UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

April 7, 2000

MEMORANDUM

SUBJECT: PP#7E04920. Cloquintocet-mexyl (Safener) in/on Wheat. Review of Analytical Methods and Residue Data. First Food Use Review.

DP Barcode:	D257181	PRAT Case:	289237
Submission No.:	S533228	Caswell No.:	None
Chemical #:	999999	Class:	Safener
Trade Name:	Discover™ Herbicide	EPA Reg. No.:	None
40 CFR:	None		

MRID Nos.: 44387454, 44387457, 44387458, 44387459, 44387460, 44387461, 44399207, 44399208, 44399209, 44399210, 44399211, 44399213, 44399216, 44399217, 44399218, 44399219, 44399220, 44399221, 44399222, 44399223, 44399224, 44399225, 44399226, 44399227, 44399228, 44399229, 44399230, 44399231, 44568401, 44568402, 44755301, 44755302, 44755303

FROM: Nancy Dodd, Chemist *Nancy Dodd*
Registration Action Branch 3
Health Effects Division (7509C)

THROUGH: Stephen Dapson, Branch Senior Scientist *Stephen C. Dapson* 04/10/2000
Registration Action Branch 3
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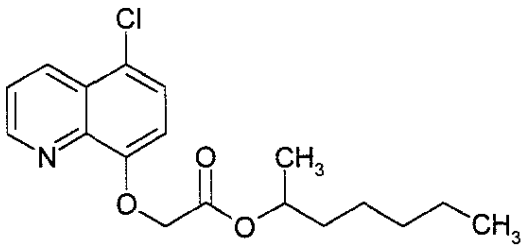
TO: Bipin Gandhi/Robert Forrest, PM Team #5
Minor Use, Inerts, and Emergency Response Branch
Registration Division (7505C)

INTRODUCTION

Novartis Crop Protection, Inc. (formerly Ciba Crop Protection) has proposed establishment of tolerances for residues of the safener cloquintocet-mexyl (acetic acid, [(5-chloro-8-quinolinyl)oxy]-, 1-methylhexyl ester; CGA-185072) in or on wheat grain at 0.02 ppm and wheat straw at 0.05 ppm. The safener is contained in the proposed formulation Discover™ Herbicide, which contains the herbicide clodinafop-propargyl (propanoic acid, (R)2-[4-[(5-chloro-3-fluoro-2-pyridinyl)oxy]phenoxy]-, 2-propynyl ester); CGA-184927). Cloquintocet-mexyl is needed in the formulation to prevent damage to the wheat due to phytotoxic effects of CGA-184927. Cloquintocet-mexyl has not been previously registered for use in the US; therefore, there are no registered uses and no proposed non-food uses. Tolerances for clodinafop-propargyl have been proposed in a concurrent petition (PP#7F04924).

Cloquintocet-mexyl is systemic, readily penetrating from the leaf surface into the leaf.

The structure of cloquintocet-mexyl is shown below:



cloquintocet-mexyl
CGA-185072

EXECUTIVE SUMMARY

Issues remain to be resolved or deficiencies exist concerning the following topics:

1. Proposed Use/Revised Section B/label
2. Nature of the Residue in Wheat
3. Nature of the Residue in Ruminants
4. Nature of the Residue in Poultry
5. Plant Analytical Methods
6. Multiresidue Methods
7. Storage Stability
8. Magnitude of the Residue in Wheat
9. Magnitude of the Residue in Processed Food/Feed
10. Rotational Crop Data
11. Revised Section F

CONCLUSIONS

OPPTS GLN 830 SERIES: PRODUCT PROPERTIES

1. The product chemistry of the technical grade of the active ingredient and the formulated products are reviewed by Registration Division.

OPPTS GLN 860.1200: PROPOSED USE

2. The Section B/label should be revised to change the feeding/grazing restriction on forage to 30 days since limited residue data are available at a 7-day PHI. Provided the above revision to the Section B/label is made, the proposed use of cloquintocet-mexyl on wheat will be adequately described. The proposed use directions will be adequate to allow an assessment of whether the residue data reflect the maximum residues likely to occur in food/feed.

OPPTS GLN 860.1300: NATURE OF THE RESIDUE IN PLANTS

3. The nature of the residue in wheat is not adequately understood for the purposes of a permanent tolerance for the following reasons pertaining to the [3-^{14}C-quinoline]CGA-185072 study:

a. Due to large amounts of the radioactivity being nonextractable with 80% aqueous acetonitrile and by Soxhlet extraction with 100% acetonitrile, only 16.0%, 0.9%, and 4.4%TRR were identified in leaves (ear emergence), leaves (milky stage), and straw (maturity), respectively. The petitioner should have attempted to extract more of the radioactivity using acid, base, and enzymes and then characterized/identified those residues.

b. Residues in grain were not identified in the field study. The identity of residues in grain resulting from application to the plant in a manner simulating expected field use are needed. The study should be conducted at a higher rate than the 2X study which was submitted.

c. The time from sampling to final analysis should be clarified for the wheat samples. If the time between sampling and final analysis of the field samples exceeded 6 months, evidence should be provided that the identity of residues did not change during the period between collection and final analysis. Such evidence would be analyses of representative substrates early in the study and at its completion. To be acceptable, such analyses should show that the basic profile of radiolabeled residues has not changed during that time.

