MEMORANDUM

Date: 5/8/00

Subject: PP#9F5051. Thiamethoxam on Various Crops. Section 3 Registration and Permanent Tolerance Request for Use of Thiamethoxam as a Seed Treatment, Soil Treatment, or Foliar Use on Barley, *Brassica* (Cole) Leafy Vegetables, Cotton, Cucurbit Vegetables, Fruiting (except Cucurbit) Vegetables, Leafy (except *Brassica*) Vegetables, Pome Fruit, Tuberous and Corm Vegetables, Sorghum, and Wheat. Section 3 Registration for Tobacco.
Residue Chemistry Review: Evaluation of Analytical Method and Residue Data.

DP Barcode: D265079
PC Code: 060109
PRAT Case: 290734
Submission Code: S558105
MRID#: 447151-03 thru -14, and 447151-34
Trade Name: ACTARA (25WG), PLATINUM (2SC), ADAGE 70WS, ADAGE 5FS
40 CFR 180: None (not currently registered)
Class: Insecticide (Neonicotinoid)

From: G. Jeffrey Herndon, Chemist
Registration Action Branch 2
Health Effects Division (7509C)

Through: Maxie Jo Nelson, Chemist, Secondary Reviewer
Registration Action Branch 2
Health Effects Division (7509C)

Through: Richard Loranger, Branch Senior Scientist
Registration Action Branch 2
Health Effects Division (7509C)

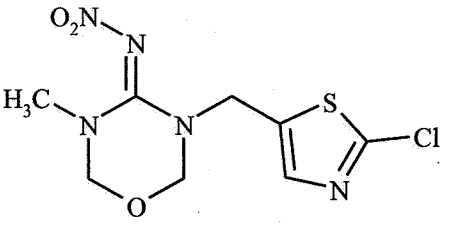
To: Tina Levine/Helene Daniel, P.M. Team #4
Insecticide/Rodenticide Branch
Registration Division (7505C)

Attached is the residue chemistry data review of PP#9F5051 from Novartis Crop Protection, Inc. (petitioner) requesting the establishment of permanent tolerances for the new neonicotinoid insecticide thiamethoxam and its metabolite CGA-322704 in/on various crops and crop groups at levels ranging from 0.02 ppm (Limit of Quantitation) to 2.0 ppm in conjunction with a Section 3 registration to apply thiamethoxam as one of 4 formulations as a seed treatment, soil treatment, or foliar application to said crops.

This data review was conducted by Dynamac Corporation (contractor) under the supervision of RAB2, HED, and has undergone secondary review and revision within RAB2 to ensure it reflects current HED and OPP policy.

This data review only addresses residue chemistry issues. Product chemistry issues have been the subject of a previous review (memo of A. Smith of TRB/RD, dated 3/18/99, D252040). A human health risk assessment will be the subject of a separate forthcoming HED memo.

THIAMETHOXAM



PERMANENT TOLERANCE PETITION (PP#9F5051) FOR USE ON TUBEROUS AND CORM VEGETABLES, LEAFY VEGETABLES, BRASSICA VEGETABLES, FRUITING VEGETABLES, CUCURBIT VEGETABLES, POME FRUITS, BARLEY, SORGHUM, WHEAT, COTTON, AND TOBACCO

(DP Barcode: D265079)

INTRODUCTION

Novartis Crop Protection, Inc., has submitted a petition for the establishment of permanent tolerances for residues of the insecticide, thiamethoxam, {3-[(2-chloro-5-thiazolyl) methyl] tetrahydro-5-methyl-*N*-nitro-4*H*-1,3,5-oxadiazin-4-imine}. The petitioner is proposing the establishment of tolerances for residues of thiamethoxam and its major metabolite, N-(2-chloro-thiazol-5-ylmethyl)-N′-methyl-N″-nitro-guanidine (CGA-322704), converted to parent equivalents in/on:

Tuberous and corm vegetables crop subgroup (1C)	0.02 ppm
Leafy vegetables crop group (4)	2.0 ppm
Head and stem *Brassica* crop subgroup (5A)	1.0 ppm
Leafy *Brassica* greens crop subgroup (5B)	2.0 ppm
Fruiting vegetables crop group (8)	0.25 ppm
Cucurbit vegetables crop group (9)	0.20 ppm
Pome fruits crop group (11)	0.20 ppm
Barley, grain	0.02 ppm
Barley, hay	0.05 ppm
Barley, straw	0.03 ppm
Cotton, undelinted seed	0.05 ppm
Cotton, gin byproducts	1.0 ppm
Sorghum, grain, forage, and stover (each)	0.02 ppm
Wheat, grain, hay, and straw (each)	0.02 ppm
Wheat, forage	0.50 ppm
Tomato, paste	0.80 ppm
Milk	0.02 ppm

In addition, Novartis has included residue data in this petition supporting the use of thiamethoxam on tobacco. Thiamethoxam is a new broad spectrum, systemic insecticide with activity against sucking and chewing insects on a wide variety of crops. Thiamethoxam belongs to a new pesticide chemical class known as the neonicotinoids. There are currently no established tolerances for residues of thiamethoxam in/on any plant or animal commodities. However, another petition (PP#9F5046, DP Barcode: D252021, G. Herndon, 3/21/00) for the use of thiamethoxam as a seed treatment on canola is currently under review by the Agency.

There are 17 volumes of residue chemistry submissions associated with this petition which are evaluated in this document.

CONCLUSIONS

OPPTS 830 Series GLNs: Product Properties

1. Review of technical and end-use product chemistry is under the purview of RD.

OPPTS GLN 860.1200: Proposed Uses

2a. The proposed use directions on the 70% WP and 5 lb.ai./gal FlC labels for seed treatment of barley, cotton, grain sorghum, and wheat are adequate.

2b. Use directions on the 25% DF and 2 lb.ai./gal FlC labels are generally adequate for the following crops: cucurbit vegetables, fruiting vegetables, tuberous and corm vegetables, and tobacco. However, maximum seasonal use rates specified for each crop on the 25% DF and 2 lb.ai./gal FlC labels should be expressed in terms of pounds of thiamethoxam a.i./A/season.

2c. The use directions for cotton on both the proposed 2 lb.ai./gal FlC and 25% DF labels should be amended. On the 2 lb.ai./gal FlC label, the statement "Do not use Platinum 2SC if seed has been treated with Adage™ 5FS seed treatment" should be changed to read "Do not use Platinum 2SC if seeds were treated with thiamethoxam". On the 25% DF label, the statement "do not apply this product if crops have been treated within the last 45 days with Tracker™ 2SC or Adage™ 5FS seed treatment" should be changed to read "do not apply this product if a soil application of thiamethoxam was previously applied prior to crop emergence, and do not apply within 45 days of planting if cotton seeds were treated with thiamethoxam".

2d. The proposed use directions for pome fruit on the 25% DF label are not adequate as the current label specifies a minimum application volume of 5 gal/A for aerial applications to pome fruit; in the absense of aerial field trial data, the minimum aerial application volume for tree crops should be 10 gal/A.

2e. HED cannot assess the adequacy of the proposed use directions for leafy vegetables and *Brassica* vegetables as the residue data for these crops are not available at this time. The use directions for these crops should be removed from the proposed labels and proposed tolerances removed from the Section F until field trial data and metabolism data (see Conclusions 6b and 6c) have been submitted, reviewed, and deemed to be adequate.

OPPTS GLN 860.1300: Nature of the Residue in Plants

3. **Wheat.** The wheat metabolism study is adequate. Total radioactive residues (TRR) were 2.1 ppm in forage, 4.5 ppm in straw, and 0.3 ppm in grain harvested from wheat grown in soil treated with [thiazol-2-^{14}C]thiamethoxam as a soil drench at 1.28 lb ai/A and aged for 25 days prior to planting. A total of 59-85% of the TRR was identified in forage and straw, and 39% of the TRR was identified in grain. The major residues identified in forage were thiamethoxam (16-53% TRR) and CGA-322704 (21-23% TRR), along with substantial amounts of CGA-265307 (9% TRR) and minor amounts (each ≤3.3% TRR) of CGA-322704-hydroxylamine-glucoside, CGA-355190, CGA-353968, and CGA-359683. At crop maturity, the principal ^{14}C-residues in wheat straw included: thiamethoxam (14.3% TRR), CGA-322704 (22.1% TRR), CGA-265307 (13.8% TRR), and CGA-359683 (8.7% TRR). Minor amounts of the following metabolites were also identified in straw at 0.3-5.8% of the TRR : CGA-322704-hydroxylamine-glucoside, CGA-355190, CGA-353968, CGA-353968-*N*-glucoside, desmethyl-CGA-353968, NOA-407475, NOA-421275, CGA-349208, and CGA-349208-*O*-glucoside. In grain, CGA-265307 (26.8% TRR) was the principal residue identified along with minor amounts of thiamethoxam (4.3% TRR) and CGA-322704 (7.5% TRR).

4a. **Rice.** The available rice metabolism data are adequate. One day following a granular application of [thiazol-^{14}C] or [oxadiazin-^{14}C]thiamethoxam to rice seedling at ~0.267 lb ai/A, ^{14}C-residues in immature leaves were 24-32 ppm; ^{14}C-residues declined steadily to 0.30-0.65 ppm in leaves by 71 days after treatment (DAT). Thiamethoxam initially accounted for 84-94% of the TRR in leaves, but declined to 15-20% of the TRR by 71 DAT. At maturity, ^{14}C-residues were highest in the straw (2.83-2.99 ppm), followed by husks (0.53-0.67 ppm) and grain (0.18-0.23 ppm). In another study using foliar applications, the TRR was 0.19-0.44 ppm in/on immature foliage sampled one hour following the second of two foliar applications of [thiazol-^{14}C] or [oxadiazin-^{14}C]thiamethoxam to rice plants at 0.045 lb ai/A, and was comprised almost entirely of parent (88-90% TRR). At maturity 21 days later, ^{14}C-residues were highest in both straw (1.01-1.08 ppm) and husks (0.96-1.16 ppm) and lowest in grain (0.03-0.05 ppm).

4b. In the granular application study, 90-99% of the TRR in straw, husks, and grain was adequately identified and/or characterized. In the foliar application study, 88-91% of the TRR in straw and husks, and 14-37% of the TRR in grain was adequately identified and/or characterized. For both the granular and foliar applications, the metabolic profile of ^{14}C-residues in mature RACs was qualitatively and quantitatively similar for the two

^{14}C-labels, with the exception of minor oxadiazine- or thiazole-ring specific metabolites. The metabolite profile was also similar between straw and husks. In addition, the metabolite profile was qualitatively similar between the early-season granular application and the late-season foliar applications.

4c. For the granular application, thiamethoxam (7-28% TRR) and CGA-322704 (7-17% TRR) were the principal ^{14}C-residues identified in straw and husks at maturity, followed by NOA-407475 (1-6% TRR). Minor amounts (0.2-4.5% TRR) of the metabolites CGA-265307, CGA-355190, CGA-353968, and desmethyl-CGA-353968 were also detected in straw and husks from both ^{14}C-labels. Thiazole-ring specific metabolites identified in straw and husks included NOA-421275 and NOA-404617 at 0.1-1.6% TRR. Oxadiazine-ring specific metabolites identified in straw and husks included NOA-405217, N-methyl-urea, and N-nitro-guanidine at 0.8-4.4% TRR. In rice grain, only 3.5-4.8% of the TRR was identified as specific thiamethoxam metabolites. The metabolite CGA-322704 accounted for 1.1-2.3% TRR in grain; other compounds detected in grain at <1% TRR included: thiamethoxam, CGA-265307, CGA-353968, desmethyl-CGA-353968, and NOA-407475. In addition to the specific metabolites, substantial amounts of the TRR in rice straw, husks, and grains were incorporated into natural plant products. Radioactivity associated with lignins, cellulose, and polysaccharide fractions accounted for 7-8% TRR in straw and 14-25% TRR in husks. In grain, 38-43% of the TRR was identified as being incorporated into starch, and 10-11% of the TRR was associated with an isolated protein fraction.

4d. Following the two foliar applications, the principal ^{14}C-residues identified in rice straw and husks were thiamethoxam (50-71% TRR) and CGA-322704 (4-11% TRR). Other metabolites identified in straw and husks, each at ≤5.2% of the TRR included: CGA-265307, CGA-355190, CGA-353968, desmethyl-CGA-353968, and NOA-407475. The two major ^{14}C-residues identified in grain also consisted of thiamethoxam (5-13% TRR) and CGA-322704 (4-11% TRR). Other metabolites identified in grain at <3% of the TRR included: CGA-265307, CGA-355190, CGA-353968, and NOA-407475.

5. Metabolism data on corn, cucumbers, and pears were reviewed previously (G.J. Herndon, 3/30/00, PP#9F5046). The metabolism of thiamethoxam in wheat and rice is similar to its metabolism demonstrated in previous plant metabolism studies, although the relative levels of individual metabolites differed among the various crops. To varying degrees, the metabolism of thiamethoxam in each of these crops 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.

6a. In a meeting held on 7/28/99 (see memo of G.J. Herndon dated 8/31/99), the Metabolism Assessment Review Committee (MARC) concluded that the residue of concern in plants (pears and corn) is understood. The residue to be regulated (for risk assessment and tolerance setting purposes) is the parent thiamethoxam and its CGA-322704 metabolite.

6b. In the MARC meeting held on 7/28/99, based on the low radioactivity present and identified in the cucumber metabolism study, the Committee recommended that another plant metabolism study be submitted to fulfill the requirement of 3 plant metabolism studies (on dissimilar crops) for OPPTS 860.1300. Based on the uses requested under PP#9F5046 and 9F5051, the Committee recommended that a new plant metabolism study be conducted on a leafy vegetable (one of the representative commodities in either Crop Group 4 or 5).

6c. RAB2 concludes that the acceptable plant metabolism studies on different plant types (pears and corn) would cover all proposed seed treatment (wheat, sorghum, barley, canola, cotton, tobacco, leafy (except *Brassica*) vegetables, *Brassica* leafy vegetables, cucurbit vegetables, and fruiting vegetables) uses (due to expected non-detectable residues), the proposed foliar treatment uses on canola and soil and foliar treatment on cotton (due to the edible portion (oil) undergoing many processing steps which would be expected to degrade or volatilize thiamethoxam residues), soil and foliar uses on tobacco, soil and foliar uses on fruiting (except cucurbit) vegetables (Crop Group 8), soil and foliar uses on cucurbit vegetables (Crop Group 9), foliar and soil treatment of tuberous and corm vegetables (Crop Subgroup 1-C), and foliar uses on pome fruit (due to acceptable pear metabolism study).

The additional leafy vegetable plant metabolism study will need to be conducted by the petitioner, reviewed and found acceptable by the Agency prior to the granting of the following proposed uses of thiamethoxam: foliar treatment of leafy (except *Brassica*) vegetables (Crop Group 4) and foliar treatment of *Brassica* leafy vegetables (Crop Group 5).

OPPTS GLN 860.1300: Nature of the Residue in Animals

7. Adequate ruminant and poultry metabolism studies were reviewed in conjunction with the permanent tolerance petition for use on canola (PP#9F5046). The metabolism of thiamethoxam in ruminants and poultry is similar. The major pathway of metabolism 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.

8a. In ruminants, the MARC concluded (meeting held on 7/28/99) that the residue of concern is parent + CGA-322704 metabolite. The parent thiamethoxam and the CGA-322704 metabolite accounted for a high percentage of the radioactivity identified in milk and muscle (the commodities with the highest dietary impact for humans) from the lactating goat study. The Committee was potentially concerned about the relatively high levels of metabolites MU-12 and N-5 in kidney and liver. However, after consulting with Alberto Protzel, the Committee concluded that these metabolites, which contain the chloro-thiazole ring but not the nitro group, would not need to be included in the tolerance expression or quantitatively used in a human health risk assessment.

8b. In poultry, based on cursory review of the laying hen metabolism study and dietary burdens, a hen feeding study and establishment of poultry commodity tolerances will not be needed for the proposed uses. If additional uses are requested later which increase the dietary burden enough to require that a laying hen feeding study be conducted, the Committee concluded that the petitioner will need to analyze for the additional metabolite CGA-265307 (in addition to the parent thiamethoxam and CGA-322704 metabolites) based on it being the major residue in eggs and fat and containing the N-nitro group. For the reasons stated under the ruminants section for MU-12 and N-5, the MARC concluded that the metabolite MU-3 would not need to be included in the tolerance expression or quantitatively used in a human health risk assessment.

OPPTS GLN 860.1340: Residue Analytical Method - Plant Commodities

9a. Novartis HPLC/UV (or MS) Method AG-675 is adequate for collecting data on residues of thiamethoxam and CGA-322704 in/on the crop commodities associated with this petition. Adequate method validation data were submitted. The validated limit of quantitation (LOQ) for residues of each analyte is 0.01 ppm for all plant matrices with the exception of fruit juices (0.005 ppm), grass (0.05 ppm), and cured tobacco (0.1 ppm). The method has been adequately radiovalidated and has undergone a successful independent laboratory validation (ILV) trial in conjunction with the permanent tolerance

petition for use on canola (PP#9F5046).

9b. A petition method validation (PMV) request has been submitted to the Analytical Chemistry Branch (ACB) of BEAD (see memo of G.J. Herndon dated 9/28/99). RAB2 requested that ACB use the proposed enforcement methods (MRID# 447035-24 and 447035-27) to validate recovery of thiamethoxam and its metabolite CGA-322704 from canola, cotton, tomato, spinach, wheat grain, milk, beef liver, and eggs. The results of the PMV request have not been received.

9c. With the submission of a method having both UV and MS detection, the issues of method specificity and confirmatory procedures have been adequately addressed.

OPPTS GLN 860.1340: Residue Analytical Methods - Animal Commodities

10a. Adequate method validation data using animal commodities have been submitted for Novartis HPLC/MS Method AG-675, and the method has undergone a successful ILV trial using milk, eggs, and beef liver. The validated LOQ for residues of thiamethoxam and CGA-322704 is 0.01 ppm each in meat, poultry, and eggs, and 0.005 ppm each in milk. This method has also been adequately radiovalidated using samples of meat and milk from the goat metabolism study. However, additional radiovalidation data are required in order to assess the efficiency of this method in recovering thiamethoxam and CGA-322704 from beef liver. This will be required as a condition of registration (see Conclusion 30g). In both the ruminant and poultry metabolism studies, microwave extraction was required to release CGA-322704 from liver.

10b. A petition method validation (PMV) request has been submitted to the Analytical Chemistry Branch (ACB) of BEAD (see memo of G.J. Herndon dated 9/28/99). RAB2 requested that ACB use the proposed enforcement methods (MRID# 447035-24 and 447035-27) to validate recovery of thiamethoxam and its metabolite CGA-322704 from canola, cotton, tomato, spinach, wheat grain, milk, beef liver, and eggs. The results of the PMV request have not been received.

OPPTS GLN 860.1360: Multiresidue Method

11a. The petitioner submitted data concerning the recovery of residues of thiamethoxam using FDA multiresidue method protocols (PAM Vol. I). Recovery of thiamethoxam was 50-60% using Protocol D and <30% using Protocol E. Using Protocol C, thiamethoxam obtained adequate detector responses to Section 302 DG5 and DG13 gas-liquid chromatography (GLC) systems. Metabolites CGA-322704 and CGA-265307 were tested using Protocol C, but did not yield adequate detector responses to any of the Section 302 DG5, DG13, and DG18 GLC systems; no further testing was conducted for the metabolites.

11b. In the memos of G.J. Herndon dated 9/28/99, the results of the multiresidue testing were forwarded to FDA (Mark Wirtz) and ACB/BEAD (Francis Griffith).

OPPTS GLN 860.1380: Storage Stability Data

12a. Data are available (PP#9F5046) from one study indicating that thiamethoxam and CGA-322704 are stable at ≤-18 C in apples, corn grain, potatoes, canola seed, and tomatoes for up to 24 and 12 months, respectively. Interim data from an on-going storage stability study indicate thiamethoxam and CGA-322704 are also stable at -20 C in canola oil, corn meal, leaf lettuce, safflower seed, and tomato puree for up to 4 months[1].

12b. In the current crop field trial studies, RACs of potato, fruiting vegetables, cucurbits, pome fruits, wheat and cotton were stored frozen for 14-27 months; samples of sorghum RACs were stored for up to 30 months, although the majority of the samples were analyzed within ~24 months. Samples from the tobacco residue study were stored frozen for up to 3 months. Processed commodities of potato, tomato, apple, grain sorghum, wheat, and cotton were stored frozen for 12-26 months from collection to analysis.

12c. The available storage stability data on thiamethoxam *per se* adequately support the residue studies on potato, fruiting vegetables (excluding tomato processed commodities), cucurbits, pome fruits, cotton, and tobacco. Although storage stability data for thiamethoxam on a commodity representative of forage, hay, or straw, are needed to support the studies on barley, wheat, and sorghum, data on leaf lettuce from an on-going study may be used support the stability of thiamethoxam in forage. Likewise, data on tomato puree from the interim study may support the tomato processing study. Data are required depicting the frozen storage stability of CGA-322704 in representative RAC and processed commodities stored for intervals reflecting the maximum storage intervals incurred by samples from all the submitted residue studies (except tobacco). However, based on the storage stability data submitted to date, RAB2 does not anticipate significant degradation of either thiamethoxam or CGA-322704 in frozen storage. As confirmation of this, RAB2 will require that the storage stability study be continued to cover the interval that the plant commodity samples were stored (up to 30 months). These data will be required as a condition of registration.

13. **Animal Commodities**. The submitted interim storage stability data indicate that residues of thiamethoxam, CGA-322704, and CGA-265307 are stable in animal commodities for up to 4 months at -20 C. In the current cattle feeding study, milk and tissue samples were stored at -20 C for up to 12 months prior to analysis. Additional data supporting the

---

[1] Results from a later interval in the on-going storage stability study were e:mailed to the Agency on 4/28/00. The conclusions in the e:mail indicate that thiamethoxam and CGA-322704 are stable in/on these matrices out to 14 months. Sufficient supporting raw data were not submitted to the Agency to allow RAB2 to fully review these results.

storage intervals reflected in the feeding study are required; the petitioner has indicated that data for longer storage intervals will be submitted with the final storage stability report. Based on the storage stability data submitted to date on both plant and animal commodities, RAB2 does not anticipate significant degradation of either thiamethoxam or CGA-322704 in frozen storage. However, as confirmation of this, RAB2 will require that the storage stability study be continued to cover the interval that the animal commodity samples were stored (up to 12 months). These data will be required as a condition of registration.

OPPTS GLN 860.1500: Crop Field Trials

14. **Tuberous and Corm Vegetable Crop Subgroup.** Provided questions concerning storage stability of CGA-322704 are resolved (see Conclusion 12c), the submitted potato residue data are adequate and support the proposed 0.02 ppm tolerance for residues of thiamethoxam in/on the tuberous and corm vegetables crop subgroup. In 16 tests, residues of thiamethoxam and CGA-322704 were each <0.01 ppm (<LOQ) in/on 31 samples of potatoes harvested ~14 days following both in-furrow and foliar applications of thiamethoxam (FlC and DF) totaling 2.7 oz ai/A (0.17 lb ai/A;1x soil rate + 1x foliar rate); one sample bore residues of thiamethoxam *per se* at 0.014 ppm. Residues of both analytes were also <0.01 ppm in/on 32 potato samples harvested 14 days following the second of two foliar application totaling 0.044 lb ai/A/season (1x foliar rate).

15. Although the petitioner is requesting tolerances on Crop Group 4 and Crop Subgroups 5A and 5B, at the time of this review, residue data were not available supporting the proposed tolerances for the Leafy vegetables (except *Brassica*) crop group, the Head and stem *Brassica* subgroup, and the Leafy *Brassica* greens subgroup (see Conclusion 2e).

16a. **Fruiting Vegetables (except Cucurbits) Crop Group.** Pending submission of supporting storage stability data (see Conclusion 12c), the submitted field trial data on tomatoes and peppers are adequate. Following the last of two foliar applications with thiamethoxam (25% DF) at 0.09 lb/ai/A/application (0.18 lb ai/A; ~1x the proposed foliar rate), with a 5-day RTI, combined residues of thiamethoxam and CGA-322704 were <0.02-0.24 ppm in 44 samples of tomatoes and peppers (bell and non-bell) harvested 0-days posttreatment. After an at-planting soil application in which thiamethoxam (FlC) was applied in-furrow, banded, or by transplant drench at 0.13 lb ai/A (1x the soil rate) followed by a single broadcast foliar application of thiamethoxam (25% DF) at 0.04 lb ai/A (0.5x the single foliar rate), for a total of 0.17 lb ai/A, combined residues were <0.02-0.11 ppm in/on 46 samples of tomatoes and peppers harvested 0-days posttreatment.

16b. The tomato and pepper residue data from the foliar applications and the soil + foliar applications support the proposed crop group tolerance of 0.25 ppm for residues of thiamethoxam and CGA-322704 in/on fruiting vegetables. HED notes that the proposed

label for the 25% DF presently prohibits foliar treatment if the crop has been treated at-planting with thiamethoxam (FlC), yet the available residue data would also allow for a combined 1x soil and a single 0.5x foliar application totaling 0.17 lb ai/A (1x maximum seasonal foliar rate).

17a. **Cucurbit Vegetables Crop Group.** Pending submission of supporting storage stability data (see Conclusion 12c), the submitted field trial data on cucurbit vegetables are adequate and support the proposed 0.2 ppm tolerance. Following the last of two foliar applications of thiamethoxam (25% DF) at 0.09 lb/ai/A/application (0.18 lb ai/A; 2x the proposed rate) with a 4-6 day RTI, residues of thiamethoxam *per se* were <0.01-0.14 ppm in/on 38 samples of cucurbits harvested 0-days posttreatment. Following a combined at-planting soil application of thiamethoxam (FlC) as an in-furrow or banded application at 0.13 lb ai/A (1x the maximum soil rate) and a single late-season foliar application of thiamethoxam (25% DF) at 0.04 lb ai/A (1x the single foliar rate) totaling 0.17 lb ai/A, residues of thiamethoxam *per se* were <0.01-0.11 ppm in/on 46 samples of cucurbits harvested 0-days posttreatment. Residues of CGA-322704 were <0.01 ppm in all treated samples.

17b. Although the two use patterns depicted in the available cucurbit field trials (a 1x soil + 1x foliar treatment and two 2x foliar treatments) do not accurately reflect the proposed use patterns (either a 1x soil treatment or two 1x foliar treatments), residues resulting from the proposed two 1x foliar applications would likely exceed the maximum combined residues (<0.12 ppm) from 1x soil+1x foliar treatment and would therefore support the proposed 0.2 ppm tolerance.

18. **Pome Fruit Crop Group.** Pending submission of supporting storage stability data (see Conclusion 12c), the submitted apple and pear field trial data are adequate and support the proposed 0.2 ppm tolerance. The combined residues of thiamethoxam and CGA-322704 were <0.03-<0.12 ppm in/on 26 apple samples and 12 pear samples harvested ~14 days following the last of four foliar applications of thiamethoxam applied successively at 1.4, 1.4, 0.7, and 0.7 oz ai/A, for a total of 0.26 lb ai/A (1.5x). The use pattern being proposed for pome fruits allows for 3 foliar applications of thiamethoxam (25% DF) at 0.7 oz ai/A/application with a 14-day PHI, or 2 foliar applications at 1.4 oz ai/A/application with a 35-day PHI. Residues in/on fruit resulting from the proposed use are likely to be below the proposed 0.2 ppm tolerance.

19. **Barley.** Pending resolution of questions concerning storage stability of CGA-322704 (see Conclusion 12c), the submitted residue data on barley are adequate and support the proposed tolerances for thiamethoxam residues in/on barley hay, (0.05 ppm), grain (0.02 ppm) and straw (0.03 ppm). The combined residues of thiamethoxam and CGA-322704 in/on barley RACs grown from seed treated with thiamethoxam (WP or FlC) at 0.07 lb ai/100 lb seed (1.4x) were <0.02-0.05 ppm in/on 30 samples of hay (soft dough stage),<0.03 ppm in/on 30 samples of straw, and <0.02 ppm in/on 24 samples of grain.

20. **Grain Sorghum.** Pending resolution of questions concerning storage stability of residues (see Conclusion 12c), the submitted residue data on grain sorghum are adequate and support the proposed tolerances for thiamethoxam residues in/on sorghum forage, grain, and stover (0.02 ppm each). Residues of thiamethoxam and CGA-322704 were each <0.01 ppm (<LOQ) in/on all samples of forage (n=20), and grain and stover (n=18 each) grown from seed treated at 0.30 lb ai/100 lb seed (1.5x). Residues of each analyte were also <LOQ in/on all forage, grain, and stover samples (n=4 each) grown from seed treated at 4.5x.

21. **Wheat.** Pending resolution of questions concerning storage stability of residues (see Conclusion 12c), the submitted residue data on wheat are adequate and support the proposed tolerances for thiamethoxam residues in/on wheat forage at 0.50 ppm and in/on wheat hay, grain, and straw each at 0.02 ppm. The combined residues of thiamethoxam and CGA-322704 were <0.02-<0.46 ppm in/on 51 samples of forage (~42-day PHI), <0.02 ppm (<LOQ) in/on 51samples each of hay and straw and 41 samples of grain grown from seed treated with thiamethoxam (70% WP or 5 lb/gal FlC) at 0.07 lb ai/100 lb seed (1.4x the proposed maximum rate). Combined residues were also <0.02 ppm in/on one sample each of forage, hay, grain and straw from a 4.2x treatment rate.

22a. **Cotton.** The submitted cotton residue data are adequate provided that the proposed 25% DF label is amended to prohibit foliar applications to cotton previously treated at-planting with a soil application of thiamethoxam (2 lb.ai./gal FlC - see Conclusion 2c). The combined residues of thiamethoxam and CGA-322704 were <0.02-<0.07 ppm in/on 26 samples of undelinted cottonseed grown from seed treated at 0.30 lb ai/100 lb seed and harvested 20-28 days following two foliar applications totaling 0.09 lb ai/A/season (1x the proposed foliar rate). Combined residues of thiamethoxam were 0.06-1.10 ppm in/on 12 samples of cotton gin byproducts harvested 20-28 days following treatment at 1x the proposed foliar rate. These data indicate that the proposed 0.05 ppm tolerance for residues of thiamethoxam in/on undelinted cottonseed is too low; a more appropriate tolerance level would be 0.1 ppm. The available data also indicate that the proposed tolerance of 1.0 ppm for residues in/on cotton gin byproducts is too low; a more appropriate tolerance level would be 1.5 ppm.

22b. Residue data for cotton are not available reflecting a combined at-planting soil application at 0.13 lb ai/A with two late-season foliar applications at 0.09 lb ai/A/application; therefore, the combined use should be deleted from the proposed 25% DF label (see Conclusion 2c). Residue data are also not available depicting residues in/on cottonseed and gin byproducts from plants treated at-planting with a single soil application of thiamethoxam (2 lb/gal FlC) at up to 0.13 lb ai/A. However, based on data from the metabolism studies and the length of the cotton growing season, residues of thiamethoxam and CGA-322704 in/on cottonseed and gin byproducts resulting from this use are unlikely to exceed the residues resulting from the two late season foliar applications. Therefore, HED will allow the proposed soil application use on the 2

lb.ai./gal FlC label.

23a. **Tobacco.** The submitted field trial data on tobacco are adequate. Following application of thiamethoxam (2 lb/gal FlC) in-furrow at planting at 2 oz ai/A together with a late-season single broadcast application of thiamethoxam (25% DF) at 0.9 oz ai/A (0.18 lb ai/A/season), combined residues of thiamethoxam and CGA-322704 were 0.09-0.23 and 0.6-0.8 ppm in/on six samples each of green and cured leaves, respectively, harvested 14 days after the last treatment. The petitioner states that this treatment represents 1x the maximum proposed label rate; however, the currently proposed labels preclude the use of the 25% DF as a foliar treatment if the crop has been treated at planting with the proposed 2 lb/gal FlC. In addition, combined residues of thiamethoxam and CGA-322704 were <0.02-0.13 and <0.2-0.8 ppm in/on six samples each of green and cured leaves, respectively, harvested 74-105 days following application of thiamethoxam (2 lb/gal FlC) as an at-planting in-furrow soil treatment alone at 0.13 lb ai/A/season (1x the proposed soil treatment maximum). A revised label is required if the petitioner intends to support the use of a sequential soil and foliar treatment.

23b. A pyrolysis study was not submitted to show what residues may occur in tobacco smoke. RAB2 is willing to waive this study provided the risk to smokers is not of concern when it is assumed all residues of parent and CGA-322704 in cured tobacco are released into the smoke.

