice |                                           |                                       |                               |                          |                 |                 |                                       |                  |
|---------------------------------------------------------------------------------------------------------|-------------------------------------------|---------------------------------------|-------------------------------|--------------------------|-----------------|-----------------|---------------------------------------|------------------|
| Surface                                                                                                 | ISR <sup>1</sup><br>(µg/cm <sup>2</sup> ) | SA <sup>2</sup><br>(cm <sup>2</sup> ) | FQ <sup>3</sup><br>(event/hr) | ED <sup>4</sup><br>(hrs) | SE <sup>5</sup> | CF <sup>6</sup> | Oral Dose <sup>7</sup><br>(mg/kg/day) | MOE <sup>8</sup> |
| Short-term                                                                                              |                                           |                                       |                               |                          |                 |                 |                                       |                  |
| carpet                                                                                                  | 0.025                                     | 20                                    | 20                            | 8                        | 0.5             | 0.001           | 0.00267                               | 3100             |
| vinyl                                                                                                   | 0.05                                      |                                       |                               | 4                        |                 |                 |                                       |                  |
| Intermediate-term                                                                                       |                                           |                                       |                               |                          |                 |                 |                                       |                  |
| carpet                                                                                                  | 0.025                                     | 20                                    | 9.5                           | 8                        | 0.5             | 0.001           | 0.00126                               | 6500             |
| vinyl                                                                                                   | 0.05                                      |                                       |                               | 4                        |                 |                 |                                       |                  |

1. ISR = indoor surface transferable residues = deposition residue (0.5 µg/cm<sup>2</sup>) x fraction of residue available for transfer from carpet vs. hard surface (0.05/0.1) 2. Surface area. 3. Frequency of hand-to-mouth events. 4. Exposure duration. 5. Saliva extraction factor. 6. Conversion factor (mg/µg). 7. Oral Dose = (ISR x SA x FQ x ED x SE x CF1)/(BW 15 kg) 8. Oral MOE = NOAEL (8.23 mg/kg/day)/Oral dose.

Based on the Agency's previous practices, a quantitative residential postapplication inhalation exposure assessment was not performed for thiamethoxam, primarily because it has a very low vapor pressure ( $5 \times 10^{-11}$  mmHg@ 25°C) and inhalation exposure is expected to be negligible as a result of indoor crack and crevice use. However, in the future HED may conduct a new residential exposure assessment (including postapplication inhalation exposure) that incorporates any potential new methods or policies for estimating exposure associated with residential use patterns as a result of the revisions to HED's Residential Standard Operating Procedures (SOPs).

### 6.3 Combined Exposure

In the previous 2007 thiamethoxam residential assessment, a combined residential assessment was performed for turf dermal and oral postapplication exposure of toddlers only. A more recent 2009 assessment (D365272, D. McNeilly, 6 August 2009) evaluated an indoor crack and crevice product and provided a revised combined residential assessment based on indoor crack and crevice use. These exposures and risks were greater than exposure/risk from the use on lawns. Therefore, the indoor exposures should be used in an aggregate assessment in order to be protective.

HED combined all non-dietary sources of postapplication exposure to obtain an estimate of potential combined exposure which could be used for the aggregate assessment. These scenarios consisted of adult and toddler dermal postapplication exposure and oral (hand-to-mouth) exposures for children 3 to 6 years of age. All postapplication scenarios resulted in combined MOEs greater than 100 and were not of concern to HED. Table 6.3 provides a summary of the combined residential indoor crack and crevice exposures and risks.

| Table 6.3. Combined Residential Exposure and Risk Estimates from Indoor Crack and Crevice Use |                                     |                  |                           |
|-----------------------------------------------------------------------------------------------|-------------------------------------|------------------|---------------------------|
| Postapplication Scenarios                                                                     | Daily Dose (mg/kg/day) <sup>1</sup> | MOE <sup>2</sup> | Combined MOE <sup>3</sup> |
| Short-term                                                                                    |                                     |                  |                           |
| Adult Dermal – indoor surface                                                                 | 0.00278                             | 430              | 430                       |
| Toddler Dermal - indoor surface                                                               | 0.08                                | 750              | 610                       |
| Hand-to-Mouth                                                                                 | 0.00267                             | 3100             |                           |
| Intermediate-term                                                                             |                                     |                  |                           |
| Adult Dermal - indoor surface                                                                 | 0.0278                              | 430              | 430                       |
| Toddler Dermal - indoor surface                                                               | 0.08                                | 750              | 680                       |
| Hand-to-Mouth                                                                                 | 0.001267                            | 6500             |                           |

<sup>1</sup> Daily Dose = see Tables 6.2.a. and 6.2.b. <sup>2</sup> Adult Dermal MOE =  $\frac{\text{NOAEL (1.2 mg/kg/day)}}{\text{Dermal Dose}}$

Child Dermal MOE =  $\frac{\text{NOAEL (60 mg/kg/day)}}{\text{Dermal Dose}}$

Child Oral MOE =  $\frac{\text{NOAEL (8.23 mg/kg/day)}}{\text{Oral Dose}}$

<sup>3</sup> Toddler Combined MOE =  $1 / [(1/\text{MOE}_{\text{Dermal}}) + (1/\text{MOE}_{\text{Hand-to-Mouth}})]$

#### 6.4 Residential Bystander Postapplication Inhalation Exposure

A postapplication inhalation assessment is not required for the presently proposed uses as residential exposure is expected to be negligible for seed treatments of agricultural commodities. Seed treatment assessments provide quantitative inhalation assessments for seed treaters and secondary handlers (i.e., planters). It is expected that these exposure estimates would be protective of most residential postapplication inhalation exposure scenarios.