4. The nature of the residue in wheat is adequately understood for the purposes of a tolerance with an expiration date. The residues of concern in wheat were determined by HED's Metabolism Assessment Review Committee (MARC) on 2/15/00 (D263289, N. Dodd, 2/25/00) to be CGA-185072 and its acid metabolite CGA-153433. HED may revisit the MARC after additional wheat metabolism data have been submitted.

OPPTS GLN 860.1300: NATURE OF THE RESIDUE IN LIVESTOCK

Ruminants

5. The nature of the residue in ruminants is not adequately understood for the purpose of a permanent tolerance for the following reason: The time between sampling and final analysis should be clarified for milk and tissues. If the time between sampling and final analysis of the samples exceeded 6 months, evidence should be provided that the identity of residues did not change during the period between collection and final analysis. Such evidence would be analyses of representative substrates early in the study and at its completion. To be acceptable, such analyses would show that the basic profile of radiolabeled residues has not changed during that time.

6. For this use on wheat, the nature of the residue in ruminants is adequately understood for the purposes of a tolerance with an expiration date. The major residue in urine, milk, and kidney was CGA-153433. Residues in muscle and liver were not determined because of interferences and low radioactivity. No attempt was made to identify residues in fat because of low radioactivity ($\leq$0.001 ppm). The residues of concern in ruminants were determined by HED's Metabolism Assessment Review Committee on 2/15/00 (D263289, N. Dodd, 2/25/00) to be CGA-185072 and its acid metabolite CGA-153433.

Poultry

7. The nature of the residue in poultry is not adequately understood for the purpose of a permanent tolerance for the following reason: The time between sampling and final analysis should be clarified for eggs and tissues. If the time between sampling and final analysis of the samples exceeded 6 months, evidence should be provided that the identity of residues did not change during the period between collection and final analysis. Such evidence would be analyses of representative substrates early in the study and at its completion. To be acceptable, such analyses would show that the basic profile of radiolabeled residues has not changed during that time.

8. For this use on wheat, the nature of the residue in poultry is adequately understood for the purposes of a tolerance with an expiration date. The major metabolite in liver, kidney, and egg white was identified by two-dimensional TLC and cochromatography as CGA-153433. Residues in egg yolk could not be identified due to low radioactivity. Because no detectable residues were found in lean meat (<0.001 ppm) and fat (<0.002 ppm), characterization/identification of residues in lean meat and fat was not attempted. The residues of concern in ruminants were determined by HED's Metabolism Assessment Review Committee on 2/15/00 (D263289, N. Dodd, 2/25/00) to be CGA-185072 and its acid metabolite CGA-153433.

OPPTS GLN 860.1340: RESIDUE ANALYTICAL METHODS

Plants

9. To establish a permanent tolerance, the following additional information is needed regarding the analytical methods used to obtain the storage stability and residue data: a) Radiovalidation data for Methods REM 138.01, 138.06, 138.10, and 138.12 are needed to demonstrate the efficiency of the methods in extracting and quantifying aged or bound residues in samples; b) Method REM 138.12 should be submitted.

10. Before EPA can determine whether adequate analytical methods are available for enforcement of permanent tolerances on wheat, the following additional information is needed for the proposed enforcement methods: a) For REM 138.01 and REM 138.06, either an interference study must be submitted which determines whether other pesticides registered on wheat will interfere with the analysis of cloquintocet-mexyl residues by the enforcement method or a specific confirmatory method such as mass spectroscopy is needed as discussed in OPPTS GLN 860.1340. Provided that a specific confirmatory method is available, the Agency will not require that an interference study be conducted; b) Confirmatory methods are needed for REM 138.01 and 138.06; c) The GC/MS confirmatory method in Method REM 138.10 includes derivatization with diazomethane. The petitioner should investigate whether another methylating agent could be substituted for diazomethane. If an alternative methylating agent is not available, EPA requires that justification for the use of diazomethane be provided. An alternative

confirmatory method for REM 138.10 would be LC/MS. REM 138.10 could be rewritten to include LC/MS as the confirmatory method instead of GC/MS; d) Adequate EPA petition method validations are needed for the proposed enforcement methods. RAB3 has requested EPA petition method validations for REM 138.01, 138.06, and 138.10. These EPA petition method validations are underway. Adequate independent laboratory validations have been provided for methods REM 138.01 and 138.06.