OPPTS GLN 860.1520: Processed Food/Feed

24. **Potato.** The submitted potato processing study is adequate provided questions pertaining to frozen storage stability of CGA-322704 residues in processed potato commodities are resolved (see Conclusion 12c). The available data indicate that the combined residues of thiamethoxam and CGA-322704 do not concentrate appreciably in granules or wet peels, but concentrate on average by 1.9x in chips. However, based upon this concentration factor and HAFT residues of 0.036 ppm (combined residues of thiamethoxam and CGA-322704) in a 7X exaggerated study, combined residues of thiamethoxam and CGA-322704 would not be expected to reach the limit of quantitation of the cold method (0.02 ppm). Therefore, a separate tolerance on chips is not needed.

25. **Tomato.** Provided questions pertaining to frozen storage stability of residues in processed tomato commodities are resolved (see Conclusion 12c), the submitted tomato processing study is adequate. The available data indicate that the combined residues of thiamethoxam and CGA-322704 concentrate by 1.7x and 3.8x in tomato puree and paste, respectively. Based upon these concentration factors and current HAFT residues of 0.14 ppm in/on tomatoes, combined residues of thiamethoxam and CGA-322704 could be expected to reach 0.24 ppm in puree and 0.53 ppm in paste. These data support the proposed tolerance of 0.80 ppm for residues of thiamethoxam in tomato paste. As residues in puree would be below the proposed 0.25 ppm tolerance for the Fruiting

Vegetables Crop Group, a separate tolerance for tomato puree is not required.

26. **Apple.** Pending submission of acceptable sample history information, the submitted processing study is adequate. A complete sample history including storage conditions for processed apple commodities is required (see Conclusion 12c). The combined residues of thiamethoxam and CGA-322704 concentrated slightly in wet pomace (1.6x), and were reduced slightly in juice (0.75x). Based upon HAFT combined residues of <0.11 ppm from the apple residue study discussed above, and an average concentration factor for wet pomace of 1.6x, combined residues of thiamethoxam and CGA-322704 could be expected to reach 0.18 ppm in wet pomace. These residues are adequately covered by the proposed tolerance for residues in/on pome fruit at 0.20 ppm.

27. **Sorghum.** Residue data are not currently required by the Agency on sorghum flour or any other processed commodity of grain sorghum. The submitted grain sorghum processing studies will be adequate once questions concerning the storage stability of CGA-322704 residues are resolved (see Conclusion 12c). In two studies conducted using samples grown from grain sorghum seed treated with thiamethoxam (70% WP) at 0.3 and 0.9 lb ai/100 lb seed (1.5 and 4.5x the proposed maximum rate), residues of thiamethoxam and CGA-322704 were each <0.01 ppm in/on four composite grain (RAC) samples, and in four sorghum flour samples.

28. **Wheat.** Pending resolution of questions concerning the storage stability of residues (see Conclusion 12c), the submitted wheat processing study is adequate and indicates that residues do not concentrate in wheat fractions processed from grain grown from seed treated at up to 4.2x the maximum proposed rate. Residues of thiamethoxam and CGA-322704 were each <0.01 ppm in grain (RAC) from 1.4x and 4.2x treatments and in the resulting wheat processed fractions.

29. **Cotton.** The submitted cottonseed processing studies are adequate and indicate that thiamethoxam residues do not concentrate in meal, hulls, or refined oil processed from cottonseeds bearing measurable weathered residues of thiamethoxam. Therefore, tolerances for residues of thiamethoxam in processed commodities of cotton are not required.

<u>OPPTS GLN 860.1480: Meat, Milk, Poultry, Eggs</u>

30a. Provided that questions are resolved concerning the storage stability of residues in animal matrices (Conclusion 13b) and the suitability of Method AG-675 for determining residues of CGA-322704 in liver (Conclusions 10a and 30g), the submitted ruminant feeding study is adequate. In the current feeding study, samples of milk and tissue were stored frozen for up to 1 year; interim data submitted with this petition only support storage intervals up to 4 months. Although additional supporting data are required, the available residue data indicate that thiamethoxam residues may transfer to milk, meat, and meat-by-

products of cattle, goats, horses, and sheep as a result of the proposed uses of thiamethoxam on animal feed items.

30b. If the dietary burden for dairy cattle is higher than beef cattle, current OPP policy dictates that the dairy cattle diet be used for setting meat, fat, and meat by-product tolerances (see minutes from ChemSAC meeting held on 4/5/00). The rationale for this is that many dairy cattle are slaughtered for meat once their milk production drops below profitable levels.

30c. Groups of three cows were dosed for 28-30 days with thiamethoxam at 2, 6, and 20 ppm, equivalent to 1.4x, 4.2x, and 14x the maximum theoretical dietary burden (MTDB; 1.43 ppm) for dairy cattle. The combined residues of thiamethoxam and CGA-322704 in milk plateaued between 7-14 days of dosing for each group. The maximum combined residues in milk from the 2 ppm dose group (1.4x) were 0.018 ppm on Day 7. Based on these data, the proposed 0.02 ppm tolerance for the combined residues of thiamethoxam and CGA-322704 in milk is appropriate. As the combined residues in fat were <LOQ from the 14x dose group, there is no reasonable expectation of the transfer of thiamethoxam residues from feed items to fat; therefore, tolerances are not required for residues in fat. Although residues of thiamethoxam and CGA-322704 were <LOQ in meat, kidneys, and liver at the 1.4x dosing level, residues of thiamethoxam were detected in muscle from the 4.2x and 14x dose groups and in kidneys from the 14x dose group. Based on these data, tolerances should be set at the combined LOQ (0.02 ppm) for residues of thiamethoxam and CGA-322704 in meat and meat-by-products of cattle, goats, horses, and sheep.

30d. Based on the results from the goat and hen metabolism studies, microwave extraction is required to release bound/conjugated residues of thiamethoxam and its CGA-322704 from liver, which accounted for the majority (> 10X additional released after microwave extraction) of the radioactivity in this organ. The proposed enforcement method (AG-675) does not include a microwave extraction step, and therefore would not be capable of extracting bound/conjugated residues of thiamethoxam and its CGA-322704 metabolite from liver. No residues of thiamethoxam or its CGA-322704 metabolites were found in liver samples from the high (20 ppm - 14X) feeding level. However, based on use of Method AG-675 (HPLC/MS) **without** a microwave extraction step, these results are expected.

30e. Given that there are questions regarding the adequacy of Method AG-675 in determining CGA-322704 residues in liver, and the fact that the combined residues of thiamethoxam and CGA-322704 were somewhat higher in kidneys than in liver in the goat metabolism study, the residue data for kidneys were used to determine the tolerance for meat-by-products.

30f. For risk assessment purposes, RAB2 has estimated residues in liver from the goat metabolism study. At a 100 ppm feeding level, residues in liver were found to be as high

as 0.90 ppm (combined thiamethoxam and CGA-322704) **after** microwave extraction. Normalized to a dietary burden of 1.43 ppm, this would equate to a residue level of 0.013 ppm. Given the uncertainties in the process and species difference (goat vs. cow), RAB2 will add a 10X factor to this level. For Tier 1 risk assessment purposes, until Conclusion 30g is resolved, a residue level of 0.13 ppm should be used for cattle, goats, horses, and sheep liver.

30g. As a condition of registration, the petitioner should modify Novartis Method AG-675 to add a microwave extraction step for liver, or propose a new enforcement method for liver. This method should be radiovalidated by Novartis and submitted to the Agency. The petitioner should use this method to reanalyze the cow liver samples from the feeding study and provide adequate storage stability data to cover the period the samples were stored. Alternatively, the petitioner can conduct a new lactating cow feeding study using the new liver method (including microwave extraction) for the analysis.

31. The proposed uses for thiamethoxam include swine and poultry feed items. The calculated MTDB of thiamethoxam for both swine and poultry is 0.025 ppm. As the lowest (2 ppm) feeding level in the current ruminant feeding study represents 80x the MTDB for swine, HED concludes that there is no reasonable expectation of the transfer of thiamethoxam residues from feed items to hog commodities. In the previously reviewed (PP#9F5046) poultry metabolism study, hens were dosed at ~100 ppm, equivalent to ~4000x the maximum dietary burden. Based on data from the metabolism study, residues of thiamethoxam and CGA-322704 in tissues and eggs would be expected to be <0.01 ppm even at a 100x feeding level. Category 180.6(a)(3) situations exist with respect to thiamethoxam residues in swine and poultry commodities, and tolerances for residues in hog and poultry commodities are not required.

OPPTS GLN 860.1850: Confined Accumulation in Rotational Crops

32. Confined rotational crop studies were previously reviewed in conjunction with the petition for thiamethoxam use on canola (PP#9F5046). These studies indicated that limited field rotational crop studies are necessary to support the proposed 120-day plant-back interval (PBI) for rotational crops, and that the metabolism of [^{14}C]thiamethoxam in rotational crops is similar to the metabolism observed in primary crops.

33. In a meeting held on 7/28/99 (see memo of G.J. Herndon dated 8/31/99), the Metabolism Assessment Review Committee (MARC) determined that the major residues from the confined rotational crop studies were the parent thiamethoxam and its CGA-322704 metabolite. CGA-265307 was a major residue still having the N-nitro group in animal feed items (e.g. wheat straw). The MARC recommended that all three compounds should be analyzed in field rotational crop studies.

OPPTS GLN 860.1900: Field Accumulation in Rotational Crops

34. Provided that questions are resolved concerning the analysis for metabolite CGA-265307 (see Conclusions 35a and 36), the storage stability of residues in/on lettuce and turnip tops, and a description of the storage conditions at the analytical facility is submitted, the limited field rotational crop study is adequate. Analysis of several samples from the 30-day PBI indicated that residues of each analyte were <0.01-0.02 ppm in/on turnip tops and wheat forage. Secondary crop samples from the 120-day PBI from three different test sites were also analyzed, and residues of thiamethoxam and CGA-322704 were each <0.01 ppm (<LOQ) in/on all representative rotational crops (leaf lettuce, turnip tops and roots, and wheat grain, straw, hay and straw).

35a. In the field rotational crop studies, the crop parts were not analyzed for the metabolite CGA-265307. In a meeting held on 7/28/99 (see memo of G.J. Herndon dated 8/31/99), the Metabolism Assessment Review Committee (MARC) determined that the major residues from the confined rotational crop studies were the parent thiamethoxam and its CGA-322704 metabolite. CGA-265307 was a major residue still having the N-nitro group in animal feed items (e.g. wheat straw). The MARC concluded that all three compounds should be analyzed in field rotational crop studies.

35b. RAB2 reexamined the results of the confined rotational crop studies submitted in conjunction with the use on canola (G.J. Herndon, 3/30/00, PP#9F5046). In mustard greens, lettuce leaves, radish tops, and turnip tops, levels of CGA-265307 were less than either thiamethoxam or CGA-322704 at all plantback intervals. In wheat forage, straw, and grain, levels of CGA-265307 were higher than either thiamethoxam or CGA-322704. In wheat grain, levels of CGA-265307 were higher than either thiamethoxam or CGA-322704 only in samples exhibiting low level residues (< or equal to 0.003 ppm).

36. The results of both the confined and field rotational crop studies indicate that, using the proposed enforcement method, measurable residues would not likely be found on direct human foods. The confined (hot) study indicated low level residues in animal feed items, which would not be likely to cause significant residues in meat, milk, poultry, or eggs. Therefore, RAB2 is willing to defer analysis for metabolite CGA-265307 as a condition of registration. As a condition of registration, the petitioner will need to either reanalyze the cold (field) samples for the CGA-265307 metabolite and provide adequate storage stability data to cover the period the samples were stored, or alternatively, the petitioner can conduct a new field rotational crop study examining the samples for residues of thiamethoxam, CGA-322704, and CGA-265307.

37. As the currently proposed labels specify a 120-day rotational crop restriction for crops not proposed for thiamethoxam use, tolerances for residues of thiamethoxam in rotational crops will not be required. Once the results of Conclusion 36 are received, a 30-day rotational crop restriction may be acceptable.

International Harmonization Issues

38. As there are no Codex, Canadian, or Mexican MRLs/tolerances established for residues of thiamethoxam in plant or animal commodities, a discussion of compatibility with U.S. tolerances is not relevant at this time.

RECOMMENDATIONS

Pending the results of ACB's validation of the plant and animal enforcement methods (Conclusions 9b. and 10b.), the risk assessment for users of tobacco (Conclusion 23b), the requested changes on the proposed labels (Conclusions 2b, 2c, 2d, 2e, and 23a), and tolerance changes (Conclusions 2e, 22a, and 30c), for the purposes of a conditional Section 3 registration on tuberous and corm vegetables, fruiting vegetables, cucurbit vegetables, pome fruit, barley, cotton, wheat, and tobacco, the residue chemistry requirements have been met. The following permanent tolerances for the combined residues of thiamethoxam and its CGA-322704 metabolite are appropriate:

tuberous and corm vegetables crop subgroup	0.02 ppm
fruiting vegetables crop group	0.25 ppm
cucurbit vegetables crop group	0.20 ppm
pome fruit crop group	0.20 ppm
barley grain	0.02 ppm
barley hay	0.05 ppm
barley straw	0.03 ppm
cotton, undelinted seed	0.10 ppm (raised)
cotton gin byproducts	1.5 ppm (raised)
sorghum grain	0.02 ppm
sorghum forage	0.02 ppm
sorghum stover	0.02 ppm
wheat grain	0.02 ppm
wheat hay	0.02 ppm
wheat straw	0.02 ppm
wheat forage	0.50 ppm
tomato paste	0.80 ppm
milk	0.02 ppm
meat of cattle, goats, horses, and sheep	0.02 ppm (new)
meat byproducts of cattle, goats, horses, and sheep	0.02 ppm (new)

Any risk issues will be addressed in the human health risk assessment, which will be the subject of a forthcoming memo by HED (see Conclusion 30f).

To remove the residue chemistry conditions of the conditional registration, the following deficiencies should be addressed: animal enforcement method for liver (Conclusions 10a and 30g), storage stability data and sample history information, (Conclusions 12c, 13, 26, and 34), reanalysis of liver samples from the feeding study (Conclusion 30g), and reanalysis of the field rotational crop study samples for CGA-265307 (Conclusion 36).

For future uses, additional plant metabolism (Conclusions 6b and 6c) and poultry metabolism studies (Conclusion 8b) may be needed.

DETAILED CONSIDERATIONS

OPPTS 830 Series GLNs: Product Properties

The review of technical and end-use product chemistry is under the purview of RD.

OPPTS GLN 860.1200: Proposed Uses

The petitioner provided specimen labels for six single active ingredient end-use products (EPs) containing the insecticide thiamethoxam (Table 1). Two of these products (Veridian and Thiamethoxam Spot On for Dogs) are not being proposed for any food or feed uses and are not discussed further in this review. The 25% water-dispersible granule (DF) formulation is being proposed for foliar application to numerous vegetable crops, cotton, pome fruits, and tobacco. The 2 lb/gal FlC formulation is being proposed for a soil treatment at planting or transplanting to numerous vegetable crops, cotton, and tobacco. The 5 lb/gal FlC and the 70% WP are being proposed for seed treatment of barley, cotton, sorghum, and wheat. Detailed summaries of the proposed use directions for these EPs are presented in Table 2.

Table 1. Specimen labels provided by Novartis Crop Protection for the registration of food use thiamethoxam EPs.

Formulation	Product Name
25% DF	Actara™ 25 WG
2 lb/gal SC	Platinum™ 2SC Insecticide [a]
5 lb/gal FlC	Adage™ 5FS Insecticide
70% WP	Adage™ 70WS Insecticide

[a] This product appears to be equivalent to another product (Tracker™ 2SC) cited in the use directions on the Actara™ 25 WG Label.

General comments and conclusions.

Use directions on the 25% DF label for *Brassica* vegetables, cucurbit vegetables, fruiting vegetables, leafy vegetables, and tuberous & corm vegetables all include the following statement: "do not apply this product if crops have already been treated with Tracker™ 2SC." As no EP for Tracker™ 2SC was submitted, HED assumes that Tracker™ 2SC is an earlier name for the proposed 2 lb/gal FlC, Platinum™ 2SC. To clarify the situation, the petition should amend the 25% DF label directions for each of these crops to prohibit the application of the 25% DF to vegetable crops which previously received a soil application of thiamethoxam. In addition, maximum seasonal use rates specified for each crop on the Actara™ and Platinum™ labels should be expressed in terms of # thiamethoxam a.i./A/season.

As residue data for leafy vegetables and *Brassica* vegetables are not available, HED cannot at this time assess the adequacy of the proposed directions for these crops.

The proposed use directions for the 70% WP and 5 lb/gal FlC formulations as seed treatments on barley, cotton, grain sorghum, and wheat are adequate. With the exception of the deficiencies noted above, use directions on the 25% DF and 2 lb/gal FlC labels are also adequate for the following crops: cucurbit vegetables, fruiting vegetables, tuberous and corm vegetables, and tobacco.

In addition to the proposed uses, HED notes that the available residue data and proposed tolerances would also support i) a use on tuberous and corm vegetables of a combined at-planting soil application of thiamethoxam (2 lb/gal FlC) at ~0.13 lb ai/A followed by two late-season foliar applications of thiamethoxam (25% DF) at 0.02 lb ai/A/application; ii) a use on fruiting and cucurbit vegetables of a combined at-planting soil application of thiamethoxam (2 lb/gal FlC) at 0.13 lb ai/A with a single late-season foliar application of thiamethoxam (25% DF) at 0.04 lb ai/A; and iii) a use on tobacco of a single foliar application of thiamethoxam (25% DF) at 0.9 oz ai/A following a soil application of thiamethoxam (2 lb/gal FlC) at transplanting at 2 oz ai/A.

The use directions for cotton on both the proposed 2 lb/gal FlC and 25% DF labels should be amended. On the 2 lb/gal FlC label, the statement "Do not use Platinum 2SC if seed has been treated with Adage™ 5FS seed treatment" should be changed to read "Do not use Platinum 2SC if seeds were treated with thiamethoxam". On the 25% DF label, the statement "do not apply this product if crops have been treated with the last 45 days with Tracker™ 2SC or Adage™ 5FS seed treatment" should be changed to read "do not apply this product within 45 days of planting if cotton seed were treated with thiamethoxam".

The proposed use directions for pome fruit on the 25% DF label are not adequate as the current label specifies a minimum application volume of 5 gal/A for aerial applications to pome fruit; in the absense of aerial residue field trial data, the minimum aerial application volume for tree crops should be 10 gal/A.

Table 2. Proposed Use Patterns for Thiamethoxam EP Labels on Food/Feed Crops and Tobacco.

Site Application Type Application Timing Application Equipment	Formulation [Product Name]	Maximum Single Application Rate (ai) [a]	Maximum Number of Applications per season	Maximum Seasonal Rate, (ai)	PHI (days)	Use Directions and Limitations [b]
Food/Feed Crop Uses						
Barley						
Seed treatment	70% WP [Adage™ 70WS] 5 lb/gal FlC [Adage™ 5FS]	0.84 oz/100 lbs seed (0.05 lb/100 lbs seed)	Not applicable (NA)	Not specified (NS)	NS	Use of treated seed for feed, food, or oil purposes is prohibited.
***Brassica* (Cole) Leafy Vegetables**						
Soil treatment incorporated at planting Ground	2 lb/gal FlC [Platinum™ 2SC]	0.11 oz/1,000 linear ft (max = 0.123 lb/A)	1	2.0 oz/A (0.125 lb/A)	NS	Apply in sufficient water and incorporate into the soil using one of the following methods: (i) preplant soil band treatment; (ii) at plant in-furrow spray; (iii) postplant drench treatment; (iv) chemigation by trickle or drip irrigation.
Foliar treatment Ground or aerial	25% DF [Actara™ 25 WG]	0.75 oz/A (0.05 lb/A)	2	1.5 oz/A (0.09 lb/A)	7 or 0	Apply in a minimum of 10 gal/A by ground or 5 gal/A by air with a 7-day retreatment interval. A 0-day PHI is proposed for crops in the leafy *Brassica* crop subgroup and a 7-day PHI is proposed for other *Brassica* crops. Do not apply if the crop has been previously treated with Tracker™ 2SC [c].

(continued; footnotes follow)

Table 2. *Continued.*

Site Application Type Application Timing Application Equipment	Formulation [Product Name]	Maximum Single Application Rate (ai) [a]	Maximum Number of Applications per season	Maximum Seasonal Rate, (ai)	PHI (days)	Use Directions and Limitations [b]
Cotton						
Seed treatment	70% WP [Adage™ 70WS] 5 lb/gal FlC [Adage™ 5FS]	3.2 oz/100 lbs seed (0.2 lb/100 lbs seed)	NA	NS	NS	Use of treated seed for feed, food, or oil purposes is prohibited.
Soil treatment incorporated at planting Ground	2 lb/gal FlC [Platinum™ 2SC]	0.11 oz/1,000 linear ft (max = 0.123 lb/A)	1	2.0 oz/A (0.125 lb/A)	NS	Apply in sufficient water and incorporate into the soil as an at-planting in-furrow spray. Do not use on cotton grown from seed treated with Adage™ 5FS.
Foliar treatment Ground or aerial	25% DF [Actara™ 25 WG]	0.75 oz/A (0.05 lb/A)	2	1.5 oz/A (0.09 lb/A)	21	Do not apply to cotton within 45 days of a previous application of Tracker™ 2SC or Adage™ 5FS seed treatment. Apply in a minimum of 10 gal/A by ground or 5 gal/A by air with a 14-day retreatment interval.
Cucurbit Vegetables						
Soil treatment incorporated at planting Ground	2 lb/gal SC [Platinum™ 2SC]	0.16 oz/1,000 linear ft (max = 0.177 lb/A)	1	2.0 oz/A (0.125 lb/A)	NS	Apply in sufficient water and incorporate into the soil using one of the following methods: (i) preplant soil band treatment; (ii) at plant in-furrow spray; (iii) postplant drench treatment; (iv) chemigation by trickle or drip irrigation.
Foliar treatment Ground or aerial	25% DF [Actara™ 25 WG]	0.75 oz/A (0.05 lb/A)	2	1.5 oz/A (0.09 lb/A)	0	Apply in a minimum of 10 gal/A by ground or 5 gal/A by air with a 5-day retreatment interval. Do not apply if the crop has been previously treated with Tracker™ 2SC.

(continued; footnotes follow)

Table 2. *Continued.*

Site Application Type Application Timing Application Equipment	Formulation [Product Name]	Maximum Single Application Rate (ai) [a]	Maximum Number of Applications per season	Maximum Seasonal Rate, (ai)	PHI (days)	Use Directions and Limitations [b]
Fruiting Vegetables (Except Cucurbits)						
Soil treatment incorporated at planting Ground	2 lb/gal FlC [Platinum™ 2SC]	0.11 oz/1,000 linear ft (max = 0.123 lb/A)	1	2.0 oz/A (0.125 lb/A)	NS	Apply in sufficient water and incorporate into soil using one of the following methods: (i) preplant soil band treatment; (ii) at plant in-furrow spray; (iii) postplant drench treatment; (iv) chemigation by trickle or drip irrigation.
Foliar treatment Ground or aerial	25% DF [Actara™ 25 WG]	1.38 oz/A (0.09 lb/A)	2	2.75 oz/A (0.17 lb/A)	0	Apply in a minimum of 10 gal/A by ground or 5 gal/A by air with a 5-day minimum retreatment interval. Do not apply if the crop has been previously treated with Tracker™ 2SC.
Leafy Vegetables (Except *Brassica* Vegetables)						
Soil treatment incorporated at planting Ground	2 lb/gal FlC [Platinum™ 2SC]	0.11 oz/1,000 linear ft (max = 0.123 lb/A)	1	2.0 oz/A (0.125 lb/A)	NS	Apply in sufficient water and incorporate into the soil by using one of the following methods: (i) preplant soil band treatment; (ii) at plant in-furrow spray; (iii) postplant drench treatment; (iv) chemigation by trickle or drip irrigation.
Foliar treatment Ground or aerial	25% DF [Actara™ 25 WG]	0.75 oz/A (0.05 lb/A)	2	1.5 oz/A (0.09 lb/A)	7	Applications may be made in a minimum of 10 gal/A by ground or 5 gal/A by air with a 7-day retreatment interval. Do not apply if the crop has been previously treated with Tracker™ 2SC.

(continued; footnotes follow)

Table 2. *Continued.*

Site Application Type Application Timing Application Equipment	Formulation [Product Name]	Maximum Single Application Rate (ai) [a]	Maximum Number of Applications per season	Maximum Seasonal Rate, (ai)	PHI (days)	Use Directions and Limitations [b]
Pome Fruits						
Prebloom (except pear) Ground or aerial	25% DF [Actara™ 25 WG]	1.13 oz/A (0.07 lb/A)	1	2.75 oz/A (0.17 lb/A)	35 (14)	Only 1 prebloom application per season is allowed. Apply a maximum of 2 applications per season for application rates of >0.69 oz ai/A with a 35-day PHI, and a maximum of 3 applications per season for application rates of ≤0.69 oz ai/A with a 14-day PHI. A minimum RTI of 10 days is specified. Apply in a minimum of 50 gal/A using ground equipment and 5 gal/A using aerial equipment.
Postbloom Ground or aerial		1.38 oz/A (0.69 oz/A)	2 (3)			
Tuberous and Corm Vegetables Crop Subgroup						
Soil treatment incorporated at planting Ground	2 lb/gal FlC [Platinum™ 2SC]	0.11 oz/1,000 linear ft (max = 0.123 lb/A)	1	2.0 oz/A (0.125 lb/A)	NS	Apply in sufficient water and incorporate into the soil using one of the following methods: (i) at plant in-furrow spray; (ii) preplant or at plant impregnated fertilizer.
Foliar treatment Ground, chemigation, or aerial	25% DF [Actara™ 25 WG]	0.38 oz/A (0.02 lb/A)	2	0.75 oz/A (0.05 lb/A)	14	Apply in a minimum of 10 gal/A by ground or 5 gal/A by air with a 7-day retreatment interval. Do not apply if the crop has been previously treated with Tracker™ 2SC.
Sorghum						
Seed treatment	70% WP [Adage™ 70WS] 5 lb/gal FlC [Adage™ 5FS]	3.2 oz/100 lbs seed (0.2 lb/100 lbs seed)	NA	NS	NS	Use of treated seed for feed, food, or oil purposes is prohibited. Do not graze or feed livestock on treated areas for 45 days after planting.

(continued; footnotes follow)

Table 2. *Continued.*

Site Application Type Application Timing Application Equipment	Formulation [Product Name]	Maximum Single Application Rate (ai) [a]	Maximum Number of Applications per season	Maximum Seasonal Rate, (ai)	PHI (days)	Use Directions and Limitations [b]
Wheat						
Seed treatment	70% WP [Adage™ 70WS] 5 lb/gal FlC [Adage™ 5FS]	0.84 oz/100 lbs seed (0.05 lb/100 lbs seed)	NA	NS	NS	Use of treated seed for feed, food, or oil purposes is prohibited. Prohibits grazing and feeding of livestock within 42 days of planting
Non-Feed/Food Crop Uses						
Tobacco						
Foliar treatment or soil drench at transplanting Ground	2 lb/gal FlC [Platinum™ 2SC]	0.3 oz/1,000 plants	1	2.0 oz/A (0.125 lb/A)	NS	Apply in sufficient water using a tray treatment or at-planting drench treatment.
Foliar treatment Ground	25% DF [Actara™ 25 WG]	0.75 oz/A (0.05 lb/A)	1	0.75 oz/A (0.05 lb/A)	14	Apply in a minimum of 40 gal/A using ground equipment.

[a] For the in-row applications, the maximum application rate per acre is based upon a minimum row spacing of 30 inches.

[a] The following rotational crop restriction is proposed for the 25% DF (Actara™ 25 WG) and 2 lb/gal SC (Platinum™ 2SC): treated areas may be replanted immediately following harvest or as soon as practical following the last application with any crop listed on these labels or to sorghum, wheat, barley, and canola. For all other crops, a 120 day plant-back interval must be observed.

The following rotational crop restriction is proposed for the 5 lb/gal FlC (Actara™ 5FS) and the 70% WP (Adage™ 70WS): treated areas may be replanted immediately following harvest or as soon as practical following the last application with any crop listed on these labels or to cucurbit vegetables, fruiting vegetables, leafy vegetables, cole crops, tuberous and corm vegetables, pome fruit, and tobacco. For all other crops, a 120 day plant-back interval must be observed.

[c] Use directions on the 25% DF label for *Brassica* vegetables, cucurbit vegetables, fruiting vegetables, leafy vegetables, and tuberous & corm vegetables all state that the 25% DF formulation should not be applied to crops previously treated with "Tracker™ 2SC". HED assumes that Tracker™ 2SC is the same product as Platinum™ 2SC.

OPPTS GLN 860.1300: Nature of the Residue in Plants

Wheat

Novartis submitted data from a study investigating the metabolism of [^{14}C]thiamethoxam in wheat grown in thiamethoxam treated soil. The in-life phase of this study was conducted by Novartis' Human Safety Department (NHSD) in Greensboro, NC; determinations of TRR in wheat samples were conducted at Novartis' Vero Beach Research Center (VBRC), FL, and the analytical determinations were conducted by NHSD. Results of this study are presented in:

> 44703513 Ray, W. (1998) Study on Green House Grown Wheat After Soil Applications of Thiazole-^{14}C-CGA-293343: Lab Project Number: ABR-98039: 520-95: ANPHI-96012. Unpublished study prepared by Novartis Crop Protection, Inc. 142 p.

In the current petition, thiamethoxam is being proposed for use on wheat and barley as a seed treatment at a rate of 0.05 lb ai/100 lbs. of seed. Although the current wheat study was actually conducted to support other studies on the accumulation of [^{14}C]thiamethoxam in confined rotational crops (OPPTS GLN 860.1850), it can also be used to represent the metabolism of thiamethoxam in wheat as a primary crop, given the short soil aging interval used in the study and the proposed use as a seed treatment on wheat. In addition, the earlier confined rotational crop studies (reviewed under PP#9F5051) conclusively demonstrated that the metabolism of thiamethoxam is similar in primary and rotated crops.

[Thiazol-2-^{14}C]thiamethoxam (specific activity - 40.3 μCi/mg; 97.8% radiochemical purity) was dissolved in methanol (MeOH), diluted with water, and applied as a soil drench to pots of a sandy loam soil at a rate equivalent to 1,442 g ai/ha (1.28 lb ai/A). The soil was then aged in the greenhouse for 25 days prior to planting of the wheat. Samples of wheat forage were harvested at 25% and 50% crop maturity, 22 and 58 days after planting (DAP), and samples of straw and grain were harvested at maturity (97 DAP). Soil samples were also collected immediately following application, at planting 25 DAT, and at each crop sampling interval. After collection, samples were stored at ≤ -18 C for up to 3 days prior to shipment by overnight carrier on dry ice to VBRC where samples were stored frozen.

Total radioactive residues (TRR)

TRR determinations were conducted by VBRC. Plant samples were radioassayed within 14-50 days of harvest, and soil samples were radioassayed within 35-131 days of sampling. Samples were ground with dry ice and radioassayed in triplicate by liquid scintillation counting (LSC) following combustion. The limit of quantitation (LOQ) for the radioassay was 0.003 and 0.0003 ppm for plant and soil samples, respectively. After radioanalysis, plant and soil samples were shipped to the analytical laboratory (NHSD) on dry ice by overnight courier or by freezer truck (two soil samples).

Total radioactive residues in wheat RACs and soil are presented in Table 3. ^{14}C-Residues were highest in wheat straw (4.455 ppm) and lowest in grain (0.307 ppm). Although ^{14}C-residues in soil declined slightly between treatment and planting (25 DAT); the major decline in soil residues occurred after planting of the wheat crop.

Table 3. Total radioactive residues in wheat RACs harvested from plants grown in a sandy loam soil treated with a soil drench of [^{14}C]thiamethoxam at 1,422 g ai/A (1.28 lb ai/A).

Matrix	Sampling interval [a]		Total Radioactive Residues (ppm) [b]
	DAP	DAT	
Forage (25% maturity)	22	47	2.105
Forage (50% maturity)	58	83	2.081
Straw	97	122	4.455
Grain	97	122	0.307
Soil	NA	0	1.586
	NA	25	1.336
	NA	47	0.378
	NA	83	0.524
	NA	122	0.124

[a] Sampling intervals are expressed as both days after planting (DAP) of crop or days after soil treatment (DAT).