#### 6.5 Spray Drift

Not applicable for seed treatment uses.

### 7.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

#### 7.1 Acute Aggregate Risk

In examining acute aggregate risk, HED has assumed that the only pathway of exposure relevant

to that time frame is dietary exposure. Therefore, the acute aggregate risk is composed of exposures to thiamethoxam residues in food and drinking water and is equivalent to the acute dietary risk discussed in Section 5.4.6. As noted in that section, the acute risk estimates are well below HED's level of concern for all population subgroups.

## 7.2 Short-Term Aggregate

References: D375247, D. McNeilly, 3 May 2010  
D359207, M. Collantes, 24 July 2009

Short-term exposures (1 to 30 days of continuous exposure) may occur as a result of entering indoor areas previously treated with a thiamethoxam indoor crack and crevice product. Exposures related to indoor activities (Table 6.3) have been combined with chronic dietary exposure estimates (as an estimate of background dietary exposure; Table 5.4.6) to assess the worst-case short-term aggregate exposure. The indoor crack and crevice scenario has higher exposure for both adults and children than the exposure levels in the turf scenario. The short-term aggregate MOEs range from 370 to 490 (Table 7.2). Since these are greater than 100, they represent aggregate risk estimates that are below HED's level of concern.

| <b>Table 7.2. Estimates of Short-term Aggregate Risks for Thiamethoxam</b> |                                |                     |                            |                                         |
|----------------------------------------------------------------------------|--------------------------------|---------------------|----------------------------|-----------------------------------------|
| Population Subgroup                                                        | Margins of Exposure (MOEs)     |                     |                            |                                         |
|                                                                            | Dietary Aggregate <sup>1</sup> | Dermal <sup>2</sup> | Hand-to-Mouth <sup>2</sup> | Total Short-Term Aggregate <sup>3</sup> |
| General U.S., population                                                   | 2,900                          | 430                 | -----                      | 370                                     |
| All infants                                                                | 2,700                          | 750                 | 3,100                      | 490                                     |
| Children 1-2 yrs                                                           | 1,600                          | 750                 | 3,100                      | 440                                     |
| Children 3-5 yrs                                                           | 1,800                          | 750                 | 3,100                      | 450                                     |
| <b>Children 6-12 yrs</b>                                                   | <b>2,500</b>                   | <b>430</b>          | -----                      | <b>370</b>                              |
| Youth 13-19 yrs                                                            | 3,500                          | 430                 | -----                      | 380                                     |
| Adults 20-49 yrs                                                           | 3,200                          | 430                 | -----                      | 380                                     |
| Adults 50+ yrs                                                             | 3,100                          | 430                 | -----                      | 380                                     |
| Females 13-49 yrs                                                          | 3,100                          | 430                 | -----                      | 380                                     |

<sup>1</sup> Dietary Aggregate MOE = Incidental Oral NOAEL (8.23 mg/kg/day) ÷ Chronic Dietary (Food + Water) Exposure (mg/kg/day; from Table 5.6.b). Values are rounded to 2 significant figures.

<sup>2</sup> Indoor crack and crevice exposure (which has higher exposure than residential turf) from Table 6.3. Hand-to-mouth is appropriate for infant and children population subgroups only.

<sup>3</sup> Total Aggregate MOE =  $1 / [(1/\text{MOE}_{\text{Dietary}}) + (1/\text{MOE}_{\text{Dermal}}) + (1/\text{MOE}_{\text{HtM}})]$ . Values rounded to 2 significant figures.

## 7.3 Intermediate-Term Aggregate Risk

Intermediate-term exposures (30 to 180 days of continuous exposure) may occur as a result of entering indoor areas previously treated with a thiamethoxam indoor crack and crevice product. Exposures related to indoor activities (Table 6.3) have been combined with chronic dietary exposure estimates (as an estimate of background dietary exposure; Table 5.6.b) to assess the

worst-case intermediate-term aggregate exposure. The indoor crack and crevice scenario has higher exposure for both adults and children than the exposure levels in the turf scenario. The intermediate-term aggregate MOEs range from 370 to 540 (Table 7.3). Since these are greater than 100, they represent intermediate-term aggregate risk estimates that are below HED's level of concern.

The difference between short- and intermediate-term aggregate risks is the frequency of hand-to-mouth events for children. For short-term exposure there are 20 events per hour and for intermediate-term exposure there are 9.5 events per hour (see Table 6.2.b). The doses and end-points for short- and intermediate-term aggregate risk are the same.

| <b>Table 7.3. Estimates of Intermediate-term Aggregate Risks for Thiamethoxam</b> |                                |                     |                            |                                                |
|-----------------------------------------------------------------------------------|--------------------------------|---------------------|----------------------------|------------------------------------------------|
| Population Subgroup                                                               | Margins of Exposure (MOEs)     |                     |                            |                                                |
|                                                                                   | Dietary Aggregate <sup>1</sup> | Dermal <sup>2</sup> | Hand-to-Mouth <sup>2</sup> | Total Intermediate-Term Aggregate <sup>3</sup> |
| General U.S. population                                                           | 2,900                          | 430                 | -----                      | 370                                            |
| All infants                                                                       | 2,700                          | 750                 | 6,500                      | 540                                            |
| Children 1-2 yrs                                                                  | 1,600                          | 750                 | 6,500                      | 470                                            |
| Children 3-5 yrs                                                                  | 1,800                          | 750                 | 6,500                      | 490                                            |
| <b>Children 6-12 yrs</b>                                                          | <b>2,500</b>                   | <b>430</b>          | -----                      | <b>370</b>                                     |
| Youth 13-19 yrs                                                                   | 3,500                          | 430                 | -----                      | 380                                            |
| Adults 20-49 yrs                                                                  | 3,200                          | 430                 | -----                      | 380                                            |
| Adults 50+ yrs                                                                    | 3,100                          | 430                 | -----                      | 380                                            |
| Females 13-49 yrs                                                                 | 3,100                          | 430                 | -----                      | 380                                            |

<sup>1</sup> Dietary Aggregate MOE = Incidental Oral NOAEL (8.23 mg/kg/day) ÷ Chronic Dietary (Food + Water) Exposure (mg/kg/day; from Table 5.6.b). Values are rounded to 2 significant figures. <sup>2</sup> Indoor crack and crevice exposure (which has higher exposure than residential turf) from Table 6.3. Hand-to-mouth is appropriate for infant and children population subgroups only. <sup>3</sup> Total Aggregate MOE =  $1/[(1/\text{MOE}_{\text{Dietary}}) + (1/\text{MOE}_{\text{Dermal}}) + (1/\text{MOE}_{\text{HtM}})]$ . Values rounded to 2 significant figures.

#### 7.4 Chronic Aggregate Risk

In examining chronic aggregate risk, HED has assumed that the only pathway of exposure relevant to that time frame is dietary exposure. Therefore, chronic aggregate risk is composed of exposures to thiamethoxam residues in food and drinking water and is equivalent to the chronic dietary risk discussed in Section 5.4.6. As noted in that section, the chronic risk estimates are below HED's level of concern for all population subgroups.

#### 7.5 Cancer Aggregate Risk

Thiamethoxam has been classified as "not likely to be carcinogenic to humans." As such, the risk of cancer from thiamethoxam is not of concern. The chronic risk assessment would be protective for any potential cancer effects.

#### 8.0 Cumulative Exposure/Risk Characterization

Thiamethoxam is a member of the neonicotinoid class of pesticides and produces, as a

metabolite, another neonicotinoid, clothianidin. Structural similarities or common effects do not constitute a common mechanism of toxicity. Evidence is needed to establish that the chemicals operate by the same, or essentially the same, sequence of major biochemical events (EPA, 2002). Although clothianidin and thiamethoxam bind selectively to insect nicotinic acetylcholine receptors (nAChR), the specific binding site(s)/receptor(s) for clothianidin, thiamethoxam, and the other neonicotinoids are unknown at this time. Additionally, the commonality of the binding activity itself is uncertain, as preliminary evidence suggests that clothianidin operates by direct competitive inhibition, while thiamethoxam is a non-competitive inhibitor. Furthermore, even if future research shows that neonicotinoids share a common binding activity to a specific site on insect nicotinic acetylcholine receptors, there is not necessarily a relationship between this pesticidal action and a mechanism of toxicity in mammals. Structural variations between the insect and mammalian nAChRs produce quantitative differences in the binding affinity of the neonicotinoids towards these receptors, which, in turn, confers the notably greater selective toxicity of this class towards insects, including aphids and leafhoppers, compared to mammals. While the insecticidal action of the neonicotinoids is neurotoxic, the most sensitive regulatory endpoint for thiamethoxam is based on unrelated effects in mammals, including effects on the liver, kidney, testes, and hematopoietic system. Additionally, the most sensitive toxicological effect in mammals differs across the neonicotinoids (*e.g.*, testicular tubular atrophy with thiamethoxam; mineralized particles in thyroid colloid with imidacloprid). Thus, there is currently no evidence to indicate that neonicotinoids share common mechanisms of toxicity, and EPA is not following a cumulative risk approach based on a common mechanism of toxicity for the neonicotinoids. 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 concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism released by EPA's Office of Pesticide Programs on EPA's website at <http://www.epa.gov/pesticides/cumulative/>.

## 9.0 Occupational Exposure/Risk Characterization

Reference: Margarita Collantes, D384997, 1 Nov 2011

Syngenta's request for the use of Cruiser® Insecticide (Reg. No. 100-941) for treatment of seeds in Crop Group 15, cereal grains (including buckwheat, pearl millet, proso millet, oats, rye, teosinte, and triticale). Cruiser® is already registered for seed treatment use on the representative commodities for Crop Group 15: sweet and field corn, rice, sorghum and wheat. In conjunction with Syngenta's request to add the remaining small grain commodities to the Cruiser® label, HED completed an updated occupational exposure assessment associated with these seed treatment uses. Cruiser® is a liquid concentrate suspension containing 47.6% thiamethoxam (5 lb ai/gallon).

### 9.1 Occupational Handler Risk

Since the Cruiser® label indicates that cereal grain seed will be treated using open loading systems and closed transfer and loading systems, a quantitative exposure/risk assessment for

handlers is based on HED's SOP #14 and Syngenta's proprietary seed treatment study, Helix® 289 FS (Novartis Crop Protection Canada Inc, J. Purdy and D. Houghton; August 22, 2000; MRID 452000-02; DP 273566).

### **Cereal Grains (Except Corn)**

HED used defaults and assumptions from Seed Treatment SOP#14 (open system), and SOP 15 (i.e. a value of **718,000 lbs** of wheat as a surrogate for all cereal grain) to assess handler risk associated with use of Cruiser® to treat cereal grain seeds. All handler scenarios resulted in MOEs greater than 100 and therefore were not of concern, with one exception. The multiple activity scenario for cereal grain resulted in a risk of concern (MOE = 72) even with use of double layers and gloves.