[b] Data are expressed in [^{14}C]thiamethoxam equivalents and are the average of triplicate analyses.

Storage stability

Prior to the initial extractions for analysis, samples of forage (50% mature), straw, and grain were stored frozen for 55-62 days and the sample of forage (25% mature) was stored frozen for 125 days. To demonstrate the stability of ^{14}C-residues in plant samples over the course of the study, the petitioner provided 2D-TLC chromatograms of extracts obtained from straw after ~2 and ~24 months of frozen storage. The metabolite profile was similar for the two extracts indicating that the ^{14}C-residues were stable under frozen storage. No additional storage stability data are required.

Extraction of residues

Radioactive residues were extracted repeatedly with MeOH:water (8:2, v/v) and filtered. Solvent extracted residues were concentrated and analyzed by 2D-TLC and HPLC. The initial solvent extractions released 76-85% of the TRR from forage and straw samples and 65% of the TRR from grain (Table 4). Post-extraction solids (PES) accounted for 15-17% of the TRR in forage, 23% of the TRR in straw, and 33% of the TRR in grain.

To further characterize ^{14}C-residues in PES fractions, the petitioner refluxed the straw PES fraction twice in MeOH:water (8:2, v/v; 6 hours each time) releasing an additional 12.5% of the TRR, and once in water/MeOH (8:2, v/v; 6 hr) releasing an additional 3.5% of the TRR. Solubilized ^{14}C-residues were analyzed by 2D-TLC. Following solvent reflux, 6.9% of the TRR remained in the residual solids of straw. The PES fractions from forage and grain were not further analyzed.

Table 4. Extraction of ^{14}C-residues in/on wheat forage, straw, and grain harvested from plants grown in a sandy loam soil treated with [^{14}C]thiamethoxam at 1,422 g ai/ha (1.28 lb ai/A).

Fraction	Forage 25% mature (2.105 ppm) [a]		Forage 50% mature (2.081ppm)		Straw (4.455 ppm)		Grain (0.307 ppm)	
	%TRR [b]	ppm [c]	% TRR	ppm	%TRR	ppm	% TRR	ppm
MeOH/water	85.3	1.796	75.8	1.577	80.1	3.568	64.8	0.199
MeOH/H_2O reflux	-- [d]	--	--	--	12.5	0.557	--	--
H_2O/MeOH reflux	--	--	--	--	3.5	0.156	--	--
Solids	14.9	0.314	17.0	0.354	6.9	0.307	32.8	0.101

[a] Sample TRR is listed in parentheses.
[b] %TRR values are not corrected for recoveries.
[c] Expressed in [^{14}C]thiamethoxam equivalents.
[d] -- = not applicable.

Characterization and identification of residues

Radioactive residues in extract fractions were initially analyzed and quantified by 2D-TLC using silica gel plates and a solvent system consisting of methylethyl ketone:acetonitrile (80:20, v:v) and ethyl acetate:isopropanol:water (65:23:12, v:v:v). ^{14}C-Residues were detected and quantified using a radioanalytic imaging system, and unlabeled reference compounds were detected using UV light. The initial solvent extracts were also analyzed by reverse phase HPLC using a linear gradient of 0.1% acetic acid to acetonitrile (ACN) with a UV (254 nm) detector and an in-line radioactivity detector. A total of 16 reference standards were used for comparison with ^{14}C-residues.

To confirm metabolite identities, individual metabolite fractions were isolated and purified from the wheat straw extract fraction (80.1% TRR) using combinations of C_{18} solid-phase extraction, preparative HPLC and TLC, and anion exchange chromatography. Isolated metabolites were identified by 2D-TLC and mass spectrometry (MS). Metabolites CGA-355190 and CGA-349208 were identified by cochromatography with reference standards, and the following metabolites were identified by TLC cochromatography and MS: thiamethoxam, CGA-322704, CGA-322704-hydroxylamine-glucoside, CGA-265307, CGA-353968, CGA-353968-*N*-glucoside, desmethyl-CGA-353968, NOA-407475, NOA-421275, CGA-349208-*O*-glucoside, and CGA-

359683. Residue components identified and characterized in wheat RACs are summarized in Table 5.

In the forage sampled at 25% crop maturity, thiamethoxam (53.0% TRR) and CGA-322704 (21.3% TRR) were the principal residues identified. By 50% crop maturity, levels of parent declined in forage to 16.3% of the TRR, while levels of CGA-322704 remained the same (23.1% TRR). The metabolite profile of the later forage sample was also more complex and included substantial amounts of CGA-265307 (9% TRR) and minor amounts (each ≤3.3% TRR) of CGA-322704-hydroxylamine-glucoside, CGA-355190, CGA-353968, and CGA-359683.

At crop maturity, the principal ^{14}C-residues in wheat straw included thiamethoxam (14.3% TRR), CGA-322704 (22.1% TRR), CGA-265307 (13.8% TRR), and CGA-359683 (8.7% TRR). Minor amounts of the following metabolites were also identified in straw: CGA-322704-hydroxylamine-glucoside (5.8% TRR), CGA-355190 (0.6% TRR), CGA-353968 (3.4% TRR), CGA-353968-*N*-glucoside (4.2% TRR), desmethyl-CGA-353968 (3.6% TRR), NOA-407475 (2.1% TRR), NOA-421275 (2.2% TRR), CGA-349208 (0.3% TRR), and CGA-349208-*O*-glucoside (4.0% TRR). In grain, CGA-265307 (26.8% TRR) was the principal residue identified along with minor amounts of thiamethoxam (4.3% TRR) and CGA-322704 (7.5% TRR).

Conclusions: The wheat metabolism study is adequate. In straw, ~92% of the TRR was adequately identified or characterized; and in forage, 76-85% of the TRR was adequately identified or characterized. Although 15-17% of the TRR (0.31-0.35 ppm) in forage remained unextracted, extraction and analysis of the related straw PES fraction identified no major metabolite fractions. A lower degree of identification/characterization was also achieved for residues in wheat grain (65% TRR), with 33% of the TRR remaining unextracted. However, data from the rice metabolism study discussed below and a previous corn metabolism study and confined rotational crop study (both reviewed under PP#9F5051) indicate that a substantial portion of the TRR in grains (>10%) is incorporated in natural plant products. Therefore, no additional analysis of wheat grain is required.

Table 5. Summary of radioactive residues characterized/identified in forage, straw, and grain from wheat grown in a sandy loam soil treated with [thiazol-2-^{14}C]thiamethoxam at 1,422 g ai/ha (1.28 lb ai/A) and aged for 25 days prior to planting.

Fraction	Forage at 25% maturity (TRR = 2.105 ppm)		Forage at 50% maturity (TRR = 2.081 ppm)		Straw (TRR = 4.455 ppm)		Grain (TRR = 0.307 ppm)	
	% TRR	ppm [a]	% TRR	ppm	% TRR	ppm	% TRR	ppm
Thiamethoxam	53.0	1.117	16.3	0.339	14.3	0.639	4.3	0.013
CGA-322704	21.3	0.449	23.1	0.481	22.1	0.987	7.5	0.023
CGA-322704-OH-amine-glucoside	-- [b]	--	2.7	0.057	5.8	0.257	--	--
CGA-355190	--	--	2.0	0.041	0.6	0.026	--	--
CGA-353968	3.2	0.068	3.3	0.069	3.4	0.151	--	--
CGA-353968-*N*-glucoside [c]	--	--	--	--	4.2	0.186	--	--
Desmethyl-CGA-353968	--	--	--	--	3.6	0.159	--	--
CGA-265307	1.5	0.032	9.0	0.188	13.8	0.616	26.8	0.082
NOA-407475 [c]	--	--	--	--	2.1	0.096	--	--
NOA-421275 [c]	--	--	--	--	2.2	0.100	--	--
CGA-349208	--	--	--	--	0.3	0.013	--	--
CGA-349208-*O*-glucoside [c]	--	--	--	--	4.0	0.182	--	--
CGA-359683	--	--	2.6	0.055	8.7	0.388	--	--
Total identified	**79.0**	**1.666**	**59.0**	**1.23**	**85.1**	**3.8**	**38.6**	**0.118**
Polar Unknown W12 [c]	--	--	--	--	2.2	0.097	--	--
Polar Cluster I [d]	6.0	0.128	10.8	0.226	4.2 [f]	0.190	22.5	0.069
Polar Cluster II [e]	--	--	5.8	0.121	0.4 [f]	0.018	3.7	0.011
Total identified or characterized	**85.0**	**1.794**	**75.6**	**1.577**	**91.9**	**4.105**	**64.8**	**0.198**
Nonextractable [g]	14.9	0.314	17.0	0.354	6.9	0.307	32.8	0.101

[a] Expressed in [^{14}C]thiamethoxam equivalents.

[b] -- = not detected.

[c] These metabolites were identified only in polar clusters I and II isolated from the initial wheat straw extract (80.1% TRR).

[d] Analysis of polar cluster I (13.1% TRR) isolated from the wheat straw solvent extract detected minor amounts (each≤3.8% TRR) of CGA-322704, CGA-265307, NOA-407475, NOA-421275, Unknown W12, CGA-353968-*N*-glucoside, and CGA-349208-*O*-glucoside.

[e] Analysis of polar cluster II (8.0% TRR) isolated from the wheat straw solvent extract detected minor amounts (each≤3% TRR) of NOA-407475, Unknown W12, CGA-353968-*N*-glucoside, and CGA-349208-*O*-glucoside.

[f] Isolated from further extractions of wheat straw PES (22.9% TRR).

[g] Analysis from MeOH/H_2O and H_2O/MeOH reflux extracts from wheat straw PES detected minor amounts (each<5% TRR) of thiamethoxam, CGA-322704, CGA-355190, CGA-353968, desmethyl-CGA-353968, CGA-265207, CGA-349208, CGA-356983, and polar clusters I and II.

Rice.

Although no uses for thiamethoxam have been proposed for rice, Novartis has submitted data pertaining to the metabolism of [^{14}C]thiamethoxam in rice following either a single early-season granular application or two mid- to late-season foliar applications. For each method of application, the petitioner conducted separate studies using [thiazol-2-^{14}C] and [oxadiazin-4-^{14}C]labeled thiamethoxam. The in-life and analytical phases of these experiments were conducted by Novartis at their research facilities in St. Aubin and Basel, Switzerland. Results from these studies are reported in:

44703514 Krauss, J. (1997) Metabolism of CGA-293343 in Greenhouse Grown Paddy Rice after Foliar Application of (Oxadiazin-4-^{14}C) Labelled Material: Lab Project Number: CMR 14/97: 769-97. Unpublished study prepared by Novartis Crop Protection AG. 64 p.

44703517 Krauss, J. (1997) Metabolism of CGA-293343 in Greenhouse Grown Paddy Rice After Foliar Application of (Thiazol-2-^{14}C) Labelled Material: Lab Project Number: CMR 11/97: 768-97. Unpublished study prepared by Novartis Crop Protection AG. 67 p.

44703518 Krauss, J. (1997) Behavior and Metabolism of CGA-293343 in Greenhouse Grown Paddy Rice After Granular Application of (Oxadiazin-4-^{14}C) Labelled Material: Lab Project Number: CMR 21/97: 767-97. Unpublished study prepared by Novartis Crop Protection AG. 91 p.

44703519 Krauss, J. (1997) Behavior and Metabolism of CGA-293343 in Greenhouse Grown Paddy Rice After Granular Application of (Thiazol-2-^{14}C) Labelled Material: Lab Project Number: CMR 5/97: 739-98R. Unpublished study prepared by Novartis Crop Protection AG. 96 p.

Both test substances were formulated as a 2% G for the granular application and as a 25% WP for the foliar applications. The 2% G formulations of [thiazol-2-^{14}C] and [oxadiazin-4-^{14}C] thiamethoxam had a final specific activity of 60.0 and 54.0 μCi/mg, respectively, and radiochemical purities of ≥97%. The 25% WP formulations of [thiazol-2-^{14}C] and [oxadiazin-4-^{14}C] thiamethoxam had a final specific activity of 54.0 and 58.9 μCi/mg, respectively, and radiochemical purities of ≥95%.

Granular Application. Each granular test substance was applied once to rice seedlings (2-3 leaf stage, 21 DAP) growing in seedling boxes in growth chambers at a rate of 1.5 g ai/seedling box. Based on the number of seedling boxes used to plant a given area with rice, this rate is equivalent to a field rate of 300 g ai/ha or 0.267 lb ai/A. Twenty-four hours after application, the rice seedlings, including the soil, were transplanted into larger containers and a 3-5 cm flood of water was added and maintained until one week prior to harvest. Samples of rice foliage were collected 1, 34, and 71 days posttreatment. Whole plants were harvested at maturity (126 or 127 DAT) and separated into grain, husks and straw. Grain and husk samples were immediately

frozen and straw samples were dried at room temperature for ~1 week. Samples of paddy water were also collected at 1-4 days intervals until 24 DAT, and at 34 and 71 DAT. A soil sample was also collected at the final harvest (~127 DAT). All samples were stored at the analytical laboratory at ≤-18 C.

Foliar Applications. Each 25% WP formulation was applied twice foliarly at 25 g ai/ha/application to flooded rice plants growing in growth chambers, for a total of 50 g ai/ha (0.045 lb ai/A). The two applications were made at ~48 and ~98 days after transplanting (70 and 120 DAP), with the second application occurring 21 days prior to harvest. Samples of rice foliage were collected 1 hour following each application, along with samples of paddy water. Whole plants were harvested at maturity, 21 days following the second application (~140 DAP) and separated into grain, husks and straw. Grain and husk samples were immediately frozen and straw samples were dried at room temperature for ~1 week. A soil sample was also collected at the final harvest. All samples were stored at the analytical laboratory at ≤-18 C.

Total radioactive residues (TRR)

TRRs in plant and soil samples were determined in triplicate by LSC following combustion, with the exception of the initial foliage sample from the granular treatment, in which the TRR was calculated as the sum of extracted and non-extracted radioactivity determined by LSC and combustion/LSC, respectively. Radioactivity in water samples was determined directly by LSC. The LOQs for the radioassays were not given.

The TRRs in rice, water, and soil samples are presented in Table 6. ^{14}C-Residues resulting from the application of the two ^{14}C-labels were similar. With the exception of husks, the granular application resulted in higher ^{14}C-residues in rice than the two foliar applications.

For the granular treatment, ^{14}C-residues in immature foliage were highest the day following application (24-32 ppm) and declined steadily at subsequent sampling intervals. Analysis of immature leaf extracts indicated that thiamethoxam accounted for 84-94% of the TRR in leaves the day after application, declining to 25-42% TRR by 34 DAT and 15-20% TRR by 71 DAT. At maturity, ^{14}C-residues were highest in the straw (2.83-2.99 ppm), followed by husks (0.53-0.67 ppm) and grain (0.18-0.23 ppm). Radioactivity in paddy water accounted for ~13% of the applied dose within 2 days of application and plateaued at ~20% of the applied dose by 6 DAT. Radioactivity in the water remained at ~20% of the dose for 3 days for the [thiazol-^{14}C]label and 10 days for the [oxadiazin-^{14}C]label before declining steadily. At harvest, ^{14}C-residues in soil were 0.12-0.15 ppm.

For the foliar applications, ^{14}C-residues were 0.20-0.30 ppm in/on immature leaves 1 hour following the first application and 0.19-0.44 ppm 1 hour following the second application. After both applications, parent accounted for 88-95% of the TRR in/on leaves. At maturity, ^{14}C-residues were highest in both straw (1.01-1.08 ppm) and husks (0.96-1.16 ppm) and lowest in grain (0.03-0.05 ppm). ^{14}C-Residues were ≤0.003 ppm in soil at harvest, considerably less than

from the granular application.

Table 6. Total radioactive residues in/on rice following application of [^{14}C]thiamethoxam as either a single granular application equivalent to 300 g ai/ha or two foliar applications each at 25 g ai/ha (50 g ai/ha/season) [a].

Matrix	Sampling interval (days) [b]	Total radioactive residues (ppm) [c]	
		[Thiazol-^{14}C]	[Oxadiazin-^{14}C]
Granular application			
Leaves	1	24.077	32.132
	34	1.379	1.202
	71	0.645	0.298
Grain	~126	0.176	0.233
Husks	~126	0.665	0.526
Straw	~126	2.989	2.830
Paddy water	34	0.004	0.029
	71	0.001	0.001
Soil	~126	0.145	0.124
Foliar applications			
Leaves	0	0.299	0.204
	50/0	0.438	0.187
Grain	71/21	0.050	0.026
Husks	71/21	1.159	0.960
Straw	71/21	1.007	1.075
Paddy water	0	0.014	0.034
	50/0	0.010	0.005
Soil	71/21	0.003	0.002

[a] The application rate for the 2% G formulation is equivalent to 0.267 lb ai/A, and the total application rate for the 25% WP formulation used for the foliar applications is 0.045 lb ai/A.

[b] Days after application. For the foliar application, sample intervals are given for both the days after the 1st and 2nd applications.

[c] Data are expressed in [^{14}C]thiamethoxam equivalents and are the average of triplicate analyses.

Storage stability data

Granular application study. Prior to extraction, immature foliage samples were stored at ≤-18 C for 1-7 months and samples of grain, husks, and straw were stored at ≤-18 C for ~1 month. Sample extracts were initially analyzed within 10 days of extraction. To demonstrate the stability of ^{14}C-residues, samples of [thiazol-^{14}C]labeled grain and straw, which were initially extracted and analyzed within ~1 month, were reextracted after ~11 months of frozen storage and again

analyzed by 2D-TLC. A sample of [oxadiazin-^{14}C]labeled grain, which was initially extracted after ~1 month, was also reextracted and analyzed after 6 months of storage; and a sample extract from [oxadiazin-^{14}C]labeled straw was reanalyzed after an additional 4 months of storage. Both the TLC chromatograms and the quantitative data indicate that ^{14}C-residues in extracts were stable over the course of the study.

Foliar application study. Prior to extraction, immature foliage samples were stored at ≤-18 C for 7-9 months and grain, husk, and straw samples were stored ≤-18 C for 2-4 months. All extracts were initially analyzed within 9 days of extraction. Although no data were provided on the stability of ^{14}C-residue in whole samples, the petition provided data on the stability of ^{14}C-residues in sample extracts. Sample extracts from grain and straw, which were obtained within 2-4 months of harvest, were analyzed by 2D-TLC within one day of extraction and again after 7-9 months of frozen storage. Both the TLC chromatograms and the quantitative data indicate that ^{14}C-residues in extracts were stable.

Sufficient data have been provided to indicate that ^{14}C-residues are stable in rice samples and extracts over the course of these studies; no additional storage stability data are required.

Extraction and hydrolysis of residues

Extraction and characterization of ^{14}C-residues were conducted at the petitioner's analytical laboratory in Basel, Switzerland. In each study, ^{14}C-residues were extracted repeatedly with ACN:water (8:2, v:v), filtered, and combined; and the extracts were analyzed by 2D-TLC. Residual solids from grain, straw and husks were then microwave extracted with ACN:water (8:2, v:v) for 5 min at 90 C, 10 min at 100 C, and 10 min at 130 C. Microwave extracts from straw and husk samples were analyzed by 2D-TLC.

For both foliar application studies, the initial cold solvent extractions released 94-103% of the TRR from immature foliage samples, and 88-95% of the TRR in these extracts was identified by 2D-TLC as parent. The distribution of ^{14}C-residues was similar between the two ^{14}C-labels and between straw and husk samples (Table 7). The initial ACN:water extraction released 80-88% of the TRR from straw and husk samples, and the subsequent microwave extraction released an additional 2-7% of the TRR. For grain, the initial extraction released 14-36% of the TRR, and microwave extraction released an additional 0.2-0.4% of the TRR. Following microwave extraction, 6-15% of the TRR remained in the residual solids from straw and husks, and 63-91% of the TRR remained in grain solids. Further characterization of non-solvent extractable ^{14}C-residues was conducted using samples from the granular application studies.

Table 7. Solvent extraction of ^{14}C-residues in/on straw, husks and grain of rice harvested 21 days following the second of two foliar applications of [^{14}C]thimethoxam (25% WP) totaling 50 g ai/ha (0.045 lb ai/A).

[Thiazol-^{14}C]thiamethoxam						
Fraction	Straw (1.007 ppm) [a]		Husks (1.159 ppm)		Grain (0.050 ppm)	
	%TRR [b]	ppm [c]	%TRR	ppm	% TRR	ppm
ACN/water	79.9 [d]	0.805	88.0 [d]	1.020	13.9 [d]	0.007
ACN/H_2O microwave	7.3 [d]	0.074	2.2 [d]	0.025	0.2	<0.001
Solids	14.5	0.146	7.5	0.087	91.4	0.046
[Oxadiazin-^{14}C]thiamethoxam						
Fraction	Straw (1.075 ppm)		Husks (0.960 ppm)		Grain (0.026 ppm)	
	%TRR [a]	ppm [b]	%TRR	ppm	% TRR	ppm
ACN/water	82.3 [d]	0.885	86.2 [d]	0.828	36.1[d]	0.009
ACN/H_2O microwave	4.3 [d]	0.046	1.6 [d]	0.015	0.4	<0.001
Solids	6.0	0.065	6.1	0.059	62.5	0.016

[a] Sample TRR is listed in parentheses.
[b] %TRR values are not corrected for recoveries.
[c] Expressed in [^{14}C]thiamethoxam equivalents.
[d] Indicates solvent fractions analyzed by 2D-TLC.

The distribution of ^{14}C-residues in a given matrix was also similar between the two ^{14}C-labels for the early-season granular application. Solvent extraction released 98-99% of the TRR from immature foliage samples harvested the day after application, of which parent accounted 84-94% TRR. By 71 days post-treatment, solvent extraction released 64-75% of the TRR from leaves, of which 15-20% of the TRR was identified as parent.

As in the foliar applications, the distribution of ^{14}C-residues was similar for the straw and husk samples (Table 8). Solvent extraction released 49-77% of the TRR from straw and husk samples, and the subsequent microwave extraction released an additional 3-8% of the TRR. Residual solids accounted for 21-27% of the TRR in straw and 34-45% of the TRR in husks. To further characterize ^{14}C-residues straw and husk samples, residual solids were extracted overnight in boiling water, releasing an additional 6-10% of the TRR that was also analyzed by 2D-TLC. The remaining solids were then extracted by refluxing in 10% NaOH for 16 hours and hot filtered. Alkaline hydrolysis released 11-16% of the TRR from straw and 19-23% of the TRR from husks. The residual solids were characterized as a consisting of cellulose and accounted for 2-3% TRR in straw and 7-12% TRR in husks. The base hydrolysate was acidified with concn. HCl to pH 1 and cooled to precipitate lignins (0.5-0.6% TRR in straw; and 3-8% TRR in husks). The acidic aqueous fraction was then partitioned with DCM, and the resulting DCM fractions (0.3-1.0% TRR) were analyzed by 2D-TLC. The remaining aqueous phase was then concentrated and precipitated with EtOH resulting in an aqueous fraction that was analyzed by 2D-TLC, and an EtOH precipitate and a water-soluble precipitate (straw only) fraction which

were not analyzed further.

Solvent extraction released only 7-8% of the TRR in rice grain from the early-season granular applications, and microwave extraction released only an additional ~1% of the TRR (Table 9). To further characterize radioactivity in grain, the residual solids were hydrolyzed twice with 0.05 N NaOH (16 hr) and centrifuged, releasing an additional 17-18% TRR. The basic extract was neutralized (pH 5.5) with HCl and centrifuged to precipitate proteins (10-11% TRR), and the aqueous fraction (6% TRR) was acidified to pH 1 and partitioned with DCM (≤0.1% TRR). The remaining aqueous phase (5% TRR) was analyzed by high voltage electrophoresis (HVE) and by 2D-TLC before and after incubation with pepsin.

The grain solids remaining following mild base hydrolysis (69-71% TRR) were hydrolyzed by refluxing in 1N HCl for 17 hours. Acid hydrolysis solubilized 67-72% of the TRR, and the remaining solids accounted for 3-5% of the TRR and were characterized as cellulose. An aliquot of each acid hydrolysate was neutralized and derivatized by refluxing with phenylhydrazine-hydrochloride, cooled, and filtered. The resulting glucosazone (38-43% TRR) was filtered and radioassayed by combustion/LSC. Another aliquot of the 1N acid hydrolysate was further hydrolyzed with 6N HCl (100 C, 15 hr) and centrifuged; the resulting 6N hydrolysate (48-55% TRR) was then analyzed by 2D-TLC. A third aliquot of the 1N acid hydrolysate was fractionated using an anion exchange column eluted sequentially with water, 0.5N HCl:MeOH (1:1, v/v), and 1N HCl:MeOH (1:1, v/v), and the resulting fractions were analyzed by 2D-TLC with or without acetylation and/or methylation. The elutant fractions from the [thiazol-^{14}C]solids were also analyzed by HVE.

Table 8. Fractionation of ^{14}C-residues in/on rice straw and husks harvested ~4 months following a single application of [^{14}C]thiamethoxam (2% G) at 300 g ai/ha (0.267 lb ai/A).

Fraction	[Thiazol-^{14}C]				[Oxadiazin-^{14}C]			
	Straw (2.989 ppm)		Husks (0.665 ppm)		Straw (2.830 ppm)		Husks (0.526 ppm)	
	%TRR [a]	ppm [b]	%TRR	ppm	%TRR	ppm	%TRR	ppm
ACN/water [c]	63.4	1.895	64.5	0.429	76.7	2.171	48.8	0.257
ACN/water microwave extract [c]	7.8	0.233	4.7	0.031	7.5	0.212	3.4	0.018
Solids	27.0	0.807	33.6	0.223	20.6	0.583	44.5	0.234
Boiling H_2O [d]	9.7	0.290	5.5	0.037	6.2	0.175	7.0	0.037
Solids	17.9	0.535	24.7	0.164	13.3	0.376	35.7	0.188
10% NaOH reflux	15.5	0.463	18.5	0.123	10.7	0.303	23.1	0.122
Acidic precipitate (lignin)	0.5	0.015	2.9	0.019	0.6	0.017	7.8	0.041
Acidic aqueous fraction	8.6	0.257	10.3	0.068	4.3	0.122	11.2	0.059
DCM [e]	0.3	0.009	0.4	0.003	0.3	0.008	1.0	0.005
Aqueous	7.8	0.233	9.6	0.064	4.2	0.119	10.2	0.054
Aqueous supernatant [f]	5.5	0.164	5.6	0.037	2.3	0.065	6.7	0.035
EtOH precipitate	0.1	0.003	0.8	0.005	1.3	0.037	3.1	0.016
water-soluble ppt.	1.7	0.051	2.4	0.016	NA	--	NA	--
Solids (cellulose)	1.5	0.045	6.6	0.044	2.8	0.079	11.8	0.062

[a] %TRR values are not corrected for recoveries.
[b] Expressed as [^{14}C]thiamethoxam equivalents.
[c] Fractions analyzed by 2D-TLC and contain the majority of identified ^{14}C-residues.
[d] Fraction contained minor amounts of parent (0.2-1.0% TRR) and other metabolites (each at ≤0.7% TRR); majority of radioactivity in fraction was characterized as being incorporated into polysaccharides/oligosaccharides (3.4-5.5% TRR).
[e] 2D-TLC analysis did not identify any metabolites.
[f] Polar fraction was separated into 2-5 diffuse unknowns by 2D-TLC analysis.

Table 9. Fractionation of ^{14}C-residues in/on rice grain harvested ~4 months following a single application of [^{14}C]thiamethoxam (2% G) at 300 g ai/ha (0.267 lb ai/A).

Fraction	[Thiazol-^{14}C] Grain (0.176 ppm) [a]		[Oxadiazin-^{14}C] Grain (0.233 ppm)	
	%TRR [b]	ppm [c]	%TRR	ppm
ACN/water [d]	8.2	0.014	6.5	0.015
ACN/water microwave	1.3	0.002	1.1	0.003
Solids	86.9	0.153	87.8	0.205
0.05N NaOH	18.3	0.032	16.7	0039
Acidic precipitate (proteins)	11.4	0.020	10.2	0.024
Acidic aqueous	6.2	0.011	5.6	0.013
DCM	0.1	<0.001	<0.1	<0.001
Aqueous [d, e]	4.9	0.009	5.3	0.012
Solids	68.5	0.121	71.1	0.166
1N HCl hydrolysate	67.0	0.118	71.5	0.167
Fraction I - sugar derivation Glucosazone (starch)	38.2	0.067	42.6	0.099
Filtrate	27.0	0.048	27.4	0.064
Fraction II - anion exchange H_2O eluate [f]	34.2	0.060	46.8	0.109
MeOH/0.5N HCl eluate [f]	6.0	0.011	6.4	0.015
MeOH/1N HCl eluate [f]	21.2	0.037	18.2	0.042
Fraction III - 6N HCl hydrolysis Hydrolysate [f]	48.0	0.84	55.2	0.129
Residual solids	14.3	0.025	12.4	0.029
Solids (cellulose)	3.3	0.006	4.8	0.011

[a] Sample TRR values in parentheses.
[b] %TRR values are not corrected for recoveries.
[c] Expressed as [^{14}C]thiamethoxam equivalents.
[d] Fractions analyzed by 2D-TLC.
[e] Characterized by petitioner as consisting of water soluble polysaccharides.
[f] No parent or metabolites were identified in these fractions by 2D-TLC analysis with or without acetylation or methylation. Radioactivity remained at the origin or formed diffuse spots.

Characterization and identification of residues

Radioactive residues in solvent extracts and aqueous fractions were analyzed and quantified by 2D-TLC using silica gel plates with tetrahydrofuran:MeOH:formic acid:H_2O (60:35:1:4) and chloroform:MeOH:formic acid:H_2O (75:20:4:2). ^{14}C-Residues were detected using a radioanalytic imaging system and quantified by LSC. Reference compounds were detected using UV light. To confirm metabolites identities, metabolite fractions isolated by normal phase 2D-TLC were analyzed by reserve-phase 1D-TLC with reference standards. A total of 19 reference standards were used for comparison, including three (NOA-407475, NOA-421276, desmethyl-CGA-353968) which were isolated from a previous corn metabolism study and identified by MS. The characterization and identification of ^{14}C-residues in rice RACs following a granular application or two foliar applications with [^{14}C]thiamethoxam are summarized in Tables 10 and 11, respectively.

With the exception of minor oxadiazine- or thiazole-ring specific metabolites, the metabolic profile of ^{14}C-residues in rice RACs was qualitatively and quantitatively similar for the two ^{14}C-labels. The day following a granular application of [^{14}C]thiamethoxam at ~300 g ai/ha, radioactivity in leaves consisted almost entirely of parent (84-94% TRR). Both the relative and absolute levels of parent declined in immature foliage at subsequent sampling interval, accounting for 25-42% TRR by 34 DAT and 15-20% TRR by 71 DAT. At maturity (~126 DAT), the metabolic profile was similar for straw and husks. Parent (7-28% TRR) and CGA-322704 (7-17% TRR) were the principal ^{14}C-residues identified in straw and husks, followed by NOA-407475 (1-6% TRR). Minor amounts (0.2-4.5% TRR) of the metabolites CGA-265307, CGA-355190, CGA-353968, and desmethyl-CGA-353968 were also detected in straw and husks from both ^{14}C-labels. Thiazole-ring specific metabolites identified in straw and husks included NOA-421275 and NOA-404617 at 0.1-1.6% TRR. Oxadiazine-ring specific metabolites identified in straw and husks included NOA-405217, N-methyl-urea, and N-nitro-guanidine at 0.8-4.4% TRR. In rice grain, only 3.5-4.8% of the TRR was identified as specific [^{14}C]thiamethoxam metabolites. The metabolite CGA-322704 accounted for 1.1-2.3% TRR in grain; other compounds detected in grain at <1% TRR included: thiamethoxam, CGA-265307, CGA-353968, desmethyl-CGA-353968, and NOA-407475.

In addition to the specific metabolites indicated above, the petitioner also demonstrated that substantial amounts of the TRR in rice straw, husks, and grains were incorporated into natural plant products. Radioactivity associated with lignins, cellulose, and polysaccharide fractions accounted for 7-8% TRR in straw and 14-25% TRR in husks. In grain, 38-43% of the TRR was identified as being incorporated into starch, and 10-11% of the TRR was associated with an isolated protein fraction.

As with the granular application, the metabolic profile resulting from the foliar application of the two ^{14}C-labels was similar qualitatively and quantitatively; no thiazole- or oxadiazine-ring specific metabolites were identified. The metabolic profile was again similar between straw and husks. In addition, the metabolite profile was similar to the profile from the granular application,

although there were quantitative differences in the metabolite levels.