HED also performed an exposure assessment based on the current Cruiser® label restriction limiting the amount of product used per day (38 gals/day) utilizing an open system, or a maximum application rate of 0.00029 lb ai/lb seed and **655,172 lbs** of cereal grain seed treated per day. All handler scenarios using the label restrictions of 38 gals/day resulted in MOEs greater than 100 using PPE (i.e. gloves) and are not of concern.

HED is currently working the Agricultural Handlers Exposure Task Force (AHEFT) in collecting survey data associated with seed treatment practices including typical and maximum amounts of seed treated per day within seed treatment facilities. Based on the preliminary findings, HED's default value (718,000 lbs seed) for the amount of wheat seeds treated per day in commercial seed treatment facilities using an open loading system is an overestimate. Survey results support the Cruiser® label restriction limiting the amount of product used per day (38 gals/day) utilizing an open system, or a maximum application rate of 0.00029 lb ai/lb seed and 655,172 lbs of cereal grain seed treated per day. Therefore, HED concludes Cruiser® label restriction limiting 38 gals/day (655,172 lbs) for wheat seed represents a reasonable representation of the amount of wheat seed typically treated using an open loading treater in commercial facilities and results in no risks of concern.

### **Corn**

HED used the assumptions from Seed Treatment SOP#14 (open system) and SOP 15 (i.e., a value of **550,000 lbs** of field corn seed treated per day) to assess handler risk associated with use of Cruiser® to treat corn seeds. All handler scenarios for corn resulted in MOEs significantly below the level of concern (LOC = MOE  $\geq$  100) even with the use of personal protective equipment (PPE) consisting of gloves and coveralls. HED then performed an exposure assessment based on the current Cruiser® label restriction limiting the amount of product used per day (38 gals/day) utilizing an open system, or a maximum application rate of 0.0088 lb ai/lb seed and **21,591 lbs** of corn seed treated per day. All handler scenarios using the label restrictions resulted in MOEs greater than 100 using PPE (i.e. gloves) and are not of concern.

As indicated above HED and AHETF are working cooperatively to obtain the most current information regarding seed treatment practices. Currently survey data on corn is not available.

However, based on available information regarding corn seed treatment facilities, equipment and practices, HED is aware that corn is a high acreage crop and large amounts of seeds are treated in commercial seed treatment facilities. Typical large seed treatment facilities that treat high acreage crops such as corn typically would not use open systems but rather state of the art closed loading systems. Therefore, HED concludes that the Cruiser® label restriction limiting the amount of product used per day (38 gals/day) for seed treatments utilizing an open system, or a maximum application rate of 0.0088 lb ai/lb seed and 21,591 lbs of corn seed treated per day, does not represent typical practice and appears to significantly underestimate the actual amount of corn seed treated in most commercial facilities. HED does not support the Cruiser® label restriction limiting the amount of product used per day (38 gals/day) utilizing an open system for treatment of corn. Therefore, **HED recommends that label specify that in the case of corn, only the closed system 215 gals/day restriction applies (no open system).**

A summary of the exposure and risk associated with the use of Cruiser® for the treatment of cereal grains and corn seed using an open system is provided in **Table 9.1.1**. This table provides calculated exposures resulting for corn using the Cruiser® label restriction limiting the amount of product used per day (38 gals/day) utilizing an open system. However, HED does not support this restriction and calculations for corn using an open system are provided only as a reference.