Immediately (1 hour) following each foliar application of [^{14}C]thiamethoxam at 25 g ai/ha (50 g ai/ha total), radioactivity in leaves consisted almost entirely of parent (88-95% TRR). At maturity, 21 days following the second application, the principal ^{14}C-residues identified in straw and husks were thiamethoxam (50-71% TRR) and CGA-322704 (4-11% TRR). Other metabolites identified in straw and husks included: CGA-265307 (≤5.2% TRR), CGA-355190 (≤4.4% TRR), CGA-353968 (≤1.8% TRR), desmethyl-CGA-353968 (≤0.4% TRR), and NOA-407475 (≤4% TRR). ^{14}C-Residues in rice grain were comparatively low (≤0.05 ppm) following the foliar applications. As in straw and husks, the two major ^{14}C-residues in grain were thiamethoxam (5-13% TRR) and CGA-322704 (4-11% TRR). Other metabolites identified in grain included: CGA-265307 (≤0.5% TRR), CGA-355190 (≤0.7% TRR), CGA-353968 (≤2.6% TRR), and NOA-407475 (≤0.3% TRR).

In addition to the analysis of plant samples, the petitioner provided data from the analysis of paddy water sampled the day after foliar application or 34 and 71 days after a granular application. Immediately following the foliar applications, ^{14}C-residues in paddy water consisted almost entirely of parent (84-98% TRR). Following granular application, ^{14}C-residues detected in paddy water by 34 DAT included: parent (27-40% TRR), CGA-355190 (21-26% TRR), CGA-322704/CGA-353968 (10-14% TRR), NOA-407475 (2-3% TRR), and NOA-404617 (9% TRR). By 71 DAT, ^{14}C-residues in paddy water included: parent (33% TRR), CGA-355190 (4% TRR), CGA-322704/CGA-353968 (9% TRR), and NOA-407475 (15% TRR).

The petitioner also provided data from the analysis of soil sampled at harvest from the granular application (140 DAT). The principal ^{14}C-residues identified in soil for both ^{14}C-labels included parent (8.7-10.0% TRR) and NOA-407475 (8.8-12.7% TRR). Other metabolites detected in paddy soil at <2% TRR included: CGA-322704, CGA-265307, CGA-355190, CGA-353968, and NOA-421275.

Conclusions: The available rice metabolism data are adequate. For the granular applications, 90-99% of the TRR in straw, husks, and grain was adequately identified and/or characterized. For the foliar application, 88-91% of the TRR in straw and husks, and 14-37% of the TRR in grain was adequately identified and/or characterized. The metabolic profile of ^{14}C-residues in rice RACs was qualitatively and quantitatively similar for the two ^{14}C-labels, with the exception of minor oxadiazine- or thiazole-ring specific metabolites. The metabolite profile was also similar between the early-season granular application and the later season foliar applications, although individual metabolite levels differed and more of the minor metabolites were identified in RACs from the granular treatment due to higher levels of ^{14}C-residues.

Table 10. Summary of the characterization/identification of ^{14}C-residues in rice straw, husks, and grain harvested at maturity following application to seedling rice of [^{14}C]thiamethoxam (2% G) at 300 g ai/ha (0.267 lb ai/A).

	[Thiazol -^{14}C]Thiamethoxam						[Oxadiazin-^{14}C]Thiamethoxam					
	Straw (2.989 ppm)		Husks (0.665 ppm)		Grain (0.176 ppm)		Straw (2.830 ppm)		Husks (0.526 ppm)		Grain (0.233 ppm)	
Metabolite/ fraction	%TRR [a]	ppm [b]	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Thiamethoxam	18.3	0.546	21.9	0.145	0.4	<0.001	28.0	0.792	7.0	0.037	--	--
CGA-322704	6.5	0.194	13.5	0.090	2.3	0.004	8.0	0.226	16.9	0.089	1.1	0.003
CGA-265307	2.9	0.087	1.1	0.007	0.2	<0.001	3.3	0.093	0.2	0.001	0.1	<0.001
CGA-355190	2.7	0.081	1.7	0.011	-- [c]	--	4.5	0.127	1.0	0.005	--	
CGA-353968	3.3	0.099	2.5	0.017	0.9	0.002	3.8	0.108	2.6	0.014	0.4	0.001
Desmethyl-CGA-353968	1.7	0.051	1.8	0.012	0.4	<0.001	2.3	0.065	1.1	0.006	0.2	<0.001
NOA-407475	4.3	0.129	1.4	0.009	0.3	<0.001	6.1	0.173	3.2	0.017	0.3	<0.001
NOA-421275	0.1	0.003	0.2	0.001	--	--	--	--	--	--	--	--
NOA-404617	1.6	0.048	0.1	<0.001	--	--	--	--	--	--	--	--
N-methyl-urea	--	--	--	--	--	--	4.2	0.119	4.4	0.023	1.4	0.003
N-nitro-guanidine	--	--	--	--	--	--	0.8	0.023	--	--	--	--
NOA-405217	--	--	--	--	--	--	2.5	0.071	--	--	--	--
CGA-359683	--	--	--	--	0.3	<0.001	--	--	--	--	--	--
Total identified	**41.4**	**1.238**	**44.2**	**0.293**	**4.8**	**0.008**	**63.5**	**1.797**	**36.4**	**0.192**	**3.5**	**0.008**
TLC unknown(s) [d]	13.5	0.403	11.7	0.078	2.0	0.004	13.1	0.371	3.4	0.018	0.2	<0.001
Unresolved ^{14}C-residue [e]	19.7	0.589	14.5	0.096	1.5	0.003	11.0	0.311	19.2	0.103	2.6	0.006
Natural products												
starch/glucose	--	--	--	--	38.2	0.067	--	--	--	--	42.6	0.099
proteins	--	--	--	--	11.4	0.020	--	--	--	--	10.2	0.024
lignins	0.5	0.015	2.9	0.019	--	--	0.6	0.017	7.8	0.041	--	--
cellulose	1.5	0.045	6.6	0.044	3.3	0.006	2.8	0.079	11.8	0.062	4.8	0.011
polysaccharides	5.5	0.164	4.4	0.029	--	--	3.4	0.096	5.2	0.027	--	--
Aqueous ^{14}C-residues	7.8	0.233	9.6	0.064	31.9	0.056	4.2	0.119	10.2	0.054	32.7	0.076
Organic ^{14}C-residues	0.3	0.009	0.4	0.003	0.1	<0.001	0.3	0.008	1.0	0.005	<0.1	0.003
Total identified/ characterized	**90.2**	**2.696**	**94.3**	**0.626**	**93.2**	**0.164**	**98.9**	**2.798**	**95.0**	**0.502**	**96.7**	**0.225**

[a] %TRR not corrected for recovery.
[b] Expressed in [^{14}C]thiamethoxam equivalents.
[c] -- = Not detected.
[d] Specific unknowns isolated by TLC each accounted for <5% of the TRR.
[e] Radioactivity on TLC plates not associated with a specific region.

Table 11. Summary of the characterization/identification of ^{14}C-residues in rice straw, husks, and grain harvested 21 days following the second of two foliar applications of [^{14}C]thiamethoxam (25% WP) totaling 50 g ai/ha/application (0.045 lb ai/A).

Metabolite/ fraction	[Thiazol -^{14}C]Thiamethoxam						[Oxadiazin-^{14}C]Thiamethoxam					
	Straw (1.007 ppm)		Husks (1.159 ppm)		Grain (0.050 ppm)		Straw (1.075 ppm)		Husks (0.960 ppm)		Grain (0.026 ppm)	
	%TRR [a]	ppm [b]	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Thiamethoxam	50.3	0.507	70.8	0.821	4.5	0.002	53.0	0.570	65.4	0.628	12.8	0.003
CGA-322704	11.4	0.115	3.6	0.042	4.2	0.002	7.7	0.083	6.3	0.060	10.6	0.003
CGA-265307	5.2	0.058	0.7	0.008	0.4	<0.001	3.8	0.041	0.1	0.001	0.5	<0.001
CGA-355190	2.6	0.026	4.4	0.051	0.1	<0.001	3.2	0.034	3.7	0.036	0.7	<0.001
CGA-353968	1.0	0.010	0.9	0.010	1.1	<0.001	1.8	0.019	0.8	0.008	2.6	0.001
Desmethyl-CGA-353968	0.2	0.002	-- [c]	--	--	--	0.4	0.004	--	--	--	--
NOA-407475	1.9	0.019	3.0	0.035	--	--	4.0	0.043	3.0	0.029	0.3	<0.001
Total identified	**72.6**	**0.737**	**83.4**	**0.967**	**10.3**	**0.005**	**73.9**	**0.794**	**79.3**	**0.762**	**27.5**	**0.007**
TLC unknowns [d]	6.2	0.062	1.2	0.011	1.1	<0.001	2.5	0.027	4.2	0.040	4.0	0.001
Unresolved ^{14}C-residue [e]	9.4	0.095	6.0	0.062	2.5	0.001	11.4	0.123	7.2	0.069	5.0	0.001
Organic fraction(s)	--	--	--	--	0.2	<0.001	--	--	--	--	0.4	<0.001
Total identified/ characterized	**88.2**	**0.894**	**90.6**	**1.040**	**14.1**	**0.007**	**87.8**	**0.944**	**90.7**	**0.871**	**36.9**	**0.009**
Residual solids	14.5	0.146	7.5	0.087	91.4	0.046	6.0	0.065	6.1	0.059	62.5	0.016

[a] %TRR not corrected for recovery.
[b] Expressed in [^{14}C]thiamethoxam equivalents.
[c] -- = Not detected.
[d] Specific unknowns isolated by TLC each accounted for ≤2.2% of the TRR.
[e] Radioactivity on TLC plates not associated with a specific region.

Proposed Metabolic Pathway in Plants:

Metabolism data on corn, cucumbers, and pears were reviewed previously (G.J. Herndon, 3/30/00, PP#9F5046). The metabolism of thiamethoxam in wheat and rice is similar to its metabolism demonstrated in previous plant metabolism studies, although the relative levels of individual metabolites differed among the various crops. To varying degrees, the metabolism of thiamethoxam in each of these crops 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 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.

In a meeting held on 7/28/99 (see memo of G.J. Herndon dated 8/31/99), the Metabolism Assessment Review Committee (MARC) concluded that the residue of concern in plants (pears and corn) is understood. The residue to be regulated (for risk assessment and tolerance setting purposes) is the parent thiamethoxam and its CGA-322704 metabolite.

In the MARC meeting held on 7/28/99, based on the low radioactivity present and identified in the cucumber metabolism study, the Committee recommended that another plant metabolism study be submitted to fulfill the requirement of 3 plant metabolism studies (on dissimilar crops) for OPPTS 860.1300. Based on the uses requested under PP#9F5046 and 9F5051, the Committee recommended that a new plant metabolism study be conducted on a leafy vegetable (one of the representative commodities in either Crop Group 4 or 5).

RAB2 concludes that the acceptable plant metabolism studies on different plant types (pears and corn) would cover all proposed seed treatment (wheat, sorghum, barley, canola, cotton, tobacco, leafy (except Brassica) vegetables, Brassica leafy vegetables, cucurbit vegetables, and fruiting vegetables) uses (due to expected non-detectable residues), the proposed foliar treatment uses on canola and soil and foliar treatment on cotton (due to the edible portion (oil) undergoing many processing steps which would be expected to degrade or volatilize thiamethoxam residues), soil and foliar uses on tobacco, soil and foliar uses on fruiting (except cucurbit) vegetables (Crop Group 8), soil and foliar uses on cucurbit vegetables (Crop Group 9), foliar and soil treatment of tuberous and corm vegetables (Crop Subgroup 1-C), and foliar uses on pome fruit (due to acceptable pear metabolism study).

The additional leafy vegetable plant metabolism will need to be conducted by the petitioner, reviewed and found acceptable by the Agency prior to the granting of the following proposed uses of thiamethoxam: foliar treatment of leafy (except Brassica) vegetables (Crop Group 4) and foliar treatment of Brassica leafy vegetables (Crop Group 5).

OPPTS GLN 860.1300: Nature of the Residue in Animals

Adequate ruminant and poultry metabolism studies were reviewed in conjunction with the permanent tolerance petition for use on canola (PP#9F5046). The metabolism of thiamethoxam in ruminants and poultry is similar. The major pathway of metabolism 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.

In ruminants, the MARC concluded (meeting held on 7/28/99) that the residue of concern is parent + CGA-322704 metabolite. The parent thiamethoxam and the CGA-322704 metabolite accounted for a high percentage of the radioactivity identified in milk and muscle (the commodities with the highest dietary impact for humans) from the lactating goat study. The Committee was potentially concerned about the relatively high levels of metabolites MU-12 and N-5 in kidney and liver. However, after consulting with Alberto Protzel, the Committee concluded that these metabolites, which contain the chloro-thiazole ring but not the nitro group, would not need to be included in the tolerance expression or quantitatively used in a human health risk assessment.

In poultry, based on cursory review of the laying hen metabolism study and dietary burdens, a hen feeding study and establishment of poultry commodity tolerances will not be needed for the proposed uses. If additional uses are requested later which increase the dietary burden enough to require that a laying hen feeding study be conducted, the Committee concluded that the petitioner will need to analyze for the additional metabolite CGA-265307 (in addition to the parent thiamethoxam and CGA-322704 metabolites) based on it being the major residue in eggs and fat and containing the N-nitro group. For the reasons stated under the ruminants section for MU-12 and N-5, the MARC concluded that the metabolite MU-3 would not need to be included in the tolerance expression or quantitatively used in a human health risk assessment.

OPPTS GLN 860.1340: Residue Analytical Method - Plants

In conjunction with the crop field trials (1998; MRID 447151-08 through -12, and 44715134), the petitioner submitted method descriptions and concurrent recovery data for a HPLC/UV or MS method (AG-675) used to determine residues of thiamethoxam and its metabolite CGA-322704 in/on crop commodities. This method has been proposed as the tolerance enforcement method for crop commodities; method validation data, and a radiovalidation and ILV trial of the method are concurrently under review by the Agency in conjunction with a permanent tolerance petition for use on canola (PP#9F5051).

Briefly, residues of thiamethoxam and CGA-322704 in **fruits**, **vegetables**, and **grains** are extracted using ACN:water (80:20, v:v), filtered, and concentrated to an aqueous remainder. Residues in the aqueous phase are purified by RP SPE on a phenyl column eluted with MeOH:water (1:1, v:v), and concentrated. The residues are salinized, partitioned into EtOAc, concentrated to dryness, redissolved in EtOAc:hexane (20:80, v:v), and then further purified by sequential normal-phase (NP) SPE through amino and alumina columns eluted with MeOH:EtOAc (3:97 and 10:90, v:v, respectively). The eluate from the alumina column is evaporated to dryness, reconstituted in a mobile phase of hexane:EtOAc:isopropanol:MeOH (11:3:1:1, v/v), and submitted to NP HPLC analysis using a Spherisorb S5 NH_2 column with UV detection at 255 nm.

Residues of thiamethoxam and CGA-322704 in **oils** are extracted using ACN:water (80:20, v:v), filtered (except oils), and partitioned with aqueous NaCl:hexane:toluene (5:2:20, v/v). The hexane layer is discarded, and residues in the aqueous layer are partitioned with ACN:toluene (98:2, v/v). The combined ACN/toluene extracts are concentrated to an aqueous remainder, and then are cleaned-up and analyzed as described above for fruits, vegetables, and grains.

Residues of thiamethoxam and CGA-322704 in **cotton**, **tobacco**, and **forage, fodder, and straw of cereal grains** are extracted using ACN:water (80:20, v:v), filtered, and concentrated to an aqueous remainder. Residues in the aqueous phase are adjusted to pH 7 using sodium phosphate buffer, and cleaned-up on a strong anion exchange SPE column. The residues are further purified on a phenyl SPE column eluted with MeOH:water (1:1,v:v), concentrated, salinized, partitioned into EtOAc, and concentrated to dryness. The residues are redissolved in EtOAc:hexane (20:80, v:v), purified on a NP alumina SPE column eluted with MeOH:EtOAc (10:90, v:v), and concentrated to dryness. The residues are then reconstituted in ACN:water (10:90, v:v) and analyzed by reverse-phase HPLC using a C_{18} column with a gradient of water to ACN with 0.1% acetic acid, and MS detection (m/z = 292 and 250 for thiamethoxam and CGA-322704, respectively).

The validated LOQ for residues of thiamethoxam and its metabolite CGA-322704 is 0.01 ppm for all crop matrices with the exception of fruit juices (0.005 ppm), grass (0.05 ppm), and cured tobacco (<0.1 ppm).

Method recovery data are presented in Table 12. For method validation, control samples of representative plant and animal matrices were fortified with thiamethoxam and CGA-322704 at 0.005-2.0 ppm. Generally, adequate recoveries were obtained for each analyte from the crop matrices examined with some exceptions. Recoveries of thiamethoxam and CGA-322704 fortified in potato chips at 0.01 ppm each were 41-103% and 50-105%, respectively, (4 of 6 recoveries were unacceptable), and required the correction of residue values in the review of the processing study data to obtain an adequate assessment of concentration of residues in chips. Recoveries of parent fortified in cottonseed hulls at 0.1 and 0.5 ppm were also low at 52-69% (3 of 4 recoveries unacceptable). Recoveries of CGA-322704 were poor from both wheat straw (53-108%; 3 of 4 recoveries unacceptable), and from cotton gin byproducts for which 8 of 11 recoveries at the 0.01-0.5 ppm fortification level were unacceptable with recoveries ranging from 42-85% ($\bar{x}$ = 63%; sd = ±12%). Representative chromatograms and sample calculations were provided.

In conjunction with the limited rotational crop study (1998; MRID 44715106), the petitioner provided concurrent recovery data from crop samples fortified with thiamethoxam and CGA-322704 at 0.01-0.5 ppm each and analyzed using method AG-675, described above. The results are presented in Table 12. Overall average recoveries of thiamethoxam and CGA-322704 from lettuce, turnip, and wheat matrices were 88% (CV=16%; n=52) and 86% (CV=17%; n=51), respectively. Apparent residues of each analyte in/on control samples of each matrix were <0.01 ppm (<LOQ). Representative chromatograms were provided.

Conclusions: Novartis HPLC/UV (or MS) Method AG-675 is adequate for collecting data on residues of thiamethoxam and CGA-322704 in/on the crop commodities associated with this petition. Adequate method validation data were submitted. The validated limit of quantitation (LOQ) for residues of each analyte is 0.01 ppm for all plant matrices with the exception of fruit juices (0.005 ppm), grass (0.05 ppm), and cured tobacco (0.1 ppm). The method has been adequately radiovalidated and has undergone a successful independent laboratory validation (ILV) trial in conjunction with the permanent tolerance petition for use on canola (PP#9F5046).

A petition method validation (PMV) request has been submitted to the Analytical Chemistry Branch (ACB) of BEAD (see memo of G.J. Herndon dated 9/28/99). RAB2 requested that ACB use the proposed enforcement methods (MRID# 447035-24 and 447035-27) to validate recovery of thiamethoxam and its metabolite CGA-0322704 from canola, cotton, tomato, spinach, wheat grain, milk, beef liver, and eggs. The results of the PMV request have not been received.

With the submission of a method having both UV and MS detection, the issues of method specificity and confirmatory procedures have been adequately addressed.

Table 12. Method recoveries from control samples fortified with thiamethoxam and CGA-322704 using HPLC/UV or MS method AG-675.

MRID	Commodity	Fortification level (ppm)	# of Samples	% Recovery of Thiamethoxam		# of Samples	% Recovery of CGA-322704	
				Range [a]	Avg ± SD		Range [a]	Avg ± SD
Method Validation Recoveries								
44715108	Wheat, grain	0.01, 0.1	4	81-100	89 ± 8	4	90-113	97 ± 11)
	Forage		4	63-135 (3)	102 ± 34	4	69-96 (1)	82 ± 14
	Straw		4	74-125 (1)	89 ± 24	4	53-108 (3)	74 ± 24
Concurrent Method Recoveries								
44715110	Potato, tubers	0.01-0.5	28	75-118	103 ± 9	28	84-116	103 ± 7
	Chips	0.01	3	41-103 (2)	63 ± 35	3	50-105 (2)	70 ± 31)
	Culls	0.01	2	104, 105	104 ± 1	2	103, 106	105 ± 2)
	Granules	0.01	2	96, 100	98± 3	2	87, 100	94 ± 10)
	Wet peel	0.01	2	97, 108	102 ± 8	2	99, 106	103 ± 5)
44715111	Tomato, fruit	0.01-1.0	35	68-115 (1)	95 ± 10	35	73-115	98 ± 9)
	Puree	0.01, 0.1	4	89-126 (1)		4	76-103	
	Paste	0.01, 0.1	4	77-88		4	77-97	
	Bell & non-bell peppers	0.01-0.5	20	89-111		20	90-113	
44715109	Cucurbits	0.01-2.0	33	78-125 (2)	96 ± 10	33	66-126 (2)	96 ± 11)
44715134	Apple, fruit	0.01-2.0	43	65-123 (3)	88 ± 12	44	73-119	88 ± 9
	Wet pomace	0.01-1.0	5	81-96		5	80-90	
	Juice	0.005-0.2	5	94-105		5	83-103	
	Pear, fruit	0.01-1.0	15	70-124 (1)		16	80-100	
44715105	Barley, grain	0.01-0.5	18	63-112 (3)	85 ± 15	17	69-109 (1)	87 ± 11
	Hay	0.01-0.5	38	59-102 (8)	78 ± 12	38	52-118 (11)	75 ± 13
	Straw	0.01-1.0	20	60-94 (7)	78 ± 11	19	50-86 (11)	68 ± 11

(Continued; footnotes follow)

Table 12. Continued.

MRID	Commodity	Fortification level (ppm)	# of Samples	% Recovery of Thiamethoxam		# of Samples	% Recovery of CGA-322704	
				Range [a]	Avg ± SD		Range [a]	Avg ± SD
44715108	Wheat, grain	0.01, 0.5	18	71-95	85 ± 8	18	77-112	91 ± 8
	Forage		27	67-147 (5)	99 ± 20	27	69-117 (1)	89 ± 11
	Hay		21	61-120 (3)	93 ± 19	21	61-124 (5)	89 ± 18
	Straw		22	70-130 (5)	99 ± 18	22	61-119 (2)	92 ± 16
	Bran		3	89-91	88 ± 6	3	82-112	89 ± 11
	Flour		2	85-88		2	82-87	
	Middlings		3	86-92		3	85-101	
	Shorts		2	87-100		2	85-102	
	Germ		2	75-88		2	72-94	
44715112	Sorghum, grain	0.01-1.0	11	85-96	89 ± 3	11	56-100 (1)	91 ± 12
	Forage		11	79-126 (1)	94 ± 16	11	78-110	93 ± 11
	Stover		10	75-98	90 ± 8	10	71-116	85 ± 15
	Flour	0.1	2	93, 104	99 ± 8	2	102, 112	107 ± 7
44715103	Tobacco, green	0.01-1.0	19	63-112 (1)	91 ± 12	19	56-90 (5)	77 ± 9
	Cured	0.1, 1.0	11	60-86 (4)	74 ± 8	11	60-78 (4)	69 ± 6
44715104	Cotton, undelinted seed	0.01-1.0	33	52-124 (5)	79 ± 13	33	59-108 (2)	79 ± 10
	Gin byproducts	0.01-0.5	11	56-108 (4)	82 ± 19	11	42-85 (8)	63 ± 12
	Meal	0.01-0.2	4	69-86 (1)	75 ± 8	4	64-86 (1)	75 ± 10
	Hulls	0.01-0.08	4	52-75 (3)	64 ± 10	4	70-90	77 ± 9
	Oil	0.01-0.1	4	91-99	95 ± 4	4	96-102	100 ± 3
44715106 (rotational crops)	Lettuce, leaf	0.01-0.1	8	84-98	91 ± 6	8	73-99	89 ± 9
	Turnips, tops	0.01-0.2	8	74-102	87 ± 10	8	78-99	89 ± 8
	Turnips, roots	0.01-0.5	7	78-114	89 ± 11	7	82-99	91 ± 7
	Wheat, forage	0.01-0.5	10	70-105	91 ± 11	10	68-99 (1)	82 ± 8
	Wheat, hay	0.01-0.5	8	68-134 (2)	94 ± 25	7	66-152 (4)	90 ± 30
	Wheat, straw	0.01-0.1	6	62-86 (2)	75 ± 9	6	54-74 (3)	65 ± 8
	Wheat grain	0.01-0.1	5	74-105	87 ± 12	5	86-102	93 ± 7

[a] Values in parentheses represent the number of samples with recoveries outside the acceptable range (70-120%).

GLN 860.1340: Residue Analytical Method - Animals

In conjunction with a previous petition for permanent tolerances on canola (PP#9F5051), Novartis submitted an method description and validation data for Novartis HPLC/UV Method AG-675 for determining residues of thiamethoxam and CGA-322704 in animal commodities. The validated LOQ for residues of thiamethoxam and CGA-322704 is 0.01 ppm each in meat, poultry, and eggs, and 0.005 ppm each in milk. A successful ILV trial for this method has been conducted using milk, eggs, and beef liver, and the method has been adequately radiovalidated using samples of meat and milk from the goat metabolism study. However, the Agency required additional radiovalidation data in order to assess the efficiency of this method in recovering residues of CGA-322704 from liver as microwave extraction was required to release CGA-322704 from liver in both the ruminant and poultry metabolism studies.

In conjunction with the current ruminant feeding study (1998; MRID 44703534), the petitioner has submitted concurrent method recovery data for HPLC/UV Method AG-675 using control samples for animal commodities.

Briefly, residues of thiamethoxam and CGA-322704 in animal commodities are extracted using ACN:water (80:20, v:v), filtered (except oils), and partitioned with aqueous NaCl:hexane: toluene (5:2:20, v/v). The hexane layer is discarded, and residues in the aqueous layer are partitioned with ACN:toluene (98:2, v/v). The combined ACN/toluene extracts are concentrated to an aqueous remainder, and are purified by RP SPE on a phenyl column eluted with MeOH:water (1:1, v:v), and concentrated. The residues are salinized, partitioned into EtOAc, concentrated to dryness, redissolved in EtOAc:hexane (20:80, v:v), and then further purified by sequential normal-phase (NP) SPE through amino and alumina columns eluted with MeOH:EtOAc (3:97 and 10:90, v:v, respectively). The eluate from the alumina column is evaporated to dryness, reconstituted in a mobile phase of hexane:EtOAc:isopropanol:MeOH (11:3:1:1, v/v), and analyzed by NP HPLC analysis using a Spherisorb S5 NH_2 column with UV detection at 255 nm. The validated LOQ for residues of thiamethoxam and its metabolite CGA-322704 is 0.01 ppm for all matrices with the exception of milk (0.005 ppm).

For method validation, control samples of beef tissues and milk were fortified with thiamethoxam and CGA-322704 each at 0.005-0.5 ppm. The results of the method recoveries are presented in Table 13. Overall method recoveries of thiamethoxam and CGA-322704 from beef tissues and milk were 69-122% ($\bar{x}$ =91%, CV=10%; n=71) and 67-113% ($\bar{x}$ =91%, CV=9%; n=71), respectively. Apparent residues of each analyte in all tissue and milk control samples were <LOQ (<0.01 and <0.005 ppm, respectively). Samples were analyzed by NHSD. Representative chromatograms were provided.

Conclusions: Adequate method validation data using animal commodities have been submitted for Novartis HPLC/MS Method AG-675, and the method has undergone a successful ILV trial using milk, eggs, and beef liver. The validated LOQ for residues of thiamethoxam and CGA-322704 is 0.01 ppm each in meat, poultry, and eggs, and 0.005 ppm each in milk. This method

has also been adequately radiovalidated using samples of meat and milk from the goat metabolism study. However, additional radiovalidation data are required in order to assess the efficiency of this method in recovering thiamethoxam and CGA-322704 from beef liver. This will be required as a condition of registration (see Conclusion 30g). In both the ruminant and poultry metabolism studies, microwave extraction was required to release CGA-322704 from liver.

A petition method validation (PMV) request has been submitted to the Analytical Chemistry Branch (ACB) of BEAD (see memo of G.J. Herndon dated 9/28/99). RAB2 requested that ACB use the proposed enforcement methods (MRID# 447035-24 and 447035-27) to validate recovery of thiamethoxam and its metabolite CGA-322704 from canola, cotton, tomato, spinach, wheat grain, milk, beef liver, and eggs. The results of the PMV request have not been received.

Table 13. Concurrent method recoveries of thiamethoxam and CGA-322704 from fortified samples of animal commodities using HPLC/UV Method AG-675.

MRID	Commodity	Fortification Range (ppm)	# of Samples	% Recovery [a]	
				Thiamethoxam	CGA-322704
44703534	Milk	0.005-0.5	43	71-115, 122; **94**	72-113; **94**
	Kidney	0.01-0.2	6	81-113; **97**	84-106; **93**
	Liver	0.01-0.5	6	73-87; **79**	71-94; **80**
	Fat	0.01-0.2	4	77-88; **84**	84-95; **90**
	Muscle	0.01-0.5	12	69; 77-96; **84**	67; 77-96; **86**

[a] Recoveries outside the acceptable range (70-120%) are listed separately. Avg. recoveries are listed in bold.

OPPTS GLN 860.1360: Multiresidue Method

The petitioner submitted data concerning the recovery of residues of thiamethoxam using FDA multiresidue method protocols (PAM Vol. I). Recovery of thiamethoxam was 50-60% using Protocol D and <30% using Protocol E. Using Protocol C, thiamethoxam obtained adequate detector responses to Section 302 DG5 and DG13 gas-liquid chromatography (GLC) systems. Metabolites CGA-322704 and CGA-265307 were tested using Protocol C, but did not yield adequate detector responses to any of the Section 302 DG5, DG13, and DG18 GLC systems; no further testing was conducted for the metabolites.

In the memos of G.J. Herndon dated 9/28/99, the results of the multiresidue testing were forwarded to FDA (Mark Wirtz) and ACB/BEAD (Francis Griffith).

OPPTS GLN 860.1380: Storage Stability Data - Plants

Acceptable storage stability data on various crops are under concurrent review by the Agency in conjunction with a permanent tolerance petition for residues of thiamethoxam in/on canola (PP#9F5051), and are briefly summarized here. Data are available from a two-year storage stability study on thiamethoxam *per se* and a one-year interim study on CGA-322704. These data indicate that residues of thiamethoxam and CGA-322704 are stable at ≤- 18 C in apples, corn grain, potato, canola seed, and tomato for up to 2 and 1 years, respectively. Interim data from an on-going storage stability study under review in the same petition indicate that residues of thiamethoxam and CGA-322704 are also stable at -20 C in canola oil, corn meal, leaf lettuce, safflower seed, and tomato puree for up to 4 months.

In the current residue field trial studies, RACs of potato, fruiting vegetables, cucurbits, pome fruits, wheat and cotton were stored frozen for 14-27 months; samples of grain sorghum RACs were stored for up to 30 months, although the majority of the samples were analyzed within ~24 months. Samples from the tobacco residue study were stored frozen for up to 3 months. Processed commodities of potato, tomato, apple, grain sorghum, wheat, and cotton were stored frozen for 12-26 months from collection to analysis.

Conclusions: Data are available (PP#9F5046) from one study indicating that thiamethoxam and CGA-322704 are stable at ≤-18 C in apples, corn grain, potatoes, canola seed, and tomatoes for up to 24 and 12 months, respectively. Interim data from an on-going storage stability study indicate thiamethoxam and CGA-322704 are also stable at -20 C in canola oil, corn meal, leaf lettuce, safflower seed, and tomato puree for up to 4 months[2].

In the current crop field trial studies, RACs of potato, fruiting vegetables, cucurbits, pome fruits, wheat and cotton were stored frozen for 14-27 months; samples of sorghum RACs were stored for up to 30 months, although the majority of the samples were analyzed within ~24 months. Samples from the tobacco residue study were stored frozen for up to 3 months. Processed commodities of potato, tomato, apple, grain sorghum, wheat, and cotton were stored frozen for 12-26 months from collection to analysis.