| TABLE: 9.1.1 Handler Risk for Thiamethoxam using HED Seed Treatment SOP# 14 (Open System) |                         |                                           |                                               |                                                        |                                           |                                      |                                          |                                     |                        |
|-------------------------------------------------------------------------------------------|-------------------------|-------------------------------------------|-----------------------------------------------|--------------------------------------------------------|-------------------------------------------|--------------------------------------|------------------------------------------|-------------------------------------|------------------------|
| Seed Crop                                                                                 | Mitigation <sup>a</sup> | Dermal Unit Exposure (mg/lb) <sup>a</sup> | Inhalation Unit Exposure (mg/lb) <sup>a</sup> | Maximum Application Rate <sup>b</sup> (lb ai /lb seed) | Amount Treated <sup>c</sup> (lb seed/day) | Dermal Dose <sup>d</sup> (mg/kg/day) | Inhalation Dose <sup>e</sup> (mg/kg/day) | Total Dose <sup>f</sup> (mg/kg/day) | Total MOE <sup>g</sup> |
| Loader/Applicator                                                                         |                         |                                           |                                               |                                                        |                                           |                                      |                                          |                                     |                        |
| Cereal Grains                                                                             | Single layer & gloves   | 0.023                                     | 0.00034                                       | 0.00029*                                               | 718,000 *                                 | 0.003991                             | 0.00118                                  | 0.00517                             | 230                    |
|                                                                                           |                         |                                           |                                               | 0.00052**                                              |                                           | 0.00715                              | 0.0021                                   | 0.00927                             | 130                    |
|                                                                                           |                         |                                           |                                               | 0.00029*                                               | 655,172**                                 | 0.0036                               | 0.0010                                   | 0.0047                              | 250                    |
| Corn (sweet and field)                                                                    | Gloves & coveralls      | 0.018                                     | 0.00034                                       | 0.0088***                                              | 550,000*                                  | 0.0726                               | 0.02742                                  | 0.1000                              | 12                     |
|                                                                                           |                         |                                           |                                               | 0.0138****                                             |                                           | 0.11385                              | 0.0430                                   | 0.1568                              | 8                      |
|                                                                                           |                         |                                           |                                               | 0.0088***                                              | 21,591***                                 | 0.00365                              | 0.00107                                  | 0.004718                            | 250                    |
| Sewer                                                                                     |                         |                                           |                                               |                                                        |                                           |                                      |                                          |                                     |                        |
| Cereal Grains                                                                             | Baseline                | 0.0062                                    | 0.00023                                       | 0.00029*                                               | 718,000 *                                 | 0.00107                              | 0.000798                                 | 0.001874                            | 640                    |
|                                                                                           |                         |                                           |                                               | 0.00052**                                              |                                           | 0.001929                             | 0.00143                                  | 0.00336                             | 360                    |
|                                                                                           |                         |                                           |                                               | 0.00029*                                               | 655,172**                                 | 0.000982                             | 0.00073                                  | 0.0017                              | 700                    |
| Corn (sweet and field)                                                                    |                         |                                           |                                               | 0.0088***                                              | 550,000*                                  | 0.0250                               | 0.0185                                   | 0.04356                             | 27                     |
|                                                                                           |                         |                                           |                                               | 0.0138****                                             |                                           | 0.0392                               | 0.0290                                   | 0.0683                              | 17                     |
|                                                                                           |                         |                                           |                                               | 0.0088*                                                | 21,591***                                 | 0.000982                             | 0.000728                                 | 0.00171                             | 700                    |
| Bagger                                                                                    |                         |                                           |                                               |                                                        |                                           |                                      |                                          |                                     |                        |
| Cereal Grains                                                                             | Single layer/ gloves    | 0.0091                                    | 0.00016                                       | 0.00029*                                               | 718,000 *                                 | 0.001579                             | 0.000555                                 | 0.002134                            | 560                    |
|                                                                                           |                         |                                           |                                               | 0.00052**                                              | 718,000*                                  | 0.002831                             | 0.000996                                 | 0.003827                            | 310                    |
|                                                                                           |                         |                                           |                                               | 0.00029*                                               | 655,172**                                 | 0.0014                               | 0.000507                                 | 0.001948                            | 620                    |
| Corn (sweet and field)                                                                    |                         |                                           |                                               | 0.0088***                                              | 550,000*                                  | 0.03670                              | 0.01290                                  | 0.04961                             | 24                     |
|                                                                                           |                         |                                           |                                               | 0.0138****                                             |                                           | 0.0575                               | 0.020                                    | 0.077                               | 15                     |
|                                                                                           |                         |                                           |                                               | 0.0088***                                              | 21,591***                                 | 0.00144                              | 0.00050                                  | 0.001948                            | 620                    |
| Multiple Activities                                                                       |                         |                                           |                                               |                                                        |                                           |                                      |                                          |                                     |                        |
| Cereal Grains                                                                             | Double layer & gloves   | 0.021                                     | 0.00016                                       | 0.00029*                                               | 718,000 *                                 | 0.003644                             | 0.0055                                   | 0.00919                             | 130                    |
|                                                                                           |                         |                                           |                                               | 0.00052**                                              |                                           | 0.0065                               | 0.0099                                   | 0.01649                             | 72                     |
|                                                                                           |                         |                                           |                                               | 0.00029*                                               | 655,172**                                 | 0.0066                               | 0.0050                                   | 0.012                               | 100                    |
| Corn (sweet and field)                                                                    | Double layer & gloves   | 0.021                                     |                                               | 0.0088***                                              | 550,000*                                  | 0.0847                               | 0.1290                                   | 0.2137                              | 6                      |
|                                                                                           |                         |                                           |                                               | 0.0138****                                             |                                           | 0.1328                               | 0.202                                    | 0.335                               | 4                      |

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|                          |       |           |           |         |         |        |     |
|--------------------------|-------|-----------|-----------|---------|---------|--------|-----|
| Single layer<br>& gloves | 0.042 | 0.0088*** | 21,591*** | 0.00665 | 0.00507 | 0.0117 | 100 |
|--------------------------|-------|-----------|-----------|---------|---------|--------|-----|

Cereal grains = Barley, buckwheat, pearl millet, proso millet, oats, rice, rye, sorghum, teosinte, triticale, and wheat

a. HED Science Advisory Council for Exposure Policy 14: Standard Operating Procedures for Seed Treatment.

b. Application Rate based on proposed label for Cruiser; EPA Reg. # 100-941

b.\* 0.75 fl oz/100 lbs x 5 lb ai/gal x 1 gal/ 128 oz = 0.00029 lb ai/lb seed

b\*\* 1.33 fl oz/100 lbs x 5 lb ai/gal x 1 gal/ 128 oz = 0.00052 lb ai/lb seed

b\*\*\*0.8 mg ai/seed x 1 lb/454,000 x 5000 seed/lb = 0.0088 lb ai/lb seed

b\*\*\*\*1.25 mg ai/seed x 1 lb/454,000 x 5000 seed/lb = 0.0137 lb ai/lb seed

c\*Based on Seed Treatment SOP 15 and seed count of 718,000 seeds/lb for cereal grains and 550,000 for corn

c\*\* Based on Cruiser label restriction for 38 gals/day = (38 gal/day x 5 lb ai/gal)/ 0.00029 lb ai/lb seed = 655,172 for cereal grains

c\*\*\* Based on Cruiser label restriction for 38 gals/day = (38 gal/day x 5 lb ai/gal)/ 0.0088 lb ai/lb seed = 21,591 for corn

d. Dermal Dose (mg/kg/day) = [ Rate (lb ai/lb seed) x UE (mg /lb ai ) x Amount of seed Treated (lb seed/day)] / BW (60 kg)] x 5% DA.

e. Inhalation Dose (mg/kg/day) = [ Rate (lb ai/ lb seed ) x UE (mg /lb ai ) x Amount of seed Treated (lb seed/day)] / BW (60 kg).

f. Total Dose (mg/kg/day) = Dermal Dose (mg/kg/day) + Inhalation Dose (mg/kg/day).

g. Total MOE = NOAEL (1.2 mg/kg/day)/Total Dose (mg/kg/day).

### Handler Exposure and Risk Using Closed System

HED used Syngenta's proprietary seed treatment exposure study, Helix® 289 FS to assess handler exposure resulting from treatment of cereal grain and corn seed with closed systems. Handler exposures were estimated based on default values of **718,000 lbs of cereal grain seed** and **550,000 lbs of corn seed** treated per day in accordance with SOP 15. All handler scenarios resulted in MOEs greater than 100 and were not of concern with one exception. The closed system treater/loader scenario for **corn** resulted in **MOEs of 58 to 90** at application rates of 0.0088 to 0.0138 lb ai/lb seed.

HED also assessed handler exposure based on the current Cruiser® label restriction limiting the amount product used per day (215 gals/day) for utilizing a closed system or a maximum application rate of 0.00029 lb ai/lb seed or 3,706,897 lbs seed/day for cereal grain seed and an application rate of 0.0088 lb ai/lb seed for 122,159 lbs of corn seed treated per day. All handler scenarios using a closed system and coveralls for treatment of cereal and corn seeds resulted in MOEs greater than 100 and are not of concern.

### Additional Characterization

#### Cereal Grains

As indicated previously, HED's default value (718,000 lbs seed) for the amount of wheat seeds treated per day in commercial seed treatment facilities using an open loading system is an overestimate based on preliminary survey data. Currently, preliminary survey data does not indicate whether data collected from facilities used open and/or closed systems. Based on the preliminary survey data, HED concludes that the suggested amount of wheat seed treated per day (3,706,897 lb seed/day) as a result of the Cruiser® label restriction limiting the amount of product used per day (215 gals/day) utilizing a closed system is excessively high. However since all closed system exposure scenarios using the default of 718,000 lbs of seed resulted in MOEs greater than 100 and were not of concern, HED has no objection to the Cruiser® label restriction limiting the amount of product used per day (8 hours) for seed treatments utilizing a closed system to 215 gals/day.

#### Corn

HED concludes that the Cruiser® label restriction limiting the amount of product used per day for seed treatments utilizing an **closed** system to 215 gals/day, or a maximum application rate of 0.0088 lb ai/lb seed and 122,159 lbs of corn seed treated per day, appears to be an underrepresentation of the actual amount corn seed treated in commercial facilities. Once the AHETF seed treatment survey is complete, HED may revisit the Cruiser® label restriction of 215 gals/day using a **closed** system for corn. Table 9.1.2 provides a summary of the MOEs for each closed system handler scenario.

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TABLE: 9.1.2 Handler Risk for Thiamethoxam using Helix Study (Closed System w/ Coveralls)

| Seed Crop                                                      | Mitigation <sup>a</sup> | Dermal Unit Exposure (mg/lb) <sup>a</sup> | Inhalation Unit Exposure (mg/lb) <sup>a</sup> | Maximum Application Rate (lb ai/lb seed) <sup>b</sup> | Amount Treated (lb seed/day) <sup>c</sup> | Dermal Dose (mg/kg/day) <sup>d</sup> | Inhalation Dose (mg/kg/day) <sup>e</sup> | Total Dose <sup>f</sup> (mg/kg/day) | Total MOE <sup>g</sup>   |
|----------------------------------------------------------------|-------------------------|-------------------------------------------|-----------------------------------------------|-------------------------------------------------------|-------------------------------------------|--------------------------------------|------------------------------------------|-------------------------------------|--------------------------|
| Treater = Loader/Applicator                                    |                         |                                           |                                               |                                                       |                                           |                                      |                                          |                                     |                          |
| Cereal Grains                                                  | double layer & gloves   | 0.0011                                    | 0.00011                                       | 0.00029*<br>0.00052**<br>0.00029*                     | 718,000*                                  | 0.000191<br>0.000342<br>0.000985     | 0.000382<br>0.000684<br>0.001971         | 0.000573<br>0.00103<br>0.00295      | 2100<br>1200<br>400      |
| Corn                                                           |                         |                                           |                                               | 0.0088***<br>0.0138****<br>0.0088***                  | 550,000*                                  | 0.004437<br>0.00695<br>0.000985      | 0.008873<br>0.0139<br>0.001971           | 0.01331<br>0.0209<br>0.002956       | 90<br>58<br>400          |
| Fork Lift                                                      |                         |                                           |                                               |                                                       |                                           |                                      |                                          |                                     |                          |
| Cereal Grains                                                  | double layer & gloves   | 0.000145                                  | 0.00001                                       | 0.00029*<br>0.00052**<br>0.00029*                     | 718,000*                                  | 2.52E-5<br>4.51E-5<br>0.00013        | 3.47E-5<br>6.22E-5<br>0.000179           | 5.99E-5<br>0.000107<br>0.00030      | 20,000<br>11,000<br>3900 |
| Corn                                                           |                         |                                           |                                               | 0.0088***<br>0.0138****<br>0.0088***                  | 550,000*                                  | 0.000585<br>0.000917<br>0.00013      | 0.000807<br>0.001265<br>0.000179         | 0.00139<br>0.002182<br>0.000309     | 860<br>550<br>3900       |
| Multiple Activities (Sewer, Bagger, Stacker w/cotton overalls) |                         |                                           |                                               |                                                       |                                           |                                      |                                          |                                     |                          |
| Cereal Grains                                                  | double layer & gloves   | 0.00037                                   | 0.000064                                      | 0.00029*<br>0.00052**<br>0.00029*                     | 718,000*                                  | 6.42E-5<br>0.000115<br>0.000331      | 0.00022<br>0.000398<br>0.001147          | 0.000286<br>0.000513<br>0.001478    | 4200<br>2300<br>810      |
| Corn                                                           |                         |                                           |                                               | 0.0088***<br>0.0138****<br>0.0088***                  | 550,000*                                  | 0.001492<br>0.00234<br>0.000331      | 0.005163<br>0.008096<br>0.001147         | 0.00665<br>0.0104<br>0.001478       | 180<br>110<br>810        |
| Multiple Activities (Sewer, Bagger, Stacker w/Tyvek Coveralls) |                         |                                           |                                               |                                                       |                                           |                                      |                                          |                                     |                          |
| Cereal Grains                                                  | double layer & gloves   | 0.00027                                   | 0.000064                                      | 0.00029*<br>0.00052**<br>0.00029*                     | 718,000*                                  | 4.68E-5<br>8.4E-5<br>0.000242        | 0.00022<br>0.000398<br>0.001147          | 0.000269<br>0.000482<br>0.001389    | 4500<br>2500<br>860      |
| Corn                                                           |                         |                                           |                                               | 0.0088***<br>0.0138****<br>0.0088***                  | 550,000*                                  | 0.00108<br>0.001708<br>0.000242      | 0.00516<br>0.00809<br>0.001147           | 0.00625<br>0.009804<br>0.00138      | 190<br>120<br>860        |