The available storage stability data on thiamethoxam *per se* adequately support the residue studies on potato, fruiting vegetables (excluding tomato processed commodities), cucurbits, pome fruits, cotton, and tobacco. Although storage stability data for thiamethoxam on a commodity representative of forage, hay, or straw, are needed to support the studies on barley, wheat, and sorghum, data on leaf lettuce from an on-going study may be used support the stability of thiamethoxam in forage. Likewise, data on tomato puree from the interim study may

---

[2] Results from a later interval in the on-going storage stability study were e:mailed to the Agency on 4/28/00. The conclusions in the e:mail indicate that thiamethoxam and CGA-322704 are stable in/on these matrices out to 14 months. Sufficient supporting raw data were not submitted to the Agency to allow RAB2 to fully review these results.

support the tomato processing study. Data are required depicting the frozen storage stability of CGA-322704 in representative RAC and processed commodities stored for intervals reflecting the maximum storage intervals incurred by samples from all the submitted residue studies (except tobacco). However, based on the storage stability data submitted to date, RAB2 does not anticipate significant degradation of either thiamethoxam or CGA-322704 in frozen storage. As confirmation of this, RAB2 will require that the storage stability study be continued to cover the interval that the plant commodity samples were stored (up to 30 months). These data will be required as a condition of registration.

OPPTS GLN 860.1380: Storage Stability Data - Livestock Commodities

Novartis submitted interim storage stability data (citation listed below) depicting the frozen storage stability of fortified residues of thiamethoxam and its metabolites CGA-322704 and CGA-265307 in eggs, milk, and tissue samples.

> 44715114 Grunenwald, M. (1998) Stability of CGA-293343, CGA-322704, and CGA-265307 in Meat, Milk, and Eggs Under Freezer Storage Conditions: 4-Month Interim Report: Lab Project Number: ABR-98102: 284-98: 346001. Unpublished study prepared by Novartis Crop Protection, Inc. 134 p.

Samples of untreated eggs, milk, and beef muscle and liver obtained from a local grocery, were fortified with thiamethoxam and CGA-322704 simultaneously, and CGA-265307 alone, each at 0.5 ppm, and stored frozen with unfortified samples at -20 C. The petitioner stated that CGA-265307 was added to the study after its initiation; consequently, separate samples analyses were conducted on this metabolite. At sampling intervals of 0, 2, and 4 months, a control sample, two freshly-fortified samples, and two stored fortified samples of each matrix were analyzed for residues of each analyte using HPLC/UV method AG-675, discussed above. The results of the interim storage stability study are presented in Table 14; data from additional storage intervals will be submitted with the final report. Samples analyses were conducted by NHSD, Greensboro, NC.

(continued; footnotes follow)

Table 14. Stability of thiamethoxam and its metabolites, CGA-322704 and CGA-265307, in beef tissues, milk, and eggs fortified at 0.5 ppm each and stored at -20 C for up to 4 months.

Commodity	Storage Period (months)	Fresh Fortification Recovery, %	Apparent Recovery in Stored Samples, %	Corrected Recovery in Stored Samples, % [a]
Thiamethoxam				
Eggs	0	88, 91	75, 85, 87	--
	3.1	92, 94	83, 93	89, 100
	4.6	89, 90	92, 92	102, 102
Milk	0	86, 88	79, 83, 90	--
	2.3	92, 100	48, 71	50, 74
	4.7	88	88, 89	100, 101
Muscle, beef	0	88, 89	80, 82, 89	--
	3.3	92, 94	88, 96	95, 103
	4.5	94, 96	89, 92	94, 97
Liver, beef	0	88, 89	79, 83, 92	--
	3	89, 95	89, 90	97, 98
	4.5	91, 92	87, 91	95, 99
CGA-322704				
Eggs	0	94, 96	80, 91, 94	--
	3.1	93, 97	93, 96	98, 101
	4.6	91, 92	95, 95	103, 103
Milk	0	91, 94	88, 92, 96	--
	2.3	99, 108	91, 97	88, 93
	4.7	90	92, 99	102, 110
Muscle, beef	0	92, 94	87, 91, 93	--
	3.3	93, 95	93, 96	99, 102
	4.5	90, 90	90, 92	100, 102
Liver, beef	0	88, 89	81, 87, 94	--
	3	87, 96	85, 85	92, 92
	4.5	91, 92	86, 89	93, 97

(continued; footnotes follow)

Table 14. Continued.

Commodity	Storage Period (months)	Fresh Fortification Recovery, %	Apparent Recovery in Stored Samples, %	Corrected Recovery in Stored Samples, % [a]
CGA-265307				
Eggs	0	94, 98	64, 93, 97	--
	3.1	90, 101	90, 94	94, 98
	4.2	93, 95	85, 87	90, 93
Milk	0	64, 90	85, 92, 93	--
	3.3	83, 89	78, 93	91, 108
	4.4	90, 94	93, 93	101, 101
Muscle, beef	0	81, 94	86, 89	--
	3.3	91	81, 86	89, 95
	4.2	95, 97	86, 87	90, 91
Liver, beef	0	77, 78	77, 80, 81	--
	3.3	78, 99	89, 97	100, 109
	4.2	89, 93	84, 88	92, 97

[a] Recoveries were calculated by the reviewer.

Conclusions: The submitted storage stability data are adequate and indicate that residues of thiamethoxam, CGA-322704, and CGA-265307 are stable in animal commodities for up to 4 months at -20 C. In the current cattle feeding study, milk and tissue samples were stored at -20 C for 8-12 months prior to analysis. Additional data are required supporting the storage intervals reflected in the feeding study; the petitioner has indicated that data for longer storage intervals will be submitted with the final storage stability report. Based on the storage stability data submitted to date on both plant and animal commodities, RAB2 does not anticipate significant degradation of either thiamethoxam or CGA-322704 in frozen storage. However, as confirmation of this, RAB2 will require that the storage stability study be continued to cover the interval that the animal commodity samples were stored (up to 12 months). This data will be required as a condition of registration.

OPPTS GLN.860.1500: Crop Field Trials

As thiamethoxam residues of concern have not been determined by the MARC, the petitioner has reported magnitude of the residue data for thiamethoxam *per se* and its metabolite CGA-322704. For the purposes of this review, residues of CGA-322704 are expressed as thiamethoxam equivalents, calculated by the reviewer using the ratio of the molecular weights (e.g., parent equivalents = CGA-322704 residue (ppm) x 291.02/249.8).

Tuberous and Corm Vegetables Crop Group

Potato

The petitioner submitted data from 36 field trials conducted in CA (2), CO (2), FL (2), ID (8), ME (2), MI (2), MN (2) , NY(2) , NC (2), ND (4), OR (2), WA (4), and WI (2) during 1996 depicting residues of thiamethoxam and CGA-322704 in/on potatoes. These data were submitted to support a proposed tolerance for residues in/on the tuberous and corm vegetable crop subgroup, and are reported in:

> 44715110 Vincent, T. (1998) CGA-293343 and CGA-215944--Magnitude of the Residues in or on Crop Subgroup 1C: Tuberous and Corm Vegetables: Lab Project Number: 43-96. Unpublished study prepared by Novartis Crop Protection, Inc. 223 p.

In 16 tests, thiamethoxam (FlC) was applied as an in-furrow application to potatoes at planting at 2 oz ai/A followed by two broadcast foliar applications of thiamethoxam (25% DF) at 0.35 oz ai/A/application with a 7-day RTI for a seasonal rate of 2.72 oz ai/A (0.17 lb ai/A/season), equivalent to 1x the maximum proposed soil + foliar rates. In another 16 tests, thiamethoxam (25% DF) was applied twice only as a late-season broadcast foliar treatment to potatoes at 0.35 oz ai/A/application with a 7-day RTI for a total of 0.71 oz ai/A (0.044 lb ai/A/season), ~1x maximum foliar rate. At two trial locations (ID and ND), the combined in-furrow/foliar application regime was also performed at exaggerated rates (0.51 and 0.85 lb ai/A/season; 4x and 7x) to generate samples for processing studies. Application methods (e.g., equipment type and spray volumes) were not reported. However, RAB2 concludes this information would not impact the tolerance level.

One control and two treated potato samples were harvested from each test 14 or 15 days following the last application. At two sites (ID and ND), potato samples from the soil+foliar treatment were also collected at 0, 1, 3, 7, 14, and 21 days posttreatment to determine residue decline. Potatoes were frozen following collection (except samples for processing) and shipped within 41 days by freezer truck or overnight courier on dry ice to Novartis, Greensboro, NC where the samples were stored frozen (~-20 C) prior to preparation for analysis. Samples were shipped to Centre Analytical Laboratories, State College, PA for analysis, however, a description of the shipping means and conditions were not provided. The petitioner stated that samples were kept frozen, from collection to analysis, for 21-27 months.

Analyses of thiamethoxam and CGA-322704 in/on potato samples were conducted using Method AG-675, described above. Residues in all control samples were <0.01 ppm for both analytes. Adequate concurrent recoveries were obtained for both compounds. Residues of thiamethoxam and CGA-322704 were <0.01 ppm (<LOQ) in/on treated samples of potatoes harvested 14 or 15 days after the last application at the 1x foliar rate and 1x soil + foliar rates (n=32 each), with the exception of one treated sample from the soil+foliar treatment that bore residues of thiamethoxam *per se* at 0.014 ppm. At 4x, residues of thiamethoxam and CGA-322704 were <0.01-0.02 and <0.01 ppm, respectively, in/on two potato tuber samples. At 7x, residues of thiamethoxam and CGA-322704 were 0.02-0.03 and <0.01-0.01 ppm, respectively in/on two potato samples. For the two residue decline studies, residues of each analyte were <LOQ in/on all potato samples (n=20) treated at 1x and harvested 0-21 days posttreatment, with the exception of the sample noted above.

Geographic representation of the residue data is adequate, and a sufficient number of tests was conducted to support a crop subgroup tolerance on tuberous and corm vegetables. A total of 32 tests at 1x were conducted on potatoes in Region 1 (4 tests), Region 5 (8 tests), Region 11 (12 tests), and Regions 2, 3, 9 and 10 (2 tests each).

Conclusions: Pending resolution of questions concerning storage stability of CGA-322704, the submitted residue data are adequate and support the proposed 0.02 ppm tolerance for the combined residues of thiamethoxam and CGA-322704 in/on the tuberous and corm vegetables crop subgroup.

In the current study, samples of potatoes were stored frozen for up to 27 months prior to analysis. Data are available indicating that residues of thiamethoxam are stable in frozen potatoes for up to 2 years; however, data from an interim study on CGA-322704 are only available for storage intervals up to 1 year. When the final report is submitted, the residue study may be considered acceptable.

Leafy Vegetables (except *Brassica* Vegetables) and *Brassica* Vegetables Crop Groups

Although the petitioner is requesting tolerances on Crop Group 4 and Crop Subgroups 5A and 5B, at the time of this review, residue data were not available supporting the proposed tolerances for the Leafy vegetables (except *Brassica*) crop group, the Head and stem *Brassica* subgroup, and the Leafy *Brassica* greens subgroup. These crops should be removed from the proposed labels and Section F.

Fruiting Vegetables (except Cucurbits) Crop Group

Peppers and Tomatoes

Novartis submitted data (citation shown below) from 51 field tests conducted during 1996/1997 depicting residues of thiamethoxam and CGA-322704 in/on the representative commodities tomatoes (32 tests) and peppers (19 tests) to support a proposed tolerance for residues in/on the fruiting vegetables crop group.

44715111 Eudy, L. (1998) CGA-293343--Magnitude of the Residue in or on Crop Group 8: Fruiting Vegetables: Final Report: Lab Project Number: 45-98: ABR-98105: 02-IR-039-97. Unpublished study prepared by Novartis Crop Protection, Inc. 277 p.

In 22 tests, thiamethoxam (25% DF) was applied twice as late-season broadcast foliar applications to tomatoes or peppers, with a 5-day RTI, for a total of 2.82 oz ai/A (0.18 lb ai/A/season; ~1x the proposed foliar rate). At two CA locations, foliar applications were also made at exaggerated rates (3x and 5x) to tomatoes to generate samples for processing studies. At most of the test sites, the petitioner also conducted side-by-side tests consisting of a single at planting in-furrow, surface banded, or transplant drench application of thiamethoxam (FlC) at 2.0 oz ai/A (1x the maximum soil application rate) followed by a single late-season broadcast foliar application of thiamethoxam (25% DF) at 0.71 oz ai/A (0.5x single foliar rate) for a total of 2.72 oz ai/A (0.17 lb ai/A). Applications were made using ground equipment in 5-58 gal/A of water for foliar and banded/in-furrow soil treatments. Transplant drench applications were made using ground equipment at 398-436 gal/A of water with the exception of two trials (FL816-tomato and TX324-pepper) in which ~30 gal/A of water was used.

One control and two treated samples of tomatoes or peppers were harvested on the day of the last application, representing the proposed PHI, and additional samples were collected at various posttreatment intervals to determine residue decline. Samples for processing were shipped frozen from the field trial sites directly to the processing facility. Other samples were shipped via ACDS freezer truck to the Novartis, Greensboro, NC where they were stored at <-15 C before preparation for analysis. The samples were then shipped frozen overnight to ADPEN Laboratories, Inc., Jacksonville, FL and stored frozen at ≤0 C prior to analysis. Samples were stored frozen, from collection to analysis, for 9-26 months.

Residues of thiamethoxam and CGA-322704 were determined using the HPLC/UV Method AG-675 described above. The petitioner presented summary residue data corrected for procedural recoveries <100%; the uncorrected results of the residue analyses are presented in Tables 15 and 16. *HED notes that in future submissions, residue data should be presented in its uncorrected form.* Adequate concurrent recoveries were obtained for both compounds. Residues in all control samples were <0.01 ppm for both analytes.

Following two foliar applications (0-day PHI) at 1x, the combined residues of thiamethoxam and

CGA-322704 were <0.02-<0.15 ppm in/on 26 samples of tomato, <0.02-<0.18 ppm in/on 12 samples of bell peppers, and <0.04-0.24 ppm in/on 6 samples of hot peppers. For the at-planting soil treatment + late-season foliar treatment (0-day PHI), combined residues of thiamethoxam and CGA-322704 were <0.02-<0.09 ppm in/on 28 samples of tomato, <0.03-0.11 ppm in/on 10 samples of bell peppers, and <0.03-<0.10 ppm in/on 8 samples of hot peppers.

Residue decline data from tests on tomato and peppers indicated consistently that residues of each analyte in/on fruiting vegetables are lower at longer posttreatment intervals.

Geographic representation of the residue data is adequate and a sufficient number of tests were conducted to support a fruiting vegetable crop group tolerance.

Conclusions: Pending submission of supporting storage stability data, the submitted field trial data on tomatoes and peppers are adequate. Following the last of two foliar treatments with thiamethoxam (25% DF) at 0.09 lb/ai/A/application (0.18 lb ai/A; ~1x the proposed rate), with a 5 day RTI, combined residues of thiamethoxam and CGA-322704 were <0.02-0.24 ppm in 44 samples of tomatoes and peppers (bell and non-bell) harvested 0-days posttreatment. Following an at-planting soil application in which thiamethoxam (FlC) was applied in-furrow, banded, or by transplant drench at 0.13 lb ai/A and a single broadcast foliar application of thiamethoxam (25% DF) at 0.04 lb ai/A, for a total of 0.17 lb ai/A (1.3x the proposed soil applied rate), combined residues were <0.02-0.11 ppm in/on 46 samples of tomatoes and peppers harvested 0-days posttreatment.

The tomato and pepper residue data from the foliar applications and the soil + foliar applications support the proposed crop group tolerance of 0.25 ppm for residues of thiamethoxam and CGA-322704 in/on fruiting vegetables. HED notes that the proposed label for the 25% DF presently prohibits foliar treatment if the crop has been treated at-planting with thiamethoxam (FlC), yet the available residue data would also allow for a combined 1x soil application and a single 0.5x foliar application totaling 0.17 lb ai/A, which is equivalent to 1x maximum seasonal foliar rate.

In the current study, samples were stored frozen for up to 26 months prior to analysis. Data are available indicating that residues of thiamethoxam are stable frozen in tomato for up to 2 years; however, data from an interim study on CGA-322704 are only available for storage intervals up to 1 year. When the final report is submitted, the residue study may be considered acceptable.

Table 15. Residues of thiamethoxam and CGA-322704 in/on tomatoes harvested following either two foliar applications of thiamethoxam (FlC) totaling 0.17-0.88 lb ai/A, or a soil and foliar application of thiamethoxam (FlC and 25% DF) totaling 0.17 lb ai/A. [a]

Trial Location and Date	Application Data			Residues (ppm) [b]		
	Appl. Type	Total (lb ai/A)	PHI	Thiamethoxam	CGA-322704	Combined
CA039 1997	Foliar twice	0.18	0	0.06, 0.07	0.04, 0.03	0.10, 0.10
			7	0.01, 0.03	0.01, 0.03	0.02, 0.06
		0.53 (3x)	0	0.20, 0.29	0.05, 0.06	0.25, 0.35
			7	0.04, 0.08	0.04, 0.07	0.08, 0.15
		0.88 (5x)	0	0.31, 0.40	0.08, 0.07	0.39, 0.47
			7	0.24, 0.40	0.14, 0.21	0.38, 0.61
CA048 1996	Foliar twice	0.18	0	0.05, 0.04	<0.01, <0.01	<0.06, <0.05
			7	0.01, 0.01	<0.01, <0.01	<0.02, <0.02
	Drench + foliar	0.17	0	0.02, 0.01	<0.01, <0.01	<0.03, <0.02
			7	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
CA049 1996	Foliar twice	0.18	0	0.06, 0.01	0.02, <0.01	0.08, <0.02
			1	0.03, 0.02	0.02, 0.01	0.05, 0.03
			3	0.03, 0.03	0.01, 0.02	0.04, 0.05
			7	0.03, 0.02	0.02, 0.01	0.05, 0.03
			21	<0.01, 0.02	0.02, 0.03	<0.03, 0.05
	In-furrow + foliar	0.17	0	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
			7	0.01, <0.01	<0.01, <0.01	<0.02, <0.02
	Banded + foliar		0	0.02, 0.01	<0.01, <0.01	<0.03, <0.02
			7	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
CA425 1997	Drench + foliar	0.17	0	0.02, 0.02	<0.01, <0.01	<0.03, <0.03
CA442 1996	Foliar twice	0.18	0	0.06, 0.08	<0.01, <0.01	<0.07, <0.09
CA443 1996	Foliar twice	0.18	0	0.10, 0.11	0.04, 0.03	0.14, 0.14
			9	0.04, 0.03	0.05, 0.05	0.09, 0.08
		0.53 (3x)	0	0.23, 0.13	0.06, 0.03	0.29, 0.16
			9	0.17, 0.12	0.16, 0.08	0.33, 0.20
		0.88 (5x)	0	0.24, 0.77	0.05, 0.13	0.29, 0.90
			9	0.26, 0.26	0.11, 0.21	0.37, 0.47
	Drench + foliar	0.18	0	0.04, 0.05	<0.01, <0.01	<0.05, <0.06
			9	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
CA444 1996	Foliar twice	0.18	0	0.06, 0.06	<0.01, <0.01	<0.07, <0.07
	Drench alone	0.13		<0.01, <0.01	<0.01, <0.01	<0.02, <0.02

(continued: footnotes follow)

Table 15. *Continued.*

Trial Location and Date	Application Data			Residues (ppm) [b]		
	Appl. Type	Total (lb ai/A)	PHI	Thiamethoxam	CGA-322704	Combined
CA524 1996	Foliar twice	0.18	0	0.04, 0.07	0.02, 0.01	0.06, 0.08
	In-furrow + foliar	0.17		0.03, 0.05	<0.01, <0.01	<0.04, <0.06
	Banded + foliar	0.17		0.02, 0.02	<0.01, <0.01	<0.03, <0.03
CA529 1996	Foliar twice	0.18	0	0.04, 0.04	<0.01, <0.01	<0.05, <0.05
	In-furrow + foliar	0.17		0.04, 0.05	<0.01, <0.01	<0.05, <0.06
	Banded + foliar	0.17		0.03, 0.03	<0.01, <0.01	<0.04, <0.04
FL404 1996	Foliar twice	0.18	0	0.04, 0.03	<0.01, <0.01	<0.05, <0.04
	Drench + foliar	0.17		0.02, 0.02	<0.01, <0.01	<0.03, <0.03
FL019 1996	Foliar twice	0.18	0	<0.01, 0.04	<0.01, <0.01	<0.02, <0.05
			1	0.02, 0.02	0.01, 0.01	0.03, 0.03
			3	<0.01, <0.01	<0.01, 0.01	<0.02, <0.02
			7	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
			14	<0.01	0.02	<0.03
	Drench + foliar	0.18	0	0.03, 0.02	<0.01, <0.01	<0.04, <0.03
			7	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
OH209 1996	Foliar twice	0.18	0	0.11, 0.14	<0.01, <0.01	<0.12, <0.15
	Drench + foliar	0.17		0.06, 0.08	<0.01, <0.01	<0.07, <0.09
PA816 1996	Foliar twice	0.18	0	0.08, 0.10	<0.01, <0.01	<0.09, <0.11
	Drench + foliar	0.17		0.04, 0.02	<0.01, <0.01	<0.05, <0.03
SC608 1996	Foliar twice	0.18	0	0.03, 0.03	<0.01, <0.01	<0.04, <0.04
			7	0.02, 0.02	0.02, 0.01	0.04, 0.03
	Drench + foliar	0.17	0	0.01, 0.01	<0.01, <0.01	<0.02, <0.02
			7	0.01, 0.01	0.02, 0.02	0.03, 0.03

[a] Applications consisted of either two foliar applications of thiamethoxam (25% DF) totaling 0.18, 0.53, or 0.88 lb ai/A/season; 1x, 3x, and 5x the proposed foliar rate) or a single at planting in-furrow, surface banded, or transplant drench application of thiamethoxam (FlC) at 2 oz ai/A (0.13 lb ai/A; 1x the maximum soil rate) followed by a single late-season foliar application of thiamethoxam (25% DF) at 0.7 oz ai/A (0.5x single foliar rate) for a total of 0.17 lb ai/A.

[b] Data are not corrected for concurrent recoveries. Residues of CGA-322704 are expressed in thiamethoxam equivalents.

Table 16. Residues of thiamethoxam and CGA-322704 in/on bell and non-bell peppers harvested following either two foliar applications of thiamethoxam (FlC), or a soil and foliar application of thiamethoxam (FlC and 25% DF) totaling 0.17 lb ai/A.

Trial Location and Date	Application Data			Residues (ppm) [a]		
	Appl. Type	Total rate (lb ai/A)	PHI	Thiamethoxam	CGA-322704	Combined
CA050 1996	Foliar twice	0.18	0	0.06, 0.05	<0.01, <0.01	<0.07, <0.06
			7	0.04, 0.03	<0.01, <0.01	<0.05, <0.04
	Drench + foliar	0.17	0	0.03, 0.03	<0.01, <0.01	<0.04, <0.04
			7	0.01, 0.01	<0.01, <0.01	<0.02, <0.02
CA051 1996 (hot pepper)	Foliar twice	0.18	0	0.22, 0.11	0.02, <0.01	0.24, <0.12
			1	0.22, 0.19	0.02, 0.02	0.24, 0.21
			3	0.16, 0.14	0.04, 0.03	0.20, 0.17
			7	0.08, 0.04	0.04, 0.02	0.12, 0.06
			14	0.04, 0.04	0.06, 0.04	0.10, 0.08
	Drench + foliar	0.18	0	0.09, 0.06	<0.01, <0.01	<0.10, <0.07
			1	0.06, 0.06	<0.01, <0.01	<0.07, <0.07
			3	0.05, 0.04	<0.01, <0.01	<0.06, <0.05
			7	0.03, 0.02	0.01, 0.01	0.04, 0.03
			14	0.02, 0.02	0.01, 0.02	0.03, 0.04
CA530 1996	Foliar twice	0.18	0	0.10, 0.07	<0.01, <0.01	<0.11, <0.08
	Drench + foliar	0.17		0.03, 0.03	<0.01, <0.01	<0.04, <0.04
FL021 1996	Foliar twice	0.18	0	0.02, 0.01	<0.01, <0.01	<0.03, <0.02
			1	0.02, 0.03	<0.01, <0.01	<0.03, <0.04
			3	0.02	<0.01	<0.03
			7	0.02, 0.02	<0.01, <0.01	<0.03, <0.03
			14	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
	Drench + foliar	0.18	0	0.03	0.01	0.04
			7	0.01, 0.03	<0.01, 0.02	<0.02, 0.05
MI724 1996	Foliar twice	0.18	0	0.07, 0.03	<0.01, <0.01	<0.08, <0.04
	Drench + foliar	0.17		0.03, 0.02	<0.01, <0.01	<0.04, <0.03
NM772 1996 (hot pepper)	Foliar twice	0.18	0	0.03, 0.08	<0.01, <0.01	<0.04, <0.09
	In-furrow + foliar	0.17		0.02, 0.02	<0.01, <0.01	<0.03, <0.03
	Banded + foliar	0.17		0.02, 0.02	<0.01, <0.01	<0.03, <0.03
NC609 1996	Foliar twice	0.18	0	0.17, 0.17	<0.01, <0.01	<0.18, <0.18
	Drench + foliar	0.17		0.07	<0.01	<0.08
TX324 1996	Foliar twice	0.18	0	0.11, 0.07	0.01, <0.01	0.12, <0.08
	Drench + foliar	0.17		0.09, 0.08	0.02, 0.02	0.11, 0.10
TX325 1996	Foliar twice	0.18	0	0.08, 0.11	<0.01, <0.01	<0.09, <0.12
	Drench + foliar	0.17		0.05, 0.05	0.02, 0.02	0.07, 0.07

[a] Data are not corrected for concurrent recoveries. Residues of CGA-322704 expressed as thiamethoxam.

Cucurbit Vegetables Crop Group

Novartis submitted data from a total of 45 field tests conducted during 1996 and 1997 depicting thiamethoxam residues in/on cucumbers (19 tests), cantaloupes (14 tests), and summer squash (12 tests) following repeated foliar or soil/foliar applications. These data were submitted (citation noted below) to support a proposed tolerance for residues in/on the cucurbit vegetables crop group.

44715109 Eudy, L. (1998) CGA-293343--Magnitude of the Residues in or on Crop Group 9: Cucurbit Vegetables: Final Report: Lab Project Number: 42-96: 98-0019: 02-IR-043-96. Unpublished study prepared by Novartis Crop Protection, Inc. 227 p.

In 19 tests, thiamethoxam (25% DF) was applied twice foliarly to cucurbits at 1.4 oz ai/A/application, at 4-6 day RTIs, for a seasonal rate of 2.82 oz ai/A (0.18 lb ai/A, 2x the proposed foliar rate). The petitioner also conducted tests in which thiamethoxam (FlC) was applied as in-furrow (19 tests) or banded (7 tests) at 2 oz ai/A (0.13 lb ai/A; 1x the maximum soil rate) followed by a single foliar application of thiamethoxam (25% DF) at 0.71 oz ai/A (1x the maximum single foliar rate), for a total of 0.17 lb ai/A. The currently proposed labels preclude the use of the 25% DF as a foliar treatment if the crop has been treated at planting with the proposed 2 lb/gal FlC.

All applications were made using ground equipment in 1-31 gal/A of water. Foliar applications were made using 25-31 gal/A of water with the exception of one trial for each crop conducted using 5 gal/A of water; soil applications were made in 1-30 gal/A of water. Except in four test, spray adjuvants (e.g., organosilicates) were added to the final spray mixture at 0.06-0.5% v/v.

One control and two treated samples of cucumber, squash, and melons were harvested at maturity on the day of application, and for one trial (CA-1), at a 3-day PHI. The samples were shipped frozen by overnight carrier, ACDS freezer truck, or personal delivery to the Novartis, Greensboro, NC, where they were stored at <-15 C. The samples were then shipped frozen (method unspecified) to EN-CAS Laboratories, Winston-Salem, NC where they were stored frozen prior to analysis. Cucurbit samples were maintained frozen, from collection to analysis, for a total of ~20-25 months.

Residues of thiamethoxam and CGA-322704 were determined using HPLC/UV Method AG-675, described above. Residues of each analyte in all control samples were <0.01 ppm (<LOQ). Adequate concurrent recoveries were obtained for both compounds. The results are presented in Table 17.

Geographic representation of tests on cucumbers, cantaloupes, and summer squash conformed to OPPTS Series 860 guidelines and an adequate number of samples was analyzed.

Among the 38 cucurbit samples treated at 2x the proposed foliar rate, residues of thiamethoxam

per se were <0.01-0.14 ppm at the 0-day PHI. For the combined 1x soil + 1x single foliar applications, residues of thiamethoxam *per se* were <0.01-0.11 ppm in/on 46 cucurbit samples at the 0-day PHI. Residues of CGA-322704 were <0.01 ppm in all treated samples. At the 3-day PHI, residues of thiamethoxam were lower than those observed at the 0-day PHI and ranged from 0.01-0.05 ppm in/on 2 samples each of cucurbits for each of the three treatment regimes.

Conclusions: Provided supporting storage stability data are forthcoming, the submitted field trial data on cucurbit vegetables are adequate and support the proposed 0.2 ppm tolerance. Although the use patterns depicted in the available field trials (a 1x soil + 1x foliar treatment and two 2x foliar treatments) do not accurately reflect the proposed use patterns (either a 1x soil treatment or two 1x foliar treatments), residues resulting from the proposed two 1x foliar applications would likely exceed the maximum combined residues of <0.12 ppm from 1x soil+1x foliar treatment and would therefore support the proposed 0.2 ppm tolerance.

In the current study, samples of cucurbits were stored frozen for up to 25 months prior to analysis. Data are available indicating that residues of thiamethoxam are stable frozen in representative crops for up to 2 years; however, data from an interim study on CGA-322704 are only available for storage intervals up to 1 year.

Table 17. Residues of thiamethoxam and CGA-322704 in/on **cucurbits** harvested 0 or 3 days following the last of either two foliar applications or a soil and foliar application of thiamethoxam (FlC and/or 25% DF) totaling ~0.17 lb ai/A/season.

Trial Location and Date	Application Data			Residues (ppm)[a]		
	Appl. Type [b]	Total rate (lb ai/A)	PHI	Thiamethoxam	CGA-322704	Combined
Cucumber						
CA-1 1996	Foliar twice	0.18	0	0.10, 0.09	<0.01, <0.01	<0.11, <0.10
			3	0.03, 0.04	<0.01, <0.01	<0.04, <0.05
	In-furrow + foliar	0.17	0	0.01, 0.02	<0.01, <0.01	<0.02, <0.03
			3	0.01, 0.01	<0.01, <0.01	<0.02, <0.02
	Banded + foliar	0.17	0	0.01, 0.02	<0.01, <0.01	<0.02, <0.03
			3	0.01, 0.01	<0.01, <0.01	<0.02, <0.02
CA-2 1996	In-furrow + foliar	0.05 [c]	0	0.03, 0.03	<0.01, <0.01	<0.04, <0.04
CA-3 1997	Foliar twice	0.18	0	0.05, 0.06	<0.01, <0.01	<0.06, <0.07
FL 1996	Foliar twice	0.18	0	0.01, 0.02	<0.01, <0.01	<0.02, <0.03
	In-furrow + foliar	0.17		0.01, 0.01	<0.01, <0.01	<0.02, <0.02
MI 1996	Foliar twice	0.18	0	0.08, 0.04	<0.01, <0.01	<0.09, <0.05
	In-furrow + foliar	0.17		0.01, <0.01	<0.01, <0.01	<0.02, <0.02
	Banded + foliar	0.17		0.01, <0.01	<0.01, <0.01	<0.02, <0.02
NC 1996	Foliar twice	0.18	0	0.04, 0.07	<0.01, <0.01	<0.05, <0.08
	In-furrow + foliar	0.07[d]		0.03, 0.03	<0.01, <0.01	<0.04, <0.04
	Banded + foliar	0.07[d]		<0.01, 0.02	<0.01, <0.01	<0.02, <0.03
SC 1996	Foliar twice	0.18	0	0.07, 0.05	<0.01, <0.01	<0.08, <0.06
	In-furrow + foliar	0.17		0.02, 0.03	<0.01, <0.01	<0.03, <0.04
TX 1996	Foliar twice	0.18	0	0.03, 0.03	<0.01, <0.01	<0.04, <0.04
	In-furrow + foliar	0.17		0.01, 0.01	<0.01, <0.01	<0.02, <0.02
WI 1996	Foliar twice	0.18	0	0.06, 0.08	<0.01, <0.01	<0.07, <0.09
	In-furrow + foliar	0.17		0.02, 0.03	<0.01, <0.01	<0.03, <0.04
Cantaloupe						
CA-1 1996	Foliar twice	0.18	0	0.05, 0.07	<0.01, <0.01	<0.06, <0.08
			3	0.05, 0.03	<0.01, <0.01	<0.06, <0.04
	In-furrow + foliar	0.17	0	0.04, 0.03	<0.01, <0.01	<0.05, <0.04
			3	0.01, 0.01	<0.01, <0.01	<0.02, <0.02
	Banded + foliar	0.17	0	0.02, 0.02	<0.01, <0.01	<0.03, <0.03
			3	0.02, 0.02	<0.01, <0.01	<0.03, <0.03
CA-2 1996	Foliar twice	0.18	0	0.14, 0.14	<0.01, <0.01	<0.15, <0.15
	In-furrow + foliar	0.17		0.04, 0.03	<0.01, <0.01	<0.05, <0.04

(continued; footnotes follow)

Table 17. *Continued.*

Trial Location and Date	Application Data			Residues (ppm)[a]		
	Appl. Type [b]	Total rate (lb ai/A)	PHI	Thiamethoxam	CGA-322704	Combined
CA-3 1996	Foliar twice	0.18	0	0.03, 0.02	<0.01, <0.01	<0.04, <0.03
	In-furrow + foliar	0.17		0.01, 0.01	<0.01, <0.01	<0.02, <0.02
GA 1996	Foliar twice	0.18	0	0.03, 0.02	<0.01, <0.01	<0.04, <0.03
	In-furrow + foliar	0.17		<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
IN 1996	Foliar twice	0.18	0	0.13, 0.09	<0.01, <0.01	<0.14, <0.10
	In-furrow + foliar	0.17		0.05, 0.02	<0.01, <0.01	<0.06, <0.03
TX 1996	Foliar twice	0.18	0	0.04, 0.01	<0.01, <0.01	<0.05, <0.02
	In-furrow + foliar	0.17		0.01, 0.02	<0.01, <0.01	<0.02, <0.03
	Banded + foliar	0.17		0.03, 0.02	<0.01, <0.01	<0.04, <0.03
Summer Squash						
CA-1 1996	Foliar twice	0.18	0	0.13, <0.01	<0.01, <0.01	<0.14, <0.02
			3	0.04, 0.05	<0.01, <0.01	<0.05, <0.06
	In-furrow + foliar	0.17	0	0.11, 0.05	<0.01, <0.01	<0.12, <0.06
			3	0.03, 0.05	<0.01, <0.01	<0.04, <0.06
	Banded + foliar	0.17	0	0.05, 0.03	<0.01, <0.01	<0.06, <0.04
			3	0.03, 0.04	<0.01, <0.01	<0.04, <0.05
FL 1996	Foliar twice	0.18	0	0.02, 0.02	<0.01, <0.01	<0.03, <0.03
	In-furrow + foliar	0.17		0.01, <0.01	<0.01, <0.01	<0.02, <0.02
	Banded + foliar	0.17		<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
GA 1996	Foliar twice	0.18	0	0.05, 0.05	<0.01, <0.01	<0.06, <0.06
	In-furrow + foliar	0.17		0.06, 0.08	<0.01, <0.01	<0.07, <0.09
MI 1996	Foliar twice	0.18	0	0.05, 0.05	<0.01, <0.01	<0.06, <0.06
	In-furrow + foliar	0.17		0.01, 0.03	<0.01, <0.01	<0.02, <0.04
NY 1996	Foliar twice	0.18	0	0.05, 0.07	<0.01, <0.01	<0.06, <0.08
	In-furrow + foliar	0.17		0.02, 0.02	<0.01, <0.01	<0.03, <0.03

[a] Uncorrected residue data. Residues expressed as thiamethoxam.

[b] Applications consisted of two foliar applications of thiamethoxam (25% DF) totaling 0.18 lb ai/A/season (2x the proposed foliar rate) or an in-furrow or surface banded at-planting application of thiamethoxam (FlC) at 0.13 lb ai/A (1x the soil application rate) followed by a single late-season foliar application of thiamethoxam (25% DF) at 0.71 oz ai/A (1x the single foliar rate) for a total of 0.17 lb ai/A.

[c] The in-furrow application was made at 0.11 oz ai/A in error.

[d] The in-furrow and banded applications were made at 0.46 oz ai/A in error.

Pome Fruits Group

Apples and Pears

Novartis submitted data (citation shown below) from 23 tests conducted in CA(4), CO, ID, MI, NC, NY(5), OH, OR (2), PA and WA (5) during 1996 depicting residues of thiamethoxam and CGA-322704 in/on apples (17 tests) and pears (6 tests) to support a proposed tolerance for residues in/on the pome fruits crop group.

44715134 Campbell, D. (1998) CGA-293343 and CGA-215944--Magnitude of the Residues in or (on) Crop Group 11: Pome Fruits: Lab Project Number: ABR-98096: 44-96: 02-IR-047-96. Unpublished study prepared by Novartis Crop Protection, Inc. 429 p.

In a total of 13 apple tests and 6 pear tests, thiamethoxam (25% DF) was as four successive foliar applications at 1.4+1.4+0.7+0.7 oz ai/A, with RTIs of 7-10 days, for a total of 0.26 lb ai/A/season (1.5x the proposed maximum seasonal rate). The proposed 25% DF label specifies a maximum of 2 post-bloom foliar applications/season at 0.7-1.4 oz ai/A/application or 3 foliar applications at ≤0.7 oz ai/A/application. At two locations (WA and NY), applications were also made to apples at exaggerated rates totaling 0.79 and 1.32 lb ai/A (~5x and ~8x) to generate samples for processing. Applications were made using ground equipment in 50-150 gal/A of water with the exception of one apple and pear test (WA) conducted using 10 gal/A of water to simulate aerial spray application. The last two applications were made in combination with the insecticide pymetrozine (CGA-215944) using spray additives (e.g., organosilicates) at rates up to 0.5% v/v.

One control and two treated samples of apples or pears were harvested 13-15 days following the last application; the proposed label specifies a PHI of 14 days for rates ≤0.7 oz ai/A or 35 days for rates >0.7 oz ai/A. Additional samples from one apple and one pear test were also collected at posttreatment intervals of 0, 1, 3, 7, and 21 days to determine residue decline. Apple samples for processing were shipped fresh within one day of harvest directly to the processing facility. The remaining samples were placed in frozen storage at the field sites for up to 50 days prior to shipment via ACDS freezer truck or overnight carrier (on dry ice) to the Novartis, Greensboro, NC where they were stored at ~-20 C prior to analysis. The maximum storage interval for apple and pear samples was 11.1-24.6 months. Additional storage stability data for CGA-322704 in apples are required to support the storage intervals depicted in the residue study.

Residues of thiamethoxam and CGA-322704 were determined using the HPLC/UV Method AG-675 described above. Apparent residues in/on all control samples of apple and pear fruit were <0.01 ppm (<LOQ) for both analytes. The petitioner presented summary residue data corrected for procedural recoveries <100%; the uncorrected results of the residue analyses are presented in Table 18. *HED notes that in future submissions, residue data should be presented in its uncorrected form.* Adequate concurrent recoveries were obtained for both compounds.

The combined residues of thiamethoxam and CGA-322704 were <0.03-<0.12 ppm in/on 26 samples of apples, and <0.03-0.09 ppm in/on 12 samples of pears treated at 1.5x the proposed maximum rate. Combined residues of thiamethoxam and CGA-322704 were <0.10-0.26 ppm and <0.16-0.73 ppm in/on two samples each of apples treated at approximately 5x and 8x the proposed seasonal rate, respectively.

In the residue decline study on apples, residues of thiamethoxam did not appear to decline over the 0-21 day posttreatment interval; however, in one trial on apples (NC), combined residues declined from <0.13 ppm to approximately <0.05 ppm at the 0- and 14-day posttreatment intervals, respectively. The residue decline study on pears indicated that residues of each analyte are lower at longer posttreatment intervals.

Geographic representation of the residue data is adequate and a sufficient number of tests were conducted to support a crop group tolerance for residues in/on pome fruits. The petitioner conducted 13 on apples and 6 tests on pears at 1.5x the proposed seasonal rate.

Conclusions: Pending submission of supporting storage stability data, the submitted apple and pear field trial data are adequate and support the proposed 0.2 ppm tolerance. The combined residues of thiamethoxam and CGA-322704 were <0.03-<0.12 ppm in/on 26 apple samples and 12 pear samples harvested ~14 days following the last of four foliar applications of thiamethoxam applied successively at 1.4, 1.4, 0.7, and 0.7 oz ai/A, for a total of 0.26 lb ai/A (1.5x). The use pattern being proposed for pome fruits allows for 3 foliar applications of thiamethoxam (25% DF) at 0.7 oz ai/A/application with a 14-day PHI, or 2 foliar applications at 1.4 oz ai/A/application with a 35-day PHI. Residues in/on fruit resulting from the proposed use are likely to be below the proposed 0.2 ppm tolerance.

Table 18. Residues of thiamethoxam and CGA-322704 in/on pome fruits harvested following the last of four broadcast foliar applications of thiamethoxam (25% WP) [a].

Test Location	Application Data		Residues (ppm) [b]		
	Total Rate (lb ai/A)	PHI	Thiamethoxam	CGA-322704	Total
Apples					
WA-627	0.26 (1.5x)	15	0.07, 0.07	<0.01, <0.01	<0.08, <0.08
	0.79 (4.6x)		0.24, 0.25	0.01, 0.01	0.25, 0.26
	1.32 (7.8x)		0.58, 0.68	0.03 [0.04][c], 0.04 [0.04]	0.62, 0.72
WA-628	0.26	14	0.11, 0.09	<0.01, <0.01	<0.12, <0.10
OR-629	0.26	14	0.04, 0.06	<0.01,<0.01	<0.05, <0.07
ID-630	0.26	14	0.04, 0.08	<0.01, <0.01	<0.05, <0.09
NC-607	0.26	0	0.12 [0.12], 0.12 [0.12]	<0.01 [<0.01], <0.01 [<0.01]	<0.13, <0.13
		14	0.04, 0.05	<0.01, <0.01	<0.05, <0.06
OH-208	0.26	14	0.03, 0.02	<0.01, <0.01	<0.04, <0.03
PA-814	0.26	14	0.08, 0.08	<0.01, <0.01	<0.09, <0.09
CO-313	0.26	14	0.03, 0.03 [0.03]	<0.01, <0.01 [<0.01]	<0.04, <0.04
NY-004	0.26	0	0.06, 0.05	<0.01, <0.01	<0.07, <0.06
		1	0.03, 0.05	<0.01, <0.01	<0.04, <0.06
		3	0.06, 0.05	<0.01, <0.01	<0.07, <0.06
		7	0.05, 0.03	<0.01, <0.01	<0.06, <0.04
		14	0.04, 0.04	<0.01, <0.01	<0.05, <0.05
		21	0.06, 0.04	<0.01, <0.01	<0.07, <0.05
	0.79	14	0.17, 0.09	0.01, <0.01	0.18, <0.10
	1.32	14	0.15, 0.15	<0.01, <0.01	<0.16, <0.16
NY-813	0.26	14	0.05, 0.09	<0.01, <0.01	<0.06, <0.10
MI-723	0.26	14	0.05, 0.03	<0.01, <0.01	<0.06, <0.04
CA-439	0.26	14	0.03, 0.05	<0.01, 0.01	<0.04, 0.06
CA-440	0.26	14	0.02, 0.03	<0.01, <0.01	<0.03, <0.04
Pears					
NY-815	0.26	14	0.02, 0.03	0.03, 0.03	0.05, 0.06
CA-047	0.26	0	0.07, 0.07	<0.01, <0.01	<0.08, <0.08
		1	0.08, 0.07	0.01, <0.01	0.09, <0.08
		3	0.07, 0.05	0.01, 0.01	0.08, 0.06
		7	0.04, 0.04	0.01, 0.01	0.05, 0.05
		14	0.02, 0.02	0.01, 0.01	0.03, 0.03
		21	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
CA-441	0.26	14	0.02, 0.02	<0.01, <0.01	<0.03, <0.03
WA-631	0.26	13	0.04, 0.04	0.03, 0.04	0.07, 0.08
WA-632	0.26	14	0.04, 0.05	0.02, 0.02	0.06, 0.07
OR-633	0.26	14	0.06, 0.04	0.03, 0.02	0.09, 0.06

[a] Thiamethoxam (25% DF) was applied four times at 1.4, 1.4, 0.7 and 0.7 oz ai/A for the 1.5x application.
[b] Uncorrected data. Residues of CGA-322704 expressed as thiamethoxam.

[c] Bracketed value represents the result of a reanalysis of the same sample.

Barley

The petitioner submitted data (citation noted below) from 17 field trials conducted in CA (2), CO, ID (2), MN, MT, ND (4), SD (2), VA (2), WA, and WY during 1996 and 1997 depicting residues of thiamethoxam and CGA-322704 in/on barley RACs grown from thiamethoxam-treated seed.

44715105 Campbell, D. (1998) CGA-293343 and Maxim 4FS-Magnitude of the Residues in or on Barley: Final Report: Lab Project Number: 02-SR-055-96: 0W-SR-201-97: 0W-SR-601-97. Unpublished study prepared by Novartis Crop Protection, Inc. 212 p.

In 15 tests, thiamethoxam (70% WP or 5 lb/gal FlC) was prepared as a seed treatment slurry and applied to barley seed at a rate of 0.07 lb ai/100 lb seed (1.4x the proposed maximum rate). The petitioner stated that this treatment rate corresponds to 0.04-0.09 lb ai/A based on a seeding rate of 57.3-132.75 lbs of seed/A. At two trial locations, seeds were also treated at an exaggerated rate of 0.21 lb ai/100 lb seed (4.2x rate) to generate samples for processing studies. A second test substance, fludioxinil (4 lb/gal FlC), which is currently registered for use on barley, and Apron® 350FS, were also added to each seed treatment, as a maintenance chemicals, at 0.08 and 0.32 oz ai/100 lb seed, respectively. Residue data were not reported for fludioxinil.

One control and two treated samples of hay, grain, and straw were harvested from each test. Mature hay was harvested at "maturity" (the soft dough stage) 56-218 DAP and dried to a moisture content of 10-20%. In two trials, samples of hay were also harvested at 21, 14, and 7 days prior to maturity, and 7 days post-maturity to provide residue decline data. Grain and straw were harvested at maturity, 81-274 DAP. After collection, the samples were frozen, and shipped frozen to Novartis, Greensboro, NC for analysis with the exception of grain samples for processing which were shipped at ambient temperatures to the processing facility, Food Protein Center at Texas A & M, Bryan, TX; the method of shipment was not indicated. Samples of hay, straw, and grain were maintained frozen (temperature unspecified) until analyzed by the petitioner, 11-17 months after collection. Additional storage stability data for CGA-322704 are required to support the intervals depicted in the residue study.

Residues of thiamethoxam and CGA-322704 in/on barley samples were determined using Method AG-675, described above. Residues in all control samples were <0.01 ppm (<LOQ) for both analytes. Adequate concurrent recoveries were obtained for both compounds. The petitioner presented summary residue data corrected for procedural recoveries <100%; the uncorrected residue data are presented in Table 19.

Residues of thiamethoxam and CGA-322704 were each <0.01 ppm (<LOQ) in/on 24 samples of grain grown from seed treated at 1.4x the proposed maximum rate. Combined residues of thiamethoxam and CGA-322704 were <0.02-0.05 ppm in/on 30 mature hay samples treated at 1.4x; only one hay sample harvested at maturity bore measurable residues of parent (0.02 ppm)

and five samples bore measurable residues of CGA-322704 at 0.01-0.03 ppm. Combined residues of thiamethoxam and CGA-322704 were <0.03 ppm in/on 30 samples of straw treated at the 1.4x rate. Residues of parent were <LOQ in/on all straw samples analyzed, and only five straw samples bore quantifiable residues of CGA-322704 at 0.01-0.02 ppm. In the two residue decline studies, residues of each analyte in/on hay samples harvested from 21 days prior to soft dough stage to 7 days after the soft dough stage were shown to decline.

Residues of each analyte were <LOQ in/on all barley RAC samples grown from seed treated at 4.2x. Bulk samples of grain from the 4.2x study were processed into barley fractions; however, as no quantifiable residues of either analyte were found in/on grain from the field trials and the two tests conducted at 4.2x, these samples were not analyzed. An adequate wheat processing study (discussed below) is also available.

Geographic representation of the residue data is adequate, and a sufficient number of tests were conducted to support tolerances for residues on barley commodities. A total of 15 tests were conducted at 1.4x in Region 7 (five tests), Region 5 (three tests), Regions 2, 10, and 11 (two tests each), and Region 9 (one test). Samples of grain from a reduced number of trials (12 of the 15 tests) were analyzed as residues of each analyte were non-quantifiable in/on all grain samples; data on barley grain are available from 12 tests (24 samples) which satisfy OPPTS.GLN 860.1500 requirements for distribution and number of tests.

Conclusions: Pending resolution of questions concerning storage stability of CGA-322704, the submitted residue data on barley are adequate and support the proposed tolerances for thiamethoxam residues in/on barley hay, (0.05 ppm), grain (0.02 ppm) and straw (0.03 ppm).

In the current study, barley RAC samples were stored frozen for up to 17 months prior to analysis. Data are available indicating that residues of thiamethoxam are stable frozen in various representative crops, including corn grain, for up to 2 years; however, data from an interim study on CGA-322704 are only available for storage intervals up to 1 year.

Table 19. Residues of thiamethoxam and CGA-322704 in/on barley hay and straw grown from seed treated with thiamethoxam (70% WP or 5 lb/gal FlC) at 0.07 or 0.21 lb ai/100 lb seed (1.4x or 4.2x).

Test Location and Date	Application Data			Residues (ppm) [a]		
	Form.	Total Rate (lb ai/100 lb seed)	DAP[b]	Thiamethoxam	CGA-322704	Total
Hay						
CA-1996	70WP	0.07	104	0.01, 0.05	0.02, 0.05	0.03, 0.11
			111	0.03, 0.02	0.05, 0.02	0.09, 0.04
			118	0.03, 0.02	0.05, 0.04	0.09, 0.07
			125 [c]	<0.01, **0.02** [d]	**0.02, 0.03**	<0.03, 0.05
			132	<0.01, 0.01	0.01, 0.03	<0.02, 0.04
	5 FlC	0.07	125	<0.01, <0.01	**0.02, 0.02**	<0.03, <0.03
CO-1997	70WP	0.07	95	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
ID-1997	70WP	0.07	90	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
		0.21		<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
MN-1997	70WP	0.07	63	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
MT-1997	70WP	0.07	88	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
ND-1-1997	70WP	0.07	46	0.11 [0.08][e] 0.03 [0.02]	0.05 [0.05] 0.02 [0.02]	0.17 [0.14] 0.05 [0.04]
			53	0.03, 0.03	0.03, 0.03	0.06, 0.06
			60	0.01, 0.02	0.02, 0.02	0.03, 0.03
			67 [c]	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
			74	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
	5 FlC	0.07	67	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
ND-2-1997	70WP	0.07	66	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
		0.21		<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
SD-1-1997	70WP	0.07	67	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
SD-2-1997	70WP	0.07	56	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
VA-1996	70WP	0.07	218	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
	5 FlC			<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
WA-1997	70WP	0.07	80	<0.01, <0.01	**0.01**, <0.01	<0.02, <0.02
WY-1997	70WP	0.07	78	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02

(continued; footnotes follow)

Table 19. *Continued.*

Test Location and Date	Application Data			Residues (ppm) [a]		
	Form.	Total Rate (lb ai/100 lb seed)	DAP[b]	Thiamethoxam	CGA-322704	Total
Straw						
CA-1996	70WP	0.07	182	<0.01, <0.01	**0.02, 0.02**	<0.03, <0.03
	5 FlC			<0.01, <0.01	**0.02, 0.02**	<0.03, <0.03
CO-1997	70WP	0.07	127	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
ID-1997	70WP	0.07	117	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
		0.21		<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
MN-1997	70WP	0.07	94	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
MT-1997	70WP	0.07	115	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
ND-1996	70WP	0.07	105	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
	5 FlC			<0.01, <0.01	<0.01, **0.01**	<0.02, <0.02
ND-1997	70WP	0.07	94	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
		0.21		<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
SD-1-1997	70WP	0.07	94	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
SD-2-1997	70WP	0.07	81	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
VA-1996	70WP	0.07	274	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
	5 FlC			<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
WA-1997	70WP	0.07	107	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
WY-1997	70WP	0.07	112	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02

[a] Uncorrected data. Residues of CGA-322704 expressed as thiamethoxam.
[b] DAP = Days after planting.
[c] For residue decline studies, hay was harvested at 21, 14, and 7 days before maturity, at maturity (67 and 125 DAP for the ND and CA tests, respectively), and at 7 days post- maturity.
[d] **Bolded** values indicate residues ≥LOQ for the proposed harvest interval ("at maturity").
[e] Samples were reanalyzed using the confirmatory LC/MS/MS method.

Grain Sorghum

The petitioner submitted data (citation shown below) from 14 field trials conducted in AR, CO, GA, KS (2), MS, NE (2), NM, OK, SD, and TX (3) during 1996 depicting residues of thiamethoxam and CGA-322704 in/on grain sorghum RACs grown from thiamethoxam-treated seed.

44715112 Eudy, L. (1998) CGA-293343--Magnitude of the Residue in or on Grain Sorghum: Final Report: Lab Project Number: 0S-IR-109-96: 0S-IR-204-96: 0S-IR-320-96. Unpublished

study prepared by Novartis Crop Protection, Inc. 302 p.

Thiamethoxam (70% WP) was applied to sorghum seed as a seed treatment slurry at 0.3 lb ai/100 lb seed (1.5x the proposed maximum rate). At two trial locations (KS and TX), seeds were also treated at an exaggerated rate of 0.9 lb ai/100 lb seed (4.5x rate) to generate samples for processing studies.

One control and two treated samples of sorghum forage, grain, and stover were harvested from each test plot at 38-48 DAP for forage and 112-274 DAP for grain and stover. The samples were shipped frozen via ACDS freezer truck to Novartis, Greensboro, NC where they were held at <-15 C prior to preparation for analysis; grain samples for processing were shipped frozen to the processing facility. The samples were then delivered frozen (dry ice) by the petitioner to EN-CAS Analytical Laboratories, Winston-Salem, NC where they kept frozen (≤-17 C) prior to analysis. Samples were maintained frozen from collection to analysis for 20.4-26.3 months for grain and stover, and 24.7-30.3 months for forage. Additional storage stability data on CGA-322704 are required to support the residue study.

Residues of thiamethoxam and CGA-322704 in/on sorghum samples were determined using Method AG-675, described above. Residues in all control samples were <0.01 ppm (<LOQ) for both analytes. Adequate concurrent recoveries were obtained for both compounds.

Residues of thiamethoxam and CGA-322704 were each <0.01 ppm (<LOQ) in/on all samples forage (n=20), grain (n=18), and stover (n=18) grown from seed treated at 1.5x the proposed maximum rate. Residues of each analyte were also <LOQ in/on all forage, grain, and stover samples (n=4 each) grown from seed treated at 4.5x.

Geographic representation of the residue data is adequate, and a sufficient number of tests were conducted to support tolerances for residues on grain sorghum. Although 12 trials were conducted, the petitioner provided data from a reduced number of trials as stipulated by OPPTS.GLN 860.1500 for uses resulting in non-quantifiable residues. Residue data were provided from a total of nine tests conducted at 1.5x in Region 5 (three tests), Regions 6 and 8 (two tests each), and Regions 4 and 7 (one test each).

Conclusions: Pending resolution of questions concerning storage stability of residues of thiamethoxam, the submitted residue data on grain sorghum are adequate and support the proposed tolerances for residues of thiamethoxam in/on sorghum forage, grain, and stover (0.02 ppm each).

In the current study, samples of sorghum grain and stover were stored frozen for up to ~2 years (20-26 months) prior to analysis; forage samples were stored frozen for up to 2.5 years (25-30 months. Data are available indicating that residues of thiamethoxam are stable frozen in various representative crops, including corn grain, for up to 2 years; however, data from an interim study on CGA-322704 are only available for storage intervals up to 1 year. To support the storage

intervals depicted on forage, data from an on-going study on lettuce may be used for which data are currently available for only 4 months of frozen storage. When the final reports are available, the sorghum study may be upgradeable.

Wheat

The petitioner submitted data (citation shown below) from 27 field tests conducted in AR, CA, CO, ID, IL, KS (4), MN (2), MO, MT (2), NE, NM, NC (2), ND (4), SD, OK (3), and TX during 1996 and 1997 depicting residues of thiamethoxam and CGA-322704 in/on wheat RACs grown from thiamethoxam-treated seed.

> 44715108 Vincent, T. (1998) CGA-293343 and Maxim 4FS--Magnitude of the Residues in or on Wheat: Interim Report: Lab Project Number: 337-96: 02-SR-073-97: 0W-SR-202-97. Unpublished study prepared by Novartis Crop Protection, Inc. 496 p.

In 26 tests, thiamethoxam formulated as a 70% WP (22 tests) or a 5 lb/gal FlC (4 tests) was prepared as a seed treatment slurry and applied to wheat seeds at 0.07 lb ai/100 lb seed (1.4x the proposed maximum rate); seeds in one test (ND) were inadvertently treated at 0.11 lb ai/100 lb seed (2x). At one trial location (ND), seeds were also treated at an exaggerated rate of 0.21 lb ai/100 lb (4.2x rate) to generate samples for processing.

A single control and two treated samples each of wheat forage, hay, grain and straw were harvested from each test plot. Forage samples were collected at 40-47 DAP with the exception of samples for the residue decline studies and one sample taken at 237 DAP (CO) due to insufficient plant material at earlier intervals; samples of hay were cut at 63-293 DAP and air dried for up to 13 days before sampling; mature grain and straw samples were collected 88-320 DAP. At two trial locations, forage samples were also harvested at 30/31, 35, 42, and 49 DAP to provide data on residue decline in forage.

After collection, the samples were frozen and shipped frozen via freezer truck to Novartis, Greensboro, NC where the samples were stored at ~-20 C prior to preparation for analysis; composite grain samples for processing were shipped frozen directly to the processing facility, Texas A & M University Food Protein Research and Development Center, Bryan, TX. The samples were then shipped overnight from Novartis (on dry ice), and were received in frozen condition by EPL-BAS, Harristown, IL, where they were stored frozen (temperature unspecified). The maximum frozen storage intervals for wheat samples were 10-23 months from collection to analysis. Additional storage stability data for CGA-322704 are required to support the intervals depicted in the residue study.

Residues of thiamethoxam and CGA-322704 in/on wheat samples were determined using the HPLC/UV or MS Method AG-675, described above. The petitioner presented summary residue data corrected for procedural recoveries <100%; the uncorrected residue data are presented in this report. Residues in all control samples for each matrix were <0.01 ppm (<LOQ) for both

analytes.

Residues of thiamethoxam *per se* were <0.01 ppm in/on all samples of grain (n=41), hay (n=51), and straw (n=51) grown from seed treated at 1.4x the proposed maximum rate. Residues of CGA-322704 were also <0.01 ppm (<LOQ) in/on all grain samples (n=41), and in/on all hay and straw samples (n=51 each) with the following exceptions: one hay sample (TX), and two straw samples (OK-777-96 test) bore residues of the metabolite at 0.01 ppm. Residues of both analytes were also <LOQ in/on grain, straw, and hay samples from the one test erroneously conducted at 2x (n=2 each), and from the 4.2x treatment (n=1 each). Combined residues of thiamethoxam and CGA-322704 were <0.02-0.46 ppm in/on 51 forage samples grown from seed treated at 1.4x and harvested at ~42 DAP (Table 20); combined residues were 0.04 and 0.10 in/on two samples from the 2x treatment, and <0.02 ppm in/on one sample from the 4.2x treatment. In the only residue decline study with quantifiable residues (OK), combine residues in/on forage samples collected from 31 to 49 DAP declined on average from 0.09 ppm to <0.02 ppm, respectively.

Geographic representation of the residue data is adequate, and a sufficient number of tests were conducted to support tolerances for residues on wheat. A total of 25 tests were conducted at 1.4x in Region 8 (7 tests), Region 5 (6 tests), Region 7 (5 tests), Regions 2 and 6 (2 tests each), and Regions 4, 10, and 11 (1 test each). Samples of grain from a reduced number of trials (20 of the 25 conducted) were analyzed as residues of each analyte were non-quantifiable in/on all grain samples; data on wheat grain are available from 20 tests performed at ~1x at (41 samples) which satisfy OPPTS.GLN 860.1500 requirements for the distribution and number of tests.

Conclusions: Pending resolution of questions concerning storage stability of CGA-322704, the submitted residue data on wheat are adequate and support the proposed tolerances for thiamethoxam residues in/on wheat forage at 0.50 ppm and in/on wheat hay, grain, and straw each at 0.02 ppm.

In the current study, wheat RAC samples were stored frozen for 10-23 months prior to analysis. Data are available indicating that residues of thiamethoxam are stable frozen in various representative crops, including corn grain, for up to 2 years; however, data from an interim study on CGA-322704 are only available for storage intervals up to 1 year. When the final storage stability report is submitted for CGA-322704, the residue study may be considered acceptable.

Table 20. Residues of thiamethoxam and CGA-322704 in/on **wheat forage** grown from seed treated with thiamethoxam (70% WP or 5 lb/gal FlC) at 0.07, 0.11, or 0.21 lb ai/100 lb seed (1.4x, 2.2x, or 4.2x the proposed maximum rate).

Test Location (code number) and Date	Application Data			Residues (ppm) [a]		
	Form.	Total Rate (lb ai/100 lb seed)	DAP[b]	Thiamethoxam	CGA-322704	Total
AR-111-1996	70WP	0.07	43	0.01, 0.01	<0.01, <0.01	<0.02, <0.02
CA-073-1997	70WP	0.07	42	[0.04, 0.05][c], 0.04	<0.01, <0.01	<0.06, <0.05
CO-323-1996	70WP	0.07	237	0.01, 0.01	<0.01, <0.01	<0.02, <0.02
ID-673-1996	70WP	0.07	42	[0.26, 0.33], [0.34, 0.30]	[0.08, 0.05], [0.07, 0.07]	0.41, 0.41
IL-001-1996	70WP	0.07	40	0.08, 0.08	0.03, 0.02	0.11, 0.10
KS-320-1996	70WP	0.07	42	<0.01, <0.01, 0.01	<0.01, <0.01, <0.01	<0.04, <0.05
KS-321-1996	70WP	0.07	42	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
KS-322-1996	70WP	0.07	42	0.01, 0.01	<0.01, 0.02	<0.02, 0.03
	5 FlC			0.03, 0.02	0.02, 0.01	0.05, 0.03
MN-509-1997	70WP	0.07	42	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
	5 FlC			<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
MO-208-1996	70WP	0.07	43	0.05, 0.03	0.02, 0.01	0.07, 0.04
MT-202-1997	70WP	0.07	47	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
MT-203-1997	70WP	0.07	47	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
NE-611-1996	70WP	0.07	42	0.03, 0.04	<0.01, <0.01	<0.04, <0.05
NM-779-1996	70WP	0.07	42	0.07, 0.06	0.02, 0.03	0.09, 0.09
NC-610-1996	70WP	0.07	42	0.30, 0.37	[0.06, 0.09], [0.06, 0.09]	0.39, 0.46
	5 FlC			0.24, 0.18	[0.06, 0.08], [0.03, 0.04, 0.04]	0.32, 0.22
ND-505-1997	70WP	0.07	42	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
		0.21		0.01	<0.01	<0.02
ND-506-1997	70WP	0.07	42	0.07, [0.03, 0.07]	0.01, 0.02	0.08, 0.09
		0.11[d]		0.03, 0.07	0.01, 0.03	0.04, 0.10
OK-777-1996	70WP	0.07	42	0.11, 0.12	0.03, 0.03	0.14, 0.15
	5 FlC			0.12, 0.13	0.03, 0.04	0.15, 0.17
OK-778-1996	70WP	0.07	31	[0.03, 0.05], [0.08, 0.09]	[<0.01, 0.02], [<0.01, 0.02]	0.07, 0.11
			35	0.03, [0.03, 0.05]	<0.01, 0.01	<0.04, 0.06
			42	0.01, 0.01	<0.01, <0.01	<0.02, <0.02
			49	0.01, 0.01	<0.01, <0.01	<0.02, <0.02
SD-507-1997	70WP	0.07	30	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
			35	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
			42	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
			49	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
TX-780-1996	70WP	0.07	47	0.17, 0.22	[0.03, 0.03], [0.04, 0.04]	0.20, 0.26

[a] Uncorrected data. Residues of CGA-322704 expressed as thiamethoxam.

[b] DAP = Days after planting.

[c] Bracketed values represent duplicate or triplicate analyses of the same samples. The highest value is used to calculate the combined "total" residues.