- a. Seed Treatment Helix study MIRD# 45200002; DP 273566.  
b. Application Rate based on proposed label for Cruiser. EPA Reg. #100-941.  
b.\*0.75 fl oz/100 lbs x 5 lb ai/gal x 1 gal/ 128 oz = 0.00029 lb ai/lb seed  
b\*\*1.33 fl oz/100 lbs x 5 lb ai/gal x 1 gal/ 128 oz = 0.00052 lb ai/lb seed  
b\*\*\*0.8 mg ai/seed x 1 lb/454,000 x 5000 seed/lb = 0.0088 lb ai/lb seed  
b\*\*\*\*1.25 mg ai/seed x 1 lb/454,000 x 5000 seed/lb = 0.0138 lb ai/lb seed

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c\*Based on Seed Treatment SOP 15 and seed count of 718,000 seeds/lb for cereal grains and 550,000 for corn

c\*\* Based on Cruiser label restriction for 215 gals/day = (215 gal/day x 5 lb ai/gal)/ 0.00029 lb ai/lb seed = 3,706,897 for cereal grains

c\*\*\* Based on Cruiser label restriction for 215 gals/day = (215 gal/day x 5 lb ai/gal)/ 0.0088 lb ai/lb seed = 122,159 for corn

d. Dermal Dose (mg/kg/day) = [ Rate (lb ai/lb seed) x UE (mg /lb ai ) x Amount Treated (lb seed/day)] / BW (60 kg)] x 5% DA.

e. Inhalation Dose (mg/kg/day) = [ Rate (lb ai/lb seed) x UE (mg /lb ai ) x Amount Treated (lb seed/day)] / BW (60 kg).

f. Total Dose (mg/kg/day) = Dermal Dose (mg/kg/day) + Inhalation Dose (mg/kg/day).

g. Total MOE = NOAEL (1.2 mg/kg/day)/ Total Dose (mg/kg/day).

### Occupational Cleaner Exposure/Risk

Because exposures for workers whose sole task is to clean commercial seed treatment equipment are assumed to be independent of application rate or the amount of seeds treated, HED conducted a short-term risk assessment using the maximum exposure value measured in the Helix® study. The exposure data was separated into cleaners who conduct a "total clean-out" and those who conduct a "partial clean-out." The MOEs ranged from 160 (total clean-out) to 790 (partial clean-out) and were not of concern. Table 9.1.3 provides a summary of the MOEs for each closed system cleaner scenario.

TABLE: 9.1.3 Cleaner Risk for Thiamethoxam using Helix Study (Closed System w/ Coveralls)

| Scenario          | Mitigation <sup>a</sup>  | Dermal Dose<br>(mg/kg bw/day) <sup>a</sup> | Inhalation Dose<br>(mg/kg bw/day) <sup>a</sup> | Adjusted<br>Dermal Dose<br>(mg/kg/day) <sup>b</sup> | Adjusted<br>Inhalation<br>Dose <sup>c</sup><br>(mg/kg/day) | Total Dose <sup>e</sup><br>(mg/kg/day) | Total<br>MOE <sup>d</sup> |
|-------------------|--------------------------|--------------------------------------------|------------------------------------------------|-----------------------------------------------------|------------------------------------------------------------|----------------------------------------|---------------------------|
| Total Clean-Out   | double layer &<br>gloves | 0.08198                                    | 0.0033                                         | 0.00403                                             | 0.0033                                                     | 0.0073                                 | 160                       |
| Partial Clean-Out |                          | 0.00669                                    | 0.00119                                        | 0.0003345                                           | 0.00119                                                    | 0.00152                                | 790                       |

a. Cleaner risk assumed independent of application rate or amount of seeds treated (Helix @ 289 FS Study MRID 45200002, DP 273566).