[d] Applied at ~2x the proposed rate in error.

Cotton

Novartis submitted data (citation shown below) from 16 field tests conducted in AL, AK, AZ, CA (4), LA, MS, NM, OK, and TX (5) during 1997 depicting residues of thiamethoxam in/on cotton:

44715104 Campbell, D. (1998) CGA-293343--Magnitude of the Residue in or on Cotton: Final Report: Lab Project Number: 34-97: 346012: 133-98A. Unpublished study prepared by Novartis Crop Protection, Inc. 252 p.

In 12 tests, cotton grown from seed treated with thiamethoxam (5 lb/gal FlC) at 0.3 lb ai/100 lb seed was treated twice foliarly with thiamethoxam (25% DF) at 0.71 oz ai/A/application, at a RTI of 14 days, for a total postemergence rate of 1.43 oz ai/A (0.09 lb ai/A; 1x the proposed maximum foliar rate). Based on the seeding rate, the petitioner calculated that the seed treatment was equivalent to 0.35-0.72 oz ai/A; therefore, the total rate of thiamethoxam applied was equivalent to 0.11-0.13 lb ai/A. At two sites (CA and TX), exaggerated foliar rates (3x and 5x the foliar rate) were also used to generate samples for processing; the seed treatment rate was not increased in these trials over the 1x.

Two control and treated samples of cotton were harvested from each test by hand or using mechanical equipment (stripper or picker) 20-28 days following the last foliar application. To examine residue decline, samples of cotton were also collected from one of the TX tests at 0, 7, 13, 25, and 28 days after the last foliar treatment. Samples were stored frozen at the test site for up to 49 days. For the field trials in which only ginned, undelinted seed was analyzed, cottonseed samples were shipped via overnight courier with dry ice or freezer truck to directly to Novartis, Greensboro, NC. Samples which required ginning to produce cotton gin byproducts (6 tests) and processed fractions (4 tests) were shipped frozen directly to the processing facility, Texas A & M University, Food Protein Development and Research Center, Bryan, TX. Following processing, the gin byproduct samples were frozen and shipped by freezer truck or overnight (on dry ice) to Novartis, Greensboro, NC. At Novartis, all samples were kept at ~-20 C prior to preparation for analysis. The maximum frozen storage intervals for cottonseed and gin byproducts were 5-14 months, from collection to analysis. The residue data for both analytes are adequately supported by existing storage stability data on representative commodities.

Residues of thiamethoxam and CGA-322704 were determined using Method AG-675, described above. Residues of each analyte in all control samples of cottonseed and cotton gin byproducts were <0.01 ppm (<LOQ) with the exception of two gin byproduct samples which bore apparent residues of CGA-322704 at 0.01 and 0.03 ppm (NM and MS tests, respectively). The petitioner provided summary data corrected for procedural recoveries <100%; uncorrected residue data from the cotton field trials are presented in Table 21.

The combined residues of thiamethoxam and CGA-322704 were <0.02-<0.04 ppm in/on 24 samples of cottonseed grown from treated seed and harvested ~21 days following last of two treatments at 1x the proposed foliar rate. Combined residues in/on cottonseed (n=4 each) treated in the same manner except at 3x or 5x the proposed foliar rate were <0.02-<0.07 and <0.02-<0.10, respectively. In the residue decline study, average residues were <0.09 ppm at 0 days posttreatment and declined to <0.05 ppm by 28 days posttreatment. HED notes that one of samples collected at 28 days posttreatment had combined residues of <0.07 ppm, exceeding the highest value obtained from all tests for the proposed 21-day PHI (<0.04 ppm).

The petitioner also provided data from cotton gin byproducts produced from cotton harvested by mechanical picker and stripper picker (3 tests each). Combined residues of thiamethoxam and CGA-322704 were 0.06-1.10 ppm in/on 12 samples of cotton gin byproduct samples derived from cotton grown from treated seed and harvested 20-28 days following last of two treatments at 1x the proposed foliar rate. From the studies performed at 3x or 5x the proposed foliar rate, combined residues in/on cotton gin byproducts were 0.48-3.90 and 0.70-5.37 ppm (n=4 each).

Geographic representation of the residue data is adequate and a sufficient number of tests were conducted. The petitioner provided data from 12 tests on cotton at the 1x rate in Region 8 (4 tests), Regions 10 and 4 (3 tests each), Regions 6 and 2 (1test each). From six of these tests the petitioner provided data on residues of thiamethoxam in/on cotton gin byproducts processed from cotton harvested by stripper picker or mechanical picker (test locations unspecified) .

Conclusions: The submitted cotton residue data are adequate provided that the proposed 25% DF label is amended to prohibit foliar applications to cotton previously treated at-planting with a soil application of thiamethoxam (2 lb/gal FlC) as residue data are not available supporting this use. Residue data are also not available depicting residues in/on cottonseed and gin byproducts from plants treated at-planting with a single soil application of thiamethoxam (2 lb/gal FlC) at up to 0.13 lb ai/A. However, based on data from the metabolism studies and the length of the cotton growing season, residues of thiamethoxam and CGA-322704 in/on cottonseed and gin byproducts resulting from this use are unlikely to exceed the residues resulting from the two late season foliar application. Therefore, HED will allow the proposed soil application use on the 2 lb/gal FlC label.

The available data from the late-season foliar applications indicate that the proposed 0.05 ppm tolerance for residues of thiamethoxam in/on undelinted cottonseed is too low considering that one residue decline sample collected at 28 days posttreatment bore combined residues of <0.07 ppm; a more appropriate tolerance level would be 0.1 ppm. In addition, the available data indicate that the proposed tolerance of 1.0 ppm for residues in/on cotton gin byproducts is too low; a more appropriate tolerance level would be 1.5 ppm. The petitioner should submit a revised label.

Table 21. Residues of thiamethoxam and CGA-322704 in/on **cottonseed** and **cotton gin byproducts** grown from seed treated with thiamethoxam (5 lb/gal FlC) at 0.3 lb ai/100 lb and harvested 21-28 days following the last of two foliar applications of thiamethoxam (25% DF) totaling 0.09, 0.27, or 0.45 lb ai/A (1x, 3x, or 5x the proposed maximum foliar rate).

Trial Location	Application Data		Residues (ppm) [a]		
	Total Foliar (lb ai/A)	PHI	Thiamethoxam	CGA-322704	Combined
Undelinted Cottonseed					
AR	0.09	21	0.01, 0.01	<0.01, <0.01	<0.02, <0.02
AL	0.09	21	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
AZ	0.09	22	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
CA-038	0.09	22	<0.01, 0.03	<0.01, <0.01	<0.02, <0.04
	0.27		0.05, 0.06	<0.01, <0.01	<0.06, <0.07
	0.45		0.09, 0.08	<0.01, <0.01	<0.10, <0.09
CA-424	0.09	21	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
LA	0.09	23	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
MS	0.09	20	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
NM	0.09	28	0.01, 0.01	<0.01, <0.01	<0.02, <0.02
OK	0.09	21	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
TX-203	0.09	0	0.10, 0.05	<0.01, <0.01	<0.11, <0.06
		7	0.02, 0.01	<0.01, <0.01	<0.03, <0.02
		13	0.03, 0.02	<0.01, <0.01	<0.04, <0.03
		25	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
		28	0.01, 0.06	<0.01, <0.01	<0.02, <0.07
TX-308	0.09	21	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
	0.27		<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
	0.45		<0.01, 0.01	<0.01, <0.01	<0.02, <0.02
TX-204	0.09	25	0.02, 0.03	<0.01, <0.01	<0.03, <0.04
Cotton Gin Byproducts [b]					
CA-038	0.09	22	0.91, 1.09	<0.01, 0.01	<0.92, 1.10
	0.27		2.40, 3.85	0.03, 0.05	2.43, 3.90
	0.45		5.29, 5.09	0.08, <0.01	5.37, <5.10
MS	0.09	20	0.04, 0.04	0.02, 0.05	0.06, 0.09
NM	0.09	28	0.33, 0.35	<0.01, <0.01	<0.34, <0.36
OK	0.09	21	0.08, 0.09	<0.01, <0.01	<0.09, <0.10
TX-308	0.09	21	0.10, 0.07	<0.01, <0.01	<0.11, <0.08
	0.27		0.46, 0.51	0.02, 0.03	0.48, 0.54
	0.45		0.67, 0.78	0.03, 0.04	0.70, 0.82
TX-204	0.09	25	0.45, 0.46	<0.01, <0.01	<0.46, <0.47

[a] Uncorrected residue data. Residues expressed as thiamethoxam.

[b] The petitioner indicated that three tests each were harvested by mechanical means (picker or stripper); the harvest method was not indicated for each test.

Tobacco

Novartis submitted data from 12 field trials conducted in KY (4) and NC (8) during 1998 depicting residues of thiamethoxam in/on tobacco. The results are reported in the following volume of data:

44715103 Campbell, D. (1998) CGA-293343 and Emamectin--Magnitude of the Residue in or on Tobacco: Interim Report: Lab Project Number: 133-98: OS-IR-606-98/NC: NE-IR-202-98/KY. Unpublished study prepared by Novartis Crop Protection, Inc. 105 p.

At each test site (3 tests), thiamethoxam (2 lb/gal FlC) was applied to tobacco at planting as an in-furrow application at 2 oz ai/A followed by a single broadcast foliar application of thiamethoxam (25% DF) at 0.9 oz ai/A, for a total of 2.9 oz ai/A (0.18 lb ai/A/season). Although the currently proposed labels preclude the use of the 25% DF as a foliar treatment if the crop has been previously treated at planting with the proposed 2 lb/gal FlC, the petitioner stated in their submission that this treatment represents the 1x maximum proposed rate. Three tests were also conducted using thiamethoxam (2 lb/gal FlC) applied only at-planting as the in-furrow soil treatment 0.13 lb ai/A/season (1x the proposed soil treatment maximum). In addition, at each test site, 3 trials each representing both treatment regimes were conducted at 2x the proposed rates. Applications were made using ground equipment at 20-23 and 9-109 gal/A of water for foliar and in-furrow treatments, respectively. Although the target rate was 100 gal/A of water for in-furrow treatments, 9.2 gal/A of water were used in one test (NC-2) in error.

Duplicate control and treated tobacco leaf samples were harvested 74-105 days following at-planting soil applications (without foliar treatment) or 14 days following the last foliar application. A one test site (NC), green leaves were also harvested at 0, 2, 7, 10, 14, and 18 days following the foliar treatments for a residue decline study. After harvest and curing (if required), samples were stored briefly at the test site and shipped directly to Novartis, Greensboro, NC, where they were stored frozen (temperature unspecified) prior to preparation and analysis. The maximum frozen storage interval for tobacco was 3 months. The residue study is adequately supported by existing storage stability data.

Residues of thiamethoxam and CGA-322704 were determined using HPLC/UV Method AG-675, described above. Residues of each analyte in all control samples of green and cured leaves were <LOQ (<0.01 and <0.1 ppm, respectively). The petitioner provided summary data corrected for procedural recoveries <100%; uncorrected residue data from the tobacco field trial are presented in Table 22.

For the in-furrow +foliar treatment (1x rate), combined residues of thiamethoxam and CGA-322704 were 0.09-0.23 ppm and 0.6-0.8 ppm in/on six samples each of green and cured leaves, respectively. Combined residues were 0.24-0.64 ppm and 1.4-3.0 ppm in/on six samples each of green and cured leaves, respectively, from the same treatment at a 2x rate. For the soil treatment alone (1x the proposed soil treatment maximum), combined residues of thiamethoxam and CGA-322704 were <0.02-0.13 ppm and <0.2-0.8 ppm in/on six samples each of green and cured leaves, respectively. Combined residues were <0.03-0.35 ppm and <0.2-1.3 ppm in/on six samples each of green and cured leaves, respectively, from the soil treatment applied alone at 2x.

In the residue decline study, combined residues decreased on average from 0.84 to 0.23 ppm at the 0- and 18-day posttreatment intervals, respectively, indicating that residues are lower at longer PHIs.

Geographic representation of tests on tobacco conformed to OPPTS Series 860 guidelines and an adequate number of samples was analyzed.

Conclusions: The submitted field trial data on tobacco are adequate. A tolerance or exemption from tolerance is not required for use of pesticides on tobacco. However, a revised label is required if the petitioner intends to support the use of a sequential soil and foliar treatment on tobacco. A pyrolysis study was not submitted to show what residues may occur in tobacco smoke. RAB2 is willing to waive this study provided the risk to smokers is not of concern when it is assumed all residues of parent and CGA-322704 in cured tobacco are released into the smoke.

Table 22. Residues of thiamethoxam and CGA-322704 in/on tobacco following either a single at planting in-furrow spray of thiamethoxam (2 lb/gal FlC) at 1x or 2x or an in-furrow application of thiamethoxam (2 lb/gal FlC) at 1x or 2x followed by a late-season broadcast foliar application of thiamethoxam (25% DF) at 1x or 2x the proposed foliar maximum rate.

Trial Location and Date	Application Data			Residues (ppm)[a]		
	Appl. Type	Total (lb ai/A)	PHI	Thiamethoxam	CGA-322704	Combined
Green Leaves						
NC-1-1998	In-furrow + foliar	0.18	0	0.95, 0.67	0.03, 0.03	0.98, 0.70
			2	0.47, 0.63	0.05, [0.07, 0.05][b]	0.52, 0.70
			7	0.87, [0.27, 0.28]	[0.05, 0.05], 0.02	0.92, 0.30
			10	[0.35, 0.41], [0.06, 0.06]	[0.04, 0.04], <0.01	0.45, <0.07
			14	0.19, 0.20	0.03, 0.03	0.22, 0.23
			18	0.16, 0.22	0.03, 0.05	0.19, 0.27
		0.36	14	[0.21, 0.23], 0.55	[0.04, 0.04], [0.09, 0.09]	0.27, 0.64
	In-furrow alone	0.13	74	0.08, 0.11	0.02, 0.02	0.10, 0.13
		0.25		0.11, 0.30	0.02, 0.05	0.13, 0.35
KY-1998	In-furrow + foliar	0.18	14	0.07, 0.08	0.02, 0.02	0.09, 0.10
		0.36		0.30, 0.28	0.07, 0.05	0.37, 0.33
	In-furrow alone	0.13	93	<0.01, <0.01	<0.01, <0.01	<0.02, <0.02
		0.25		0.02, 0.03	<0.01, <0.01	<0.03, <0.04
NC-2-1998	In-furrow + foliar	0.18	14	0.11, 0.16	0.03, 0.03	0.14, 0.19
		0.36		0.20, 0.28	0.04, 0.06	0.24, 0.34
	In-furrow alone	0.13	105	0.05, 0.08	0.02, 0.02	0.07, 0.10
		0.25		0.10, 0.07	0.03, 0.02	0.13, 0.09
Cured Leaves [c]						
NC-1998	In-furrow + foliar	0.18	14	0.20, 0.27	0.51, 0.51	0.71, 0.78
		0.36		0.84, 0.71	2.19, 1.46	3.03, 2.17
	In-furrow alone	0.13	74	0.23, 0.17	0.59, 0.37	0.82, 0.54
		0.25		0.34, 0.44	0.58, 0.87	0.92, 1.31
KY-1998	In-furrow + foliar	0.18	14	0.33, 0.39	0.30, 0.21	0.63, 0.60
		0.36		0.84, 0.86	0.59, 0.88	1.43, 1.74
	In-furrow alone	0.13	93	<0.1, <0.1	<0.1, <0.1	<0.2, <0.2
		0.25		<0.1, <0.1	<0.1, <0.1	<0.2, <0.2
VA-1998	In-furrow + foliar	0.18	14	0.13, 0.13	0.53, 0.63	0.66, 0.76
		0.36		0.35, 0.32	1.48, 1.31	1.83, 1.63
	In-furrow alone	0.13	105	<0.1, <0.1	0.24, 0.28	<0.34, <0.38
		0.25		<0.1, <0.1	0.50, 0.46	0.60, 0.56

[a] Uncorrected residue data. Residues expressed as thiamethoxam.

[b] Bracketed values represent the results of duplicate analyses of the same samples; the total combined residues are calculated using the highest value.

[c] Flu-cured (NC and VA) and burley (KY) tobacco are represented.

OPPTS GLN 860:1520: Processed Food/Feed

Potato

In conjunction with the magnitude of the residue study on potato (1998; MRID 44715110), the petitioner submitted data depicting residues of thiamethoxam in/on potato processed commodities.

In two tests conducted in ID and ND, thiamethoxam (FlC and 25% DF) was applied to potatoes at rates totaling 0.04, 0.17, 0.51, and 0.85 lb ai/A (0.4x, 1.4x, 4x, and 7x the proposed seasonal rate, respectively). At harvest (14 days posttreatment), potato samples were promptly shipped at ambient temperatures by overnight carrier to the processing facility, National Food Laboratory, Inc., Dublin, CA where they were processed using simulated commercial practices into culls, wet peels and trimmings, granules, and chips. The samples were processed within 15 days of harvest, frozen, and shipped within 9 days by freezer truck to Novartis, Greensboro, NC. The samples were stored at approximately -20 C at Novartis for 2 years prior to extraction and analysis. Supporting storage stability data are required for residues of CGA-322704.

Residues of thiamethoxam and CGA-322704 in potato tubers and processed fractions were determined by the HPLC/UV or MS (chips only) Method AG-675 described above. The LOQ for each analyte in/on potato processed commodities is 0.01 ppm. Apparent residues of each analyte were <0.01 ppm (<LOQ) in/on all control samples. Residues of each analyte were <LOQ in/on one sample each of composite potato (RAC) and processed fractions from the 0.4x and 1.4x processing study. The results of the processing studies conducted at 4x and 7x rates are shown in Table 23.

In the study conducted in ID, residues of thiamethoxam and CGA-322704 were each <0.01 ppm in/on one composite potato sample (RAC) treated at 4x and 7x, and residues did not appreciably concentrate in any of the processed potato commodities. In the ND study, combined residues in/on potato RAC samples were ~0.036 ppm after both 4x and 7x treatment, and concentrated in chips on average by 1.9x. Residues of each analyte do not concentrate appreciably in granules or wet peels. However, based upon this concentration factor and HAFT residues of 0.036 ppm (combined residues of thiamethoxam and CGA-322704) in a 7X exaggerated study, combined residues of thiamethoxam and CGA-322704 would not be expected to reach the limit of quantitation of the cold method (0.02 ppm). Therefore, a tolerance on chips is not needed.

Table 23. Residues of thiamethoxam in commodities processed from potatoes harvested 14 days after the last application of thiamethoxam (FlC and 25% DF) at exaggerated rates (4x and 7x the proposed maximum rate).

Matrix	Total Appl. Rate (lb ai/A)	Residues (ppm) [a]			Concentration Factor [b]	Average Concentration Factor
		Thiamethoxam	CGA-322704	Combined		
ID Trial Location						
Potato tuber (RAC)	0.51 (4x)	<0.01	<0.01	<0.02	NA	NA
	0.85 (7x)	<0.01	<0.01	<0.02		
Culls	0.51	<0.01	<0.01	<0.02	--	--
	0.85	<0.01	<0.01	<0.02	--	
Wet peel & trimmings	0.51	<0.01	<0.01	<0.02	--	--
	0.85	<0.01	<0.01	<0.02	--	
Granules	0.51	0.013	<0.01	<0.023	1.15	1.3x
	0.85	0.019	<0.01	<0.029	1.45	
Chips	0.51	<0.01, [<0.01][c]	<0.01, [<0.01]	<0.02, [<0.02]	--	1.1x
	0.85	<0.01, [<0.01]	<0.01, [0.011]	<0.02, [<0.023]	1.15	
ND Trial Location						
Potato tuber (RAC)	0.51 (4x)	0.018	0.016	0.037	NA	NA
	0.85 (7x)	0.019	0.014	0.035		
Culls	0.51	0.032	0.02	0.055	1.5	1.2x
	0.85	0.015	0.011	0.028	0.8	
Wet peel & trimmings	0.51	0.016	<0.01	<0.026	0.7	1.0x
	0.85	0.027	0.012	0.041	1.2	
Granules	0.51	0.018	0.017	0.038	1.0	1.2x
	0.85	0.024	0.019	0.046	1.3	
Chips	0.51	0.016	0.013	0.031	0.8	1.9x
	0.85	0.051 [d]	0.043 [d]	0.101	2.9	

[a] Residue values are uncorrected; CGA-322704 is expressed as thiamethoxam.
[b] Based on the combined residues of each analyte, expressed as thiamethoxam
[c] Bracketed values represent the results of a confirmatory analysis of the same chip samples using LC/MS/MS; the corresponding concentration factor was calculated using the results of the reanalysis.
[d] Corrected for recoveries of thiamethoxam or CGA-322704 of 45% and 54%, respectively; all other residue values in the ND study are uncorrected.

Conclusions: The submitted potato processing study is adequate provided questions pertaining to frozen storage stability of CGA-322704 residues in processed potato commodities are resolved (see below). The available data indicate that the combined residues of thiamethoxam and CGA-322704 do not concentrate appreciably in granules or wet peels, but concentrate on average by 1.9x in chips. However, based upon this concentration factor and HAFT residues of 0.036 ppm (combined residues of thiamethoxam and CGA-322704) in a 7X exaggerated study, combined residues of thiamethoxam and CGA-322704 would not be expected to reach the limit of

quantitation of the cold method (0.02 ppm). Therefore, a separate tolerance on chips is not needed.

In the current study, samples of potato commodities were stored frozen for up to 2 years prior to analysis. Data are available indicating that residues of thiamethoxam are stable frozen in potatoes tubers for up to 2 years; however, data from an interim study on CGA-322704 are only available for storage intervals up to 1 year. When the final report is submitted, the residue study may be considered acceptable.

Tomato

In conjunction with the magnitude of the residue studies on tomatoes, the petitioner submitted data (1998; MRID 44715111) depicting residues of thiamethoxam and CGA-322704 in/on tomato processed commodities.

In two tests conducted in CA in 1996 and 1997, thiamethoxam (25% DF) was applied twice foliarly to tomatoes at rates totaling 0.18, 0.53, and 0.88 lb ai/A (1x, 3x, 5x the proposed maximum seasonal rate, respectively). A single control and treated sample of tomato fruit were harvested on the day of the last application and at either 7 or 9 days posttreatment from each test location. On the day of collection, the samples were hand-delivered under ambient conditions directly to the processing facility, National Food Laboratory, Inc., Dublin, CA. The samples were held briefly at 16-24 C, and were then promptly processed using simulated commercial practices into paste and puree, and frozen. The samples were then shipped frozen by ACDS freezer truck or overnight carrier to Novartis, Greensboro, NC, and stored frozen. The samples were then shipped frozen overnight to ADPEN Laboratories, Inc., Jacksonville, FL and stored frozen at ≤0 C prior to analysis. Samples from the 1996 and 1997 trials were stored frozen for approximately 23 and 9 months, respectively, from collection to analysis. Data are required depicting the storage stability of CGA-322704 in tomato fruit, and both analytes in tomato puree for up to 2 years.

Residues of thiamethoxam and CGA-322704 in tomato and tomato processed fractions were determined by Method AG-675 described above. The LOQ for each analyte in/on tomato processed commodities is 0.01 ppm. Apparent residues of each analyte were <0.01 ppm (<LOQ) in/on all control tomato samples. The results of the processing studies are shown in Table 24.

Combined residues of thiamethoxam and CGA-322704 were 0.05-0.09 ppm, 0.17-0.32 ppm, and 0.20-0.39 ppm in/on one sample of composite unwashed tomato fruit (RAC) treated at 1x, 3x, and 5x, respectively, at each of the posttreatment intervals. Residues concentrated on average by 1.7x in puree and 3.8x in paste. Based upon HAFT combined residues of 0.14 ppm from the tomato residue study discussed above, and average concentration factors for paste, the combined residues of thiamethoxam and CGA-322704 could be expected to reach 0.24 ppm in puree and 0.53 ppm in paste.

Table 24. Residues of thiamethoxam in commodities processed from tomatoes harvested 0-9 days after the last application of thiamethoxam (25% DF) at 1x, 3x, and 5x the proposed maximum rate.

Matrix	Total Appl. Rate (lb ai/A)	PHI	Residues (ppm) [a]			Concentration Factor [b]	Average Concentration Factor
			Thiamethoxam	CGA-322704	Combined		
Tomato fruit, unwashed (RAC) CA-039 1997 Trial	0.18 (1x)	0	0.04	0.02	0.06	NA	NA
		7	0.04	0.05	0.09		
	0.53 (3x)	0	0.13	0.04	0.17		
		7	0.16	0.11	0.27		
	0.88 (5x)	0	0.25	0.08	0.33		
		7	0.23	0.15	0.38		
Puree	0.18	0	0.02	0.01	0.03	0.5x	1.5x
		7	0.02	0.04	0.06	0.7x	
	0.53	0	0.09	0.03	0.12	0.7x	
		7	0.22	0.28	0.50	1.9x	
	0.88	0	0.61	0.49	1.10	3.3x	
		7	0.38	0.41	0.79	2.1x	
Paste	0.18	0	0.11	0.15	0.26	4.3x	3.8x
		7	0.04	0.07	0.11	1.2x	
	0.53	0	0.46	0.39	0.85	5.0x	
		7	0.36	0.47	0.83	3.1x	
	0.88	0	0.99	0.77	1.76	5.3x	
		7	0.69	0.70	1.39	3.7x	
Tomato fruit, unwashed (RAC) CA-443 1996 Trial	0.18 (1x)	0	0.03	0.02	0.05	NA	NA
		9	0.02	0.03	0.05		
	0.53 (3x)	0	0.16	0.05	0.21		
		9	0.17	0.15	0.32		
	0.88 (5x)	0	0.16	0.04	0.20		
		9	0.23	0.16	0.39		
Puree	0.18	0	0.05	0.06	0.11	2.2x	1.8x
		9	0.05	0.09	0.14	2.8x	
	0.53	0	0.16	0.14	0.30	1.4x	
		9	0.21	0.22	0.43	1.3x	
	0.88	0	0.18	0.12	0.30	1.5x	
		9	0.34	0.28	0.62	1.6x	
Paste	0.18	0	0.11	0.12	0.23	4.6x	3.8x
		9	0.10	0.16	0.26	5.2x	
	0.53	0	0.32	0.27	0.59	2.8x	
		9	0.40	0.44	0.84	2.6x	
	0.88	0	0.42	0.29	0.71	3.6x	
		9	0.82	0.69	1.51	3.9x	

[a] Values are uncorrected; CGA-322704 expressed as thiamethoxam.
[b] Based on the combined residues of each analyte, expressed as thiamethoxam.

Conclusions: Provided questions pertaining to frozen storage stability of residues in processed tomato commodities are resolved (see below), the submitted tomato processing study is adequate. The available data indicate that the combined residues of thiamethoxam and CGA-322704 concentrate by 1.7x and 3.8x in tomato puree and paste, respectively. Based upon these concentration factors and current HAFT residues of 0.14 ppm in/on tomatoes, combined residues of thiamethoxam and CGA-322704 could be expected to reach 0.24 ppm in puree and 0.53 ppm in paste. These data support the proposed tolerance of 0.80 ppm for residues of thiamethoxam in tomato paste. As residues in puree would be below the proposed 0.25 ppm tolerance for the Fruiting Vegetables Crop Group, a separate tolerance for tomato puree is not required.

In each of the current processing studies, samples of tomato commodities were stored frozen for 9 or 26 months. The petitioner is conducting a storage stability study on tomato puree for which data are now available through 4 months of storage. In addition, data are available indicating that residues of thiamethoxam are stable frozen in tomato fruit for up to 2 years; however, data from an interim study on CGA-322704 are only available for storage intervals up to 1 year. When data from the final reports are available, these studies may be upgradeable to acceptable.

Apples

In conjunction with the magnitude of the residue study on apples (1998; MRID 44715134), the petitioner provided data from two processing studies depicting residues of thiamethoxam in/on apple processed commodities.

In two tests conducted in NY and WA, thiamethoxam (25% DF) was applied as four foliar applications to apples at rates totaling 0.26, 0.79, and 1.32 lb ai/A (1.5x, 4.7x, and 7.8x the proposed seasonal rate, respectively).

A single 200 lb bulk control and treated sample of apples were collected from each rate and test site 14 or 15 days following the last application, and were shipped fresh on the same day to the processing facility, National Food Laboratory, Inc., Dublin, CA. The samples were received within 24 hours, were processed into wet pomace and juice using simulated commercial procedures within one day of receipt, and were then stored (temperature unspecified) for 17-18 days prior to frozen shipment via ACDS freezer truck to the Novartis, Greensboro, NC. The samples were stored in freezers (temperature unspecified) at Novartis for 9-11 months prior to analysis. Samples from the processing study were stored for a total of 10-12 months from collection to analysis. Data on the storage conditions immediately following processing at the National Food Laboratory (9/12-9/30/96), and at Novartis in the "S-building freezers" (9/30/96-9/10/97) are required to confirm that the samples were maintained frozen for the duration of storage.

Residues of thiamethoxam and CGA-322704 in apple fruit and processed fractions were determined by the HPLC/UV Method AG-675 described above. Apparent residues of each analyte were <0.01 ppm (<LOQ) in/on all control apple samples. The results of the processing studies are shown in Table 25.

The combined residues of thiamethoxam and CGA-322704 were <0.05-0.12 ppm, <0.12-0.22

ppm, and <0.14-0.64 ppm in/on one sample each of composite unwashed apple fruit (RAC) treated at 1.5x, 4.7x, and 7.8x, respectively, harvested at 14-15 days posttreatment. Residues concentrated slightly in wet pomace (1.6x), and were reduced slightly in juice (0.75x). Based upon HAFT combined residues of <0.11 ppm from the apple residue study discussed above, and an average concentration factor for wet pomace of 1.6x, combined residues of thiamethoxam and CGA-322704 could be expected to reach 0.18 ppm in wet pomace. These residues are adequately covered by the proposed tolerance for residues in/on pome fruits at 0.20 ppm; therefore a separate tolerance for residues in apple, wet pomace are not required.

Table 25. Residues of thiamethoxam in commodities processed from apples harvested 14-15 days after the last of four applications of thiamethoxam (25% DF) totaling 1.5x, 4.7x, and 7.8x the proposed maximum seasonal rate.

Matrix	Total Appl. Rate (lb ai/A)	Residues (ppm) [a]			Concentration Factor [b]	Average Concentration Factor
		Thiamethoxam	CGA-322704	Combined		
WA Test						
Fruit, unwashed (RAC)	0.26 (1.5x)	0.10	0.02	0.12	NA=not applicable	NA
	0.79 (4.7x)	0.20	0.02	0.22		
	1.32 (7.8x)	0.59	0.04 [0.05][c]	0.64		
Wet pomace	0.26	0.12	0.03	0.15	1.3x	1.5x
	0.79	0.39	0.03 [0.03]	0.42	1.9x	
	1.32	0.85	0.06 [0.07]	0.92	1.4x	
Juice	0.26	0.11	0.02 [0.02]	0.13	1.1x	1.1x
	0.79	0.23	0.02 [0.02]	0.25	1.1x	
	1.32	0.63	0.04 [0.05]	0.68	1.1x	
NY Test						
Fruit, unwashed (RAC)	0.26 (1.5x)	0.04	<0.01	<0.05	NA	NA
	0.79 (4.7x)	0.11	<0.01	<0.12		
	1.32 (7.8x)	0.13	<0.01	<0.14		
Wet pomace	0.26	0.07	<0.01	<0.08	1.6x	1.6x
	0.79	0.16	0.01	0.17	1.4x	
	1.32	0.22	0.02 [0.02]	0.24	1.7x	
Juice	0.26	0.01	<0.01	<0.02	0.4x	0.4x
	0.79	0.05	<0.01	<0.06	0.5x	
	1.32	0.04	<0.01	<0.05	0.4x	

[a] Residue values are uncorrected; CGA-322704 is expressed as thiamethoxam.
[b] Based on the combined residues of each analyte, expressed as thiamethoxam
[c] Bracketed values represent the results of a reanalysis of a single sample.

Conclusions: Pending submission of acceptable sample history information, the submitted processing study is adequate. A complete sample history including storage conditions for processed apple commodities is required. Specifically, data on the storage conditions immediately following processing at the National Food Laboratory, Dublin, CA (9/12-9/30/96) and at Novartis, Greensboro, NC (9/30/96-9/10/97) are required to confirm that the samples were maintained frozen for the duration of storage.