b. Adjusted Dermal Dose = Dermal Dose (mg/kg bw/day) x dermal absorption factor (5%)

c. Adjusted Inhalation Dose = Inhalation Dose (mg/kg bw/day) x inhalation absorption factor (100%)

d. Total Dose = Dermal Dose (mg/kg/day) + Inhalation Dose (mg/kg/day)

e. Total MOE = Short Term NOAEL (1.2 mg/kg/day)/Total Dose (mg/kg/day)

## Secondary Handler Seed Treatment Exposure and Risk

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Secondary handler exposure scenarios for seed treatment consist of the farmer purchasing bags of treated seed, placing the seed in the hopper and applying seed to fields. Exposures during planting activities were estimated using information provided in the HED SOP#14 and # 15 as well as information submitted by the registrant. All secondary handler scenarios for seed planters resulted in MOEs greater than 100 and are not of concern. The seed planter's MOEs are summarized in Table 9.1.4.

### 9.2 Post-Application Exposure

In the case of seed treatment uses, postapplication exposure is considered to be that encountered by those who purchase and plant the treated seeds. Such exposures and risks are addressed above (Secondary Handler), summarized in Table 9.1.4, and are not of concern.

### 9.3 Restricted Entry Interval

Since no quantitative postapplication assessment was completed for treated seeds after they have been planted, the restricted entry interval (REI) is based on the acute dermal toxicity, eye irritation and skin irritation effects of the active ingredient, thiamethoxam. The thiamethoxam technical material is classified as Category III for acute oral and Category IV for acute dermal and eye irritation. Thiamethoxam is not a dermal sensitizer. Acute toxicity categories III and IV chemicals require a 12-hour REI.

The Worker Protection Standard (WPS) allows workers to enter treated areas without restriction if there will be no contact with anything that has been treated with the pesticide. For purposes of seed treatment, once the seeds are planted, workers can enter during the REI, *provided* they do not contact the soil/media subsurface that contains the treated seeds. Certain tasks may involve contact with the soil subsurface (e.g. repair of certain irrigation equipment) and they are covered by the REI. Therefore, HED concurs with the 12-hour REI on the proposed label.

TABLE 9.1.4. Secondary Handler (Planter) Risk for Thiamethoxam

| Seed Crop | Dermal Unit Exposure (mg/lb) <sup>a</sup> | Inhalation Unit Exposure (mg/lb) <sup>a</sup> | Maximum Application Rate <sup>b</sup> (lb ai /lb seed) | Lbs Seeds Planted per Acre <sup>c</sup> | Acres Planted per day <sup>c</sup> | Dermal Dose <sup>d</sup> (mg/kg/day) | Inhalation Dose <sup>e</sup> (mg/kg/day) | Total Dose <sup>f</sup> (mg/kg/day) | Total MOE <sup>g</sup> |
|-----------|-------------------------------------------|-----------------------------------------------|--------------------------------------------------------|-----------------------------------------|------------------------------------|--------------------------------------|------------------------------------------|-------------------------------------|------------------------|
| Cereal    | 0.25                                      | 0.0034                                        | 0.00029                                                | 150                                     | 200                                | 0.001813                             | 0.000493                                 | 0.002306                            | 520                    |
| Grains    |                                           |                                               | 0.00052                                                |                                         |                                    | 0.00325                              | 0.000884                                 | 0.004134                            | 290                    |
| Corn      |                                           |                                               | 0.0088                                                 | 15                                      |                                    | 0.0055                               | 0.00149                                  | 0.00699                             | 170                    |
|           |                                           |                                               | 0.0138                                                 |                                         |                                    | 0.0086                               | 0.00234                                  | 0.0109                              | 110                    |

a. HED Science Advisory Council for Exposure Policy 14: Standard Operating Procedures for Seed Treatment.

b. Application Rate based on proposed label for Cruiser; EPA Reg. #100-941.

c. Based on information provided by SOP 15.

d. Dermal Dose (mg/kg/day) = [Rate (lb ai/lb seed) x UE (mg /lb ai ) x Seeds Planted/A x Acres/day x DA (0.05)/ BW (60 kg)]

e. Inhalation Dose (mg/kg/day) = [Rate (lb ai/lb seed) x UE (mg /lb ai ) x Seeds Planted/A x Acres/day/ BW (60 kg)]

f. Total Dose (mg/kg/day) = Dermal Dose (mg/kg/day) + Inhalation Dose (mg/kg/day).

g. Total MOE = NOAEL (1.2 mg/kg/day)/Total Dose (mg/kg/day).

## 10.0 References

### References:

Dennis McNeilly, 13 July 2011, D391723. Thiamethoxam. Petition to Establish Permanent Tolerances for Crop Group 15 Commodities: Buckwheat, Pearl Millet, Proso Millet, Oats, Rye, Teosinte, Triticale; and, Wild Rice. Summary of Analytical Chemistry and Available Residue Chemistry Data.

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ExpoSAC Policy 14: *Standard Operating Procedures (SOPs) for Seed Treatment*, May 1, 2003.

ExpoSAC Policy 15: *Amount of Seed Treated or Planted per Day*, March 2, 2004.

HED Draft Standard Operating Procedures (SOP's) for Residential Exposure Assessments (12/18/97), and the Revisions to the Standard Operating Procedures (SOP's) for Residential Exposure Assessment (Science Advisory Council for Exposure Policy 12, Revised February 22, 2001).