The available data indicate that the combined residues of thiamethoxam do not concentrate appreciably in wet pomace (1.6x), and are slightly reduced on average in juice (0.75x). Based upon HAFT combined residues of <0.11 ppm from the apple residue study discussed above, and an average concentration factor for wet pomace of 1.6x, combined residues of thiamethoxam and CGA-322704 could be expected to reach 0.18 ppm in wet pomace. These residues are adequately covered by the proposed tolerance for residues in/on pome fruit at 0.20 ppm. Therefore, tolerances for residues of thiamethoxam in processed apple commodities are not required.

Grain Sorghum

In conjunction with the magnitude of the residue study on grain sorghum (1998; MRID 44715112) described above, the petitioner submitted data depicting thiamethoxam residues in grain sorghum processed commodities. In two side-by-side tests conducted in KS and TX, thiamethoxam (70% WP) was applied to sorghum seed as a seed treatment slurry at 0.3 and 0.90 lb ai/100 lb seed (1.5x and 4.5x the proposed maximum rate) to generate samples for processing.

A single control and treated sample of grain were collected from each test 116 or 174 days after planting. Samples from the KS test site were shipped on the day of harvest by UPS (ambient conditions), and samples from the TX test were stored frozen for 1 week at the field site prior to shipment by ACDS freezer truck, to the processing facility. At the processing facility, the Food Protein Center, Texas A & M University, Bryan, TX, samples were held at ≤-12 C prior to and after processing into grain sorghum fractions using simulated commercial procedures. The samples were then shipped frozen (packed in dry ice) via overnight carrier to Novartis, Greensboro, NC where they were held at <-15 C prior to frozen delivery by the petitioner to EN-CAS Analytical Laboratories, Winston-Salem, NC. The samples were held at EN-CAS at ≤-17 C) prior to analysis. Samples of grain and flour from the processing study were stored frozen for up to ~2 years from collection to analysis. Additional storage stability data on CGA-322704 are required to support the intervals depicted in the residue study as data from the interim study on this analyte only provides data for up to one year of storage.

Residues of thiamethoxam and CGA-322704 in grain and flour were determined by Method AG-675, described above. The LOQ for each analyte in/on grain sorghum flour is 0.01 ppm. Apparent residues of each analyte were <0.01 ppm (<LOQ) in/on all control samples. Residues of each analyte were <LOQ in/on four samples of composite grain (RAC) and flour samples from the 1.5x and 4.5x processing studies.

Conclusions: HED notes that residue data are not currently required by the Agency on sorghum flour or any other processed commodity of grain sorghum. However, the submitted grain sorghum processing studies will be adequate once questions concerning the storage stability of CGA-322704 residues are resolved.

Samples of grain and flour from the processing study were stored frozen for up to 2 years from collection to analysis. Storage stability data are available indicating that thiamethoxam is stable in corn grain and various other commodities for up to 2 years; data on CGA-322704 are only available for up to 1 year of frozen storage from an interim study. Although storage stability data for CGA-322704 are required for the storage intervals up to 2 years to upgrade this study,

Wheat

In conjunction with the magnitude of the residue study on wheat (1998; MRID 44715108) described above, the petitioner submitted data depicting residues of thiamethoxam in wheat processed commodities. In three tests conducted in KS and ND, thiamethoxam (70% WP) was applied to wheat seed as a seed treatment at 0.07 (2 tests) and 0.21 lb ai/100 lb seed (1.4x and 4.2x the proposed maximum rate) to generate samples for processing.

A single control and treated bulk sample of grain were harvested from each test at 98 (ND) or 274 (KS) DAP and were stored at the test sites (temperature unspecified) for up to 2 weeks. The samples were then shipped by ACDS freezer truck directly to the processing facility, Texas A & M University, Food Protein Research and Development Center, Bryan, TX. Grain samples were processed into wheat fractions using simulated commercial procedures within ~1-3 months of receipt; samples were kept at ≤-12 C prior to and after processing. The samples were then shipped frozen on dry ice to the petitioner (Greensboro, NC) via overnight carrier. The samples were stored frozen (~-20 C) at Novartis for ~7-12 months prior to shipment overnight (on dry ice) to the analytical laboratory, EPL- BAS, Harristown, IL, where they were stored frozen (temperature unspecified) for an additional 1-1½ months prior to analysis. Samples of RAC grain samples were stored frozen for 12-15 months from harvest to analysis, and processed commodities were stored frozen for 9-14 months. Additional storage stability data on CGA-322704 are required to support the intervals depicted in the residue study as data from the interim study on this analyte only provides data for up to one year of storage.

Residues of thiamethoxam and CGA-322704 in wheat commodities were determined by Method AG-675, described above. Apparent residues of each analyte were below the 0.01 ppm (<LOQ) for each analyte in/on all control samples with one notable exception: one bran control sample from the KS study conducted at 1.4x bore apparent residues of CGA-322704 at 0.02 ppm. Residues of CGA-322704 in the two associated treated (1.4x) samples of bran were also 0.025 and 0.04 ppm. The petitioner attributed these values to interfering peaks and rejected these values. In all other treated samples (4 samples each), residues of each analyte were <LOQ in grain (RAC) and in germ, bran, middlings, shorts, and low grade flour from the 1.4x (n=3 each) and 4.5x (n=1 each) processing studies.

Conclusions: Pending resolution of questions concerning the storage stability of residues in wheat commodities, the submitted wheat processing study is adequate and indicates that residues do not concentrate in wheat fractions processed from grain grown from seed treated at up to 4.2x.

Samples of grain and processed wheat commodities from the processing studies were stored frozen for up to 15 months from collection to analysis. Storage stability data are available indicating that thiamethoxam is stable in corn grain and various other commodities for up to 2 years; data on CGA-322704 are only available for up to 1 year of frozen storage from an interim study. Storage stability data for CGA-322704 are required for the storage intervals up to 15 months. In addition, data on representative processed commodities are required. The petitioner is currently conducting a study on cornmeal and other processed commodities - for which interim data through 4 months are available - that may satisfy this requirement when the final report is submitted.

Cotton

In conjunction with the magnitude of the residue study on cotton (1998; MRID 44715104), the petitioner provided data from two processing studies depicting residues of thiamethoxam in/on cottonseed processed commodities.

In two tests conducted in CA and TX, cotton grown from seed treated with thiamethoxam (5 lb/gal FlC) at 0.3 lb ai/100 lb seed was treated twice foliarly with thiamethoxam (25% DF) at post-emergence rates totaling 0.09, 0.27, or 0.45 lb ai/A (1, 3, or 5x the proposed maximum foliar rate).

A single bulk control and treated sample of cotton (100 lbs each) were harvested from each test plot ~21 days following the last foliar application, and were stored frozen at the test site for up to 2 days prior to frozen shipment to the processing facility, Texas A & M University, Food Protein Development and Research Center, Bryan, TX. The samples were processed into cottonseed fractions using simulated commercial procedures and frozen, and then were shipped by overnight carrier on dry ice to Novartis, Greensboro, NC. At Novartis, all samples were kept at ~-20 C at prior to preparation for analysis. The maximum frozen storage intervals for undelinted cottonseed (RAC) and cotton processed commodities were 9-14 months, from collection to analysis. The residue data for both analytes are adequately supported by existing storage stability data on representative commodities.

Residues of thiamethoxam and CGA-322704 in cottonseed and processed fractions were determined by Method AG-675 described above. Apparent residues of each analyte were <0.01 ppm (<LOQ) in/on all control samples. Residues of each analyte were <0.01 ppm in all samples of cottonseed (RAC) and processed commodities (n=1 each at 1x, 3x, and 5x) from the study conducted in TX. The results of the processing study conducted in CA are shown in Table 26.

The combined residues of thiamethoxam and CGA-322704 were <0.04, <0.05, and <0.12 ppm in/on one sample each of undelinted cottonseed RAC treated at 1x, 3x, and 5x, respectively, and residues did not concentrate in meal, hulls, or refined oil.

Table 26. Residues of thiamethoxam in cottonseed commodities processed from cottonseed grown from seed treated with thiamethoxam (5 lb/gal FlC) at 0.3 lb ai/100 lb seed and harvested 22 days following the last of two foliar applications of thiamethoxam (25% DF) totaling 0.09, 0.27, or 0.45 lb ai/A (1x, 3x, or 5x the proposed maximum foliar rate).

Matrix	Total Appl. Rate (lb ai/A)	Residues (ppm) [a]			Concentration Factor [b]	Average Concentration Factor
		Thiamethoxam	CGA-322704	Combined		
Undelinted Seed (RAC) CA Trial	0.09 (1x)	0.03	<0.01	<0.04	NA	NA
	0.27 (3x)	0.04	<0.01	<0.05		
	0.45 (5x)	0.11	<0.01	<0.12		
Meal	0.09	<0.01	<0.01	<0.02	--	--
	0.27	<0.01	<0.01	<0.02	--	
	0.45	0.01	<0.01	<0.02	--	
Hulls	0.09	<0.01	<0.01	<0.02	--	--
	0.27	<0.01	<0.01	<0.02	--	
	0.45	0.02	<0.01	<0.03	--	
Oil, refined	0.09	<0.01	<0.01	<0.02	--	--
	0.27	<0.01	<0.01	<0.02	--	
	0.45	<0.01	<0.01	<0.02	--	

[a] Residue values are uncorrected; CGA-322704 is expressed as thiamethoxam.
[b] Based on the combined residues of each analyte, expressed as thiamethoxam

Conclusions: The submitted cotton processing studies are adequate, and indicate that residues of thiamethoxam do not concentrate in cottonseed meal, hulls, or refined oil processed from samples of cottonseed RAC bearing measurable weathered residues of thiamethoxam. Therefore, tolerances for residues of thiamethoxam in processed commodities of cotton are not required.

OPPTS GLN 860.1480: Meat, Milk, Poultry, Eggs

The petitioner submitted data depicting the magnitude of the residue of thiamethoxam and its metabolite CGA-322704 in meat and milk from cattle. The biological phase of the study was conducted by Novartis Crop Protection, VBRC, Vero Beach, FL, and the analytical phase was conducted at Novartis Crop Protection, Inc., Greensboro, NC. The study results are included in the following report:

44703534 Campbell, D. (1998) CGA-293343--Magnitude of the Residues in Meat and Milk Resulting from the Feeding of Three Levels to Dairy Cattle: Lab Project Number: ABR-98052: 46-97: BIOL-97006. Unpublished study prepared by Novartis Crop Protection, Inc. 180 p.

Using the proposed tolerances, the maximum theoretical dietary burden (MTDB) of thiamethoxam for beef cattle is 0.733 ppm, based on a diet consisting of 20% cotton gin byproducts, 25% wheat forage, and 50% barley or wheat grain (Table 27). The MTDB for dairy cattle is 1.43 ppm, based on a diet consisting of 60% wheat forage, 20% cotton gin byproducts, and 20% barley or wheat grain.

Table 27. Cattle feed items with proposed tolerances for thiamethoxam residues and their potential contribution to the dietary burden.

Commodity	% Dry matter	Proposed tolerance (ppm)	% of Beef diet	Beef - dietary burden (ppm)	% of Dairy diet	Dairy - dietary burden (ppm)
Apple pomace	40	0.2	40	0.20	20	0.10
Barley grain	88	0.02	50	0.011	40	0.009
Barley hay	88	0.05	25	0.014	60	0.034
Barley straw	89	0.03	10	0.003	10	0.003
Cottonseed	88	0.05	25	0.014	25	0.014
Cotton gin byproducts	90	1.0	20	0.222	20	0.222
Potato culls	20	0.02	75	0.075	40	0.040
Canola seed meal	88	0.02	15	0.003	15	0.003
Sorghum grain	86	0.02	40	0.009	40	0.009
Sorghum forage	35	0.02	40	0.023	50	0.028
Sorghum stover	88	0.02	25	0.006	15	0.003
Wheat grain	89	0.02	50	0.011	40	0.009
Wheat forage	25	0.50	25	0.500	60	1.200
Wheat hay	88	0.02	25	0.006	60	0.014
Wheat straw	88	0.02	10	0.002	10	0.002

Three groups of three Holstein cows were dosed daily with thiamethoxam at 2, 6, or 20 ppm via gelatin capsules for 28-30 days. These dose levels are equivalent to 1.4x, 4.2x, and 14x the MTDB for dairy cattle. Milk was collected on Days 1, 3, 7, 14, 21, and 26. One additional cow served as a control. The control and one treated cow from each dose group were sacrificed on Day 28, a second cow from each group was sacrificed on Day 29 and the third cow on Day 30. Tenderloin and round muscle, omental and perirenal fat, liver, and kidneys were collected from each animal. Samples were shipped frozen to the analytical facility and stored at -20 C. The maximum storage intervals from sampling to analysis were 11.5 months for milk and 12.5 months for tissues. A supporting storage stability study is in progress; interim data are presented above in Section 860.1380.

Residues of thiamethoxam and CGA-322704 were analyzed using Novartis Analytical Method AG-675 (HPLC/MS), described above in Section 860.1340. Adequate concurrent recoveries were obtained for each analyte, and apparent residues of each analyte in control samples of each matrix were <LOQ. The LOQs were 0.005 ppm for each analyte in milk and 0.01 ppm for each analyte in tissues. The results of residue analyses are summarized in Table 28.

The combined residues in milk plateaued for each dose group between 7-14 days of dosing. For the 2 ppm (1.4x) dose group, the maximum combined residues of thiamethoxam and CGA-322704 in milk was 0.018 ppm, and the maximum residue of thiamethoxam *per se* was 0.01 ppm, each on Day 7. The maximum combined residues of thiamethoxam and CGA-322704 in milk were 0.07 ppm on Day 26 from cows dosed at 6 ppm (4.2x) and were 0.25 ppm on Day 7 from cows dosed at 20 ppm (14x). For the range of doses used, there was a linear relationship between the dosing level and residues in milk.

For both omental and perirenal fat, combined residues were less than the combined LOQ of 0.02 ppm in samples from the high-dose group; fat samples from the low- and mid-dose levels were not analyzed. In liver, the combined residues were also <0.02 ppm (<LOQ) in samples from all dose groups; however, adequacy of the analytical method in extracting residues of CGA-322704 from liver remains to be resolved (see Section 860.1340). Combined residues in kidney from the high dose group were <0.02-<0.05 ppm (maximum residues of thiamethoxam *per se* at 0.04 ppm), and were <0.02 ppm (<LOQ) in kidney samples from the low- and mid-dose levels. Combined residues in muscle (tenderloin and round) were <0.03-<0.07 ppm at the high-dose feeding level, and <0.02 ppm (<LOQ) for all samples from the low- and mid-dose levels. Maximum residues of thiamethoxam *per se* were 0.01 and 0.06 ppm in muscle samples from the low- and mid-dose groups, respectively.

Conclusions: Provided that questions are resolved concerning the storage stability of residues in animal matrices and the suitability of Method AG-675 for determining residues of CGA-322704 in liver, the submitted ruminant feeding study is adequate. The data indicate that residues of thiamethoxam may transfer to milk, meat, and meat-by-products as a result of the proposed uses of thiamethoxam on animal feed items.

If the dietary burden for dairy cattle is higher than beef cattle, current OPP policy dictates that the dairy cattle diet be used for setting meat, fat, and meat by-product tolerances (see minutes from ChemSAC meeting held on 4/5/00). The rationale for this is that many dairy cattle are

slaughtered for meat once their milk production drops below profitable levels.

Groups of three cows were dosed for 28-30 days with thiamethoxam at 2, 6, and 20 ppm, equivalent to 1.4x, 4.2x, and 14x the maximum theoretical dietary burden (MTDB; 1.43 ppm) for dairy cattle. The combined residues of thiamethoxam and CGA-322704 in milk plateaued between 7-14 days of dosing for each group. The maximum combined residues in milk from the 2 ppm dose group (1.4x) were 0.018 ppm on Day 7. Based on these data, the proposed 0.02 ppm tolerance for the combined residues of thiamethoxam and CGA-322704 in milk is appropriate. As the combined residues in fat were <LOQ from the 14x dose group, there is no reasonable expectation of the transfer of thiamethoxam residues from feed items to fat; therefore, tolerances are not required for residues in fat. Although residues of thiamethoxam and CGA-322704 were <LOQ in meat, kidneys, and liver at the 1.4x dosing level, residues of thiamethoxam were detected in muscle from the 4.2x and 14x dose groups and in kidneys from the 14x dose group. Based on these data, tolerances should be set at the combined LOQ (0.02 ppm) for residues of thiamethoxam and CGA-322704 in meat and meat-by-products of cattle, goats, horses, and sheep.

Based on the results from the goat and hen metabolism studies, microwave extraction is required to release bound/conjugated residues of thiamethoxam and its CGA-322704 from liver, which accounted for the majority (> 10X additional released after microwave extraction) of the radioactivity in this organ. The proposed enforcement method (AG-675) does not include a microwave extraction step, and therefore would not be capable of extracting bound/conjugated residues of thiamethoxam and its CGA-322704 metabolite from liver. No residues of thiamethoxam or its CGA-322704 metabolites were found in liver samples from the high (20 ppm - 14X) feeding level. However, based on use of Method AG-675 (HPLC/MS) WITHOUT a microwave extraction step, these results are expected.

Given that there are questions regarding the adequacy of Method AG-675 in determining CGA-322704 residues in liver, and the fact that the combined residues of thiamethoxam and CGA-322704 were somewhat higher in kidneys than in liver in the goat metabolism study, the residue data for kidneys were used to determine the tolerance for meat-by-products.

For risk assessment purposes, RAB2 has estimated residues in liver from the goat metabolism study. At a 100 ppm feeding level, residues in liver were found to be as high as 0.90 ppm (combined thiamethoxam and CGA-322704) **after** microwave extraction. Normalized to a dietary burden of 1.43 ppm, this would equate to a residue level of 0.013 ppm. Given the uncertainties in the process and species difference (goat vs. cow), RAB2 will add a 10X factor to this level. For Tier 1 risk assessment purposes, until Conclusion 30g is resolved, a residue level of 0.13 ppm should be used for cattle, goats, horses, and sheep liver.

As a condition of registration, the petitioner should modify Novartis Method AG-675 to add a microwave extraction step for liver, or propose a new enforcement method for liver. This method should be radiovalidated by Novartis and submitted to the Agency. The petitioner should use this method to reanalyze the cow liver samples from the feeding study and provide adequate storage stability data to cover the period the samples were stored. Alternatively, the petitioner can conduct a new lactating cow feeding study using the new liver method (including microwave

extraction) for the analysis.

The proposed uses for thiamethoxam include swine and poultry feed items. The calculated MTDB of thiamethoxam for both swine and poultry is 0.025 ppm. As the lowest (2 ppm) feeding level in the current ruminant feeding study represents 80x the MTDB for swine, HED concludes that there is no reasonable expectation of the transfer of thiamethoxam residues from feed items to hog commodities. In the previously reviewed (PP#9F5046) poultry metabolism study, hens were dosed at ~100 ppm, equivalent to ~4000x the maximum dietary burden. Based on data from the metabolism study, residues of thiamethoxam and CGA-322704 in tissues and eggs would be expected to be <0.01 ppm even at a 100x feeding level. Category 180.6(a)(3) situations exist with respect to thiamethoxam residues in swine and poultry commodities, and tolerances for residues in hog and poultry commodities are not required.

Table 28. Residues of thiamethoxam and CGA-322704 in milk and tissues from cows dosed with thiamethoxam at 2, 6, or 20 ppm for 28-30 days.

Matrix	Residues (ppm)[a]		
	Thiamethoxam	CGA-322704	Combined [b]
2 ppm (1.4x) dose			
Milk Day 1	0.006, 0.009, 0.009	<0.005, 0.005, <0.005	<0.011, 0.01, <0.014
Day 3	<0.005, 0.007, 0.008	<0.005 (n=3)	<0.010, <0.012, <0.013
Day 7	0.007, 0.01, 0.008	<0.005, 0.006, <0.005	<0.012, 0.018, <0.013
Day 14	0.008, 0.007, 0.007	<0.005 (n=3)	<0.013, <0.012, <0.012
Day 21	0.007 (n=3)	<0.005 (n=3)	<0.012 (n=3)
Day 26	0.007, 0.008, 0.007	<0.005 (n=3)	<0.012, <0.013, <0.012
Muscle, tenderloin	<0.01 (n=3)	<0.01 (n=3)	<0.02 (n=3)
Muscle, round	<0.01 (n=3)	<0.01 (n=3)	<0.02 (n=3)
Liver	<0.01 (n=3)	<0.01 (n=3)	<0.02 (n=3)
Kidney	<0.01 (n=3)	<0.01 (n=3)	<0.02 (n=3)
6 ppm (4.2x) dose			
Milk Day 1	0.03, 0.03, 0.02	0.01, 0.009, <0.005	0.05, 0.04, <0.03
Day 3	0.04, 0.05, 0.03	0.02, 0.02, 0.005	0.06, 0.06, 0.03
Day 7	0.02, 0.04, 0.02	0.01, 0.01, 0.006	0.03, 0.05, 0.02
Day 14	0.04, 0.03, 0.03	0.02, 0.02, 0.007	0.06, 0.05, 0.03
Day 21	0.03/0.03, 0.05/0.03, 0.04/0.03 [c]	0.01/0.01, 0.02/0.01, 0.007/0.005 [c]	0.04, 0.05, 0.04
Day 26	0.04, 0.05, 0.04	0.02, 0.02, 0.009	0.06, 0.07, 0.05
Muscle, tenderloin	0.01, 0.01, <0.01	<0.01 (n=3)	<0.02 (n=3)
Muscle, round	<0.01, 0.01, <0.01	<0.01 (n=3)	<0.02 (n=3)
Liver	<0.01 (n=3)	<0.01 (n=3)	<0.02 (n=3)
Kidney	<0.01 (n=3)	<0.01 (n=3)	<0.02 (n=3)
20 ppm (14x) dose			
Milk Day 1	0.08, 0.13, 0.09	0.03, 0.04, 0.03	0.12, 0.18, 0.12
Day 3	0.10, 0.15, 0.10	0.03, 0.06, 0.04	0.13, 0.21, 0.14
Day 7	0.13, 0.17, 0.09	0.05, 0.07, 0.03	0.18, 0.25, 0.12
Day 14	0.10, 0.17, 0.10	0.03, 0.06, 0.04	0.14, 0.24, 0.15
Day 21	0.14, 0.12, 0.11	0.04, 0.05, 0.04	0.19, 0.18, 0.15
Day 26	0.07, 0.12, 0.09	0.02, 0.05, 0.03	0.10, 0.17, 0.12
Muscle, tenderloin	0.02, 0.04, 0.03	<0.01 (n=3)	<0.03, <0.05, <0.04
Muscle, round	0.03, 0.06, 0.03	<0.01 (n=3)	<0.04, <0.07, <0.04
Liver	<0.01 (n=3)	<0.01 (n=3)	<0.02 (n=3)
Kidney	0.01, 0.04, 0.03	<0.01 (n=3)	<0.02, <0.05, <0.04
Fat, omental	<0.01 (n=3)	<0.01 (n=3)	<0.02 (n=3)
Fat, perirenal	<0.01 (n=3)	<0.01 (n=3)	<0.02 (n=3)

[a] Residues were corrected for concurrent recoveries <100%.
[b] Combined residues expressed as thiamethoxam.
[c] Duplicate analyses.

OPPTS GLN 860.1850: Confined Accumulation in Rotational Crops

Confined rotational crop studies were previously reviewed in conjunction with the petition for thiamethoxam use on canola (PP#9F5046). These studies indicated that limited field rotational crop studies are necessary to support the proposed 120-day plant-back interval (PBI) for rotational crops, and that the metabolism of [^{14}C]thiamethoxam in rotational crops is similar to the metabolism observed in primary crops.

In a meeting held on 7/28/99 (see memo of G.J. Herndon dated 8/31/99), the Metabolism Assessment Review Committee (MARC) determined that the major residues from the confined rotational crop studies were the parent thiamethoxam and its CGA-322704 metabolite. CGA-265307 was a major residue still having the N-nitro group in animal feed items (e.g. wheat straw). The MARC recommended that all three compounds should be analyzed in field rotational crop studies.

OPPTS GLN 860.1900: Field Accumulation in Rotational Crops

Novartis submitted data (citation shown below) depicting residues of thiamethoxam and CGA-322704 in representative rotational crops from limited field studies conducted in 1997-1998. Data from the confined rotational crop study, which was reviewed in conjunction with a previous petition on canola (PP#9F5051), indicated that limited rotational crop field trials were required in order to assess the need for tolerances for residues in rotational crops planted at the proposed 120-day PBI. The in-life and analytical phases of this study were conducted by Novartis.

> 44715106 Campbell, D. (1998) CGA-293343-Field Accumulation in Rotational Crops: Lab Project Number: 107-97: 346010: 107-97-A. Unpublished study prepared by Novartis Crop Protection, Inc. 201 p.

The rotational field trials were conducted in Fresno County, CA, Indian River County, FL, and Champaign County, IL on soil textures ranging from sand (FL) to silty clay loam (IL); the IL trials were conducted on different plots at the same location at which the U.S. confined study was performed. Peppers, leaf lettuce, and mustard greens were planted as the primary crop. The petitioner stated that the highest proposed maximum seasonal use rate is 0.17 lb ai/A on tomatoes and peppers. HED notes that the highest maximum seasonal use rate on the proposed thiamethoxam labels for any rotated crop is 0.215 lb ai/A on cotton, resulting from an at-planting soil application at 0.125 lb ai/A followed by two foliar applications totaling 0.09 lb ai/A. However, HED has concluded that the combined soil and foliar use on cotton should be deleted from the proposed labels as no residue data are available to support this use (see Conclusion 20b). Once this use is deleted, the highest maximum seasonal use rate would be the 0.17 lb ai/A rate for fruiting vegetables.

At each test site, thiamethoxam (FlC) was applied to the primary crop as an in-furrow application

at planting (leaf lettuce and mustard greens) or as a transplant drench (peppers) at 2.2 oz ai/A (0.134 lb ai/A) followed 30-51 days later by a broadcast foliar application of the 25%DF at 0.71 oz ai/A (0.04 lb ai/A), for a total of 0.179 lb ai/A/season (1x the maximum seasonal rate). The in-furrow and drench applications were made in 10 and 400 gal of water/A, respectively, and the foliar application was made in 25 gal of water/A, each using ground equipment. At the CA and FL sites, leaf lettuce and peppers were allowed to mature and desiccate, and were cultivated into the soil on the day of planting of the rotational crops; mustard greens at the IL sites were clean cut and removed~1 day after the last application, and the plots were rototilled prior to planting of the rotational crops.

At each test site, single control and duplicate treated plots were planted with leaf lettuce, turnips, and wheat as representative rotational crops at PBIs of approximately 30, 120, and 180 days after the final application of thiamethoxam. The crops received water, fertilizer, and maintenance pesticides as necessary; adequate information pertaining to the growing conditions was provided.

A single control and two treated samples of the various RACs for each crop were harvested from each PBI at each test site. Representative rotational crop samples from the 120-day PBI from three different sites, and from the 30-day PBI from two CA sites were analyzed. The following sample information pertains only to those samples for which residue data were generated. Lettuce and turnip samples were harvested at maturity 44-152 DAP, and the turnips were separated into roots and tops. Wheat forage was sampled between the 6-8" stage and jointing at 62-217 DAP. Wheat hay was cut between the boot and soft dough stage (99-241 DAP) and was air dried to a moisture content of 10-20% prior to sampling. Wheat grain and straw samples were collected at maturity (159-292 DAP).

Crop samples were placed in frozen storage following collection (temperature unspecified), and remained stored at the field test sites for up to 84 days prior to shipment. Samples were shipped frozen by overnight carrier and by other unspecified means to the analytical laboratory, NHSD, with the following exception: on the day of harvest, 120-day PBI lettuce samples from the IL site were shipped at ambient temperatures by overnight carrier, and were frozen immediately upon receipt by NHSD. Sample storage conditions at NHSD were not provided. From collection to analysis, crop samples were stored frozen for up to 9 months. Data are available indicating that residues of both analytes are stable in representative grain and root crops (corn and potato) for up to 1 year; however, data are needed to support the storage intervals incurred by turnip tops and leaf lettuce (7-9 months).

The following additional data are required: (i) a description of the storage conditions for all samples at the analytical facility, and (ii) data depicting the frozen storage stability of residues in lettuce for up to 9 months; a study on lettuce, for which interim (4-month) data has been submitted, is in progress.

Residues of thiamethoxam and CGA-322704 were determined in the treated and control samples using the adequate HPLC/UV or MS (wheat hay and straw only) Method AG-675, discussed

above. For the 30-day PBI, samples from two CA tests only were analyzed, and residues of each analyte were <0.01-0.02 ppm in/on leaf lettuce, turnip tops and roots, and wheat forage hay (Table 29). All samples from the 120-day PBI from each test site were analyzed, and residues of thiamethoxam and CGA-322704 were each <0.01 ppm (<LOQ) in/on all representative rotational crop commodities (leaf lettuce, turnip tops and roots, and wheat grain, straw, hay and straw). Apparent residues of both analytes were <LOQ (<0.01 ppm) in all control samples of each matrix.

Conclusions: Provided that questions are resolved concerning the analysis for metabolite CGA-265307 (see below), the storage stability of residues in/on lettuce and turnip tops, and a description of the storage conditions at the analytical facility is submitted, the limited field rotational crop study is adequate. Analysis of several samples from the 30-day PBI indicated that residues of each analyte were <0.01-0.02 ppm in/on turnip tops and wheat forage. Secondary crop samples from the 120-day PBI from three different test sites were also analyzed, and residues of thiamethoxam and CGA-322704 were each <0.01 ppm (<LOQ) in/on all representative rotational crops (leaf lettuce, turnip tops and roots, and wheat grain, straw, hay and straw).

In the field rotational crop studies, the crop parts were not analyzed for the metabolite CGA-265307. In a meeting held on 7/28/99 (see memo of G.J. Herndon dated 8/31/99), the Metabolism Assessment Review Committee (MARC) determined that the major residues from the confined rotational crop studies were the parent thiamethoxam and its CGA-322704 metabolite. CGA-265307 was a major residue still having the N-nitro group in animal feed items (e.g. wheat straw). The MARC concluded that all three compounds should be analyzed in field rotational crop studies.

RAB2 reexamined the results of the confined rotational crop studies submitted in conjunction with the use on canola (G.J. Herndon, 3/30/00, PP#9F5046). In mustard greens, lettuce leaves, radish tops, and turnip tops, levels of CGA-265307 were less than either thiamethoxam or CGA-322704 at all plantback intervals. In wheat forage, straw, and grain, levels of CGA-265307 were higher than either thiamethoxam or CGA-322704. In wheat grain, levels of CGA-265307 were higher than either thiamethoxam or CGA-322704 only in samples exhibiting low level residues (< or equal to 0.003 ppm).

The results of both the confined and field rotational crop studies indicate that, using the proposed enforcement method, measurable residues would not likely be found on direct human foods. The confined (hot) study indicated that low level residues in animal feed items, which would not be likely to cause significant residues in meat, milk, poultry, or eggs. Therefore, RAB2 is willing to defer analysis for metabolite CGA-265307 as a condition of registration. As a condition of registration, the petitioner will need to either reanalyze the cold (field) samples for the CGA-265307 metabolite and provide adequate storage stability data to cover the period the samples were stored, or alternatively, the petitioner can conduct a new field rotational crop study examining the samples for residues of thiamethoxam, CGA-322704, and CGA-265307.

As the currently proposed labels specify a 120-day rotational crop restriction for crops not proposed for thiamethoxam use, tolerances for residues of thiamethoxam in rotational crops will not be required. Once the results of Conclusion 36 are received, a 30-day rotational crop restriction may be acceptable.

Table 29. Residues in representative rotational crops planted 30 days following a transplant drench and a broadcast foliar application of thiamethoxam (4L and 25%WG, respectively) to peppers totaling 0.179 lb ai/A/season (~1x maximum seasonal rate). [a]

Location	Crop/commodity	Residues (ppm)	
		Thiamethoxam	CGA-322704
Fresno County, CA	Wheat, forage	0.02, 0.02	0.02, 0.02
	Wheat, hay	<0.01, <0.01	<0.01, <0.01
	Lettuce	<0.01, <0.01	<0.01, <0.01
	Turnips, tops	0.01, <0.01	<0.01, <0.01
	Turnips, roots	<0.01, <0.01	<0.01, <0.01

[a] Samples from the 30-day PBI from FL and IL were not analyzed.

International Harmonization Issues

As there are no Codex, Canadian, or Mexican MRLs/tolerances established for residues of thiamethoxam in plant or animal commodities, a discussion of compatibility with U.S. tolerances is not relevant at this time.

cc: G.J. Herndon, PP#9F5051, PP#9F5046, RAB2 RF