11. Provided that the petition method validations which are being conducted by EPA are successful, adequate enforcement methods (MRID #'s 44399211, 44399213, and 44755302) are available to enforce tolerances with an expiration date on wheat.

Animals

12. Analytical/enforcement methods for animal commodities are not needed since tolerances on animal commodities are not needed for this use on wheat (as explained in Conclusions 21 and 22 below).

OPPTS GLN 860.1360: MULTIRESIDUE METHODS (1998: MRID 44755301)

13. Multiresidue method testing data for CGA-185072 and CGA-153433 in wheat grain have been submitted. CGA-185072 and CGA-153433 were tested through the FDA multiresidue methods according to the decision tree and protocols in the Pesticide Analytical Manual, Volume I (PAM I), Appendix II, Transmittal 96-1 (1/96). CGA-185072 was tested per Protocols C, D, and E. CGA-153433 was tested per Protocols B and C. RAB3 (D255566, N. Dodd, 5/12/99) has forwarded the submitted multiresidue methods data to FDA for review to determine sufficiency.

OPPTS GLN 860.1650: SUBMITTAL OF ANALYTICAL REFERENCE STANDARDS

14. The petitioner was requested (via memos from Susan Stanton, RD, to Karen Stumpf on 4/5/99 and 4/6/99) to send the analytical reference standards and Material Safety Data Sheets for CGA-185072 and CGA-153433 to US EPA, National Pesticide Standards Repository/Analytical Chemistry Branch/OPP, 710 Mapes Road, Fort George G. Meade, MD 20755-5350. The petitioner indicated to Susan Stanton, Registration Division/EPA, in April 1999 that the reference standards and Material Safety Data Sheets were sent. The EPA petition method validations are underway.

OPPTS GLN 860.1380: STORAGE STABILITY DATA

15. Storage stability data were submitted for CGA-185072 in wheat grain and straw. CGA-185072 declined 17% in wheat grain stored at -18°C for 728 days. CGA-185072 declined 31% in wheat straw stored at -18°C for 731 days. The storage times for CGA-185072 in grain and straw in the storage stability studies are adequate to cover maximum storage times for CGA-185072 in grain and straw residue samples (62 days for grain and 70 days for straw in the US residue data and 574 days for grain and straw in the Canadian residue data). (Note: Since degradation was shown for CGA-185072 in wheat grain and straw, storage stability data will be required for any future uses on all crops/substrates for which tolerances are requested.)

16. Storage stability data were also submitted for CGA-153433 in wheat grain and straw. Residues of CGA-153433 were stable in wheat straw stored at -18°C for 380 days. Pending receipt of the additional information requested below for MRID 44399210, HED tentatively concludes that CGA-153433 is stable in wheat grain stored at -20°C for 727 days. The storage times for CGA-153433 in grain and straw in the storage stability studies are adequate to cover maximum storage times for CGA-153433 in grain and straw residue samples (i.e., 95 days for grain and 141 days for straw in US residue data and 341 days for grain and straw in the Canadian residue data).

17. Adequate storage stability data have not been submitted. The following additional storage stability data are needed:

a. Additional data are needed for Study 300/91 (MRID 44399210). Raw data, including residues (ppm) found and representative chromatograms (for standards, controls, freshly fortified samples, and stored samples) should be submitted. Storage containers should be described. The method used to analyze the storage stability samples should be submitted or identified by number as a submitted method.

b. No storage stability data were submitted for forage. Storage stability data for forage are needed for the 105-day storage interval for CGA-185072 and the 218-day storage interval for CGA-153433 in US residue samples. If the Canadian residue studies could be used (i.e., upgraded to acceptable), storage stability data for forage would be needed for the 434-day storage interval for CGA-185072 and CGA-153433 in the Canadian residue samples so that the tolerance could be adjusted for any storage degradation; however, HED is not recommending that the petitioner attempt to upgrade the Canadian residue studies to an acceptable level.

c. No storage stability data were submitted for wheat processed commodities. The storage time between processing and analysis was ≤25 days for CGA-185072; storage stability data are not needed for CGA-185072 in processed commodities since they were analyzed within 30 days of their production (OPPTS 860.1520). The storage time between processing and analysis for CGA-153433 was 51 days for aspirated grain, 45 and 125 days for germ, 45 days for bran, 42 days for middlings and shorts, and 37 days for low grade flour and patent flour. Storage stability

data for CGA-153433 in aspirated grain fractions are not needed since this is an early season use and residues are not expected to occur in aspirated grain fractions. Storage stability data are not needed for bran, flour, middlings, and shorts since these matrices are similar to grain and can be covered by the storage stability data on grain. Storage stability data are needed for CGA-153433 in wheat germ for 45 and 125 days.

OPPTS GLN 860.1500: MAGNITUDE OF THE RESIDUE IN PLANTS

18. The proposed use indicates that forage could be fed/grazed at a 7-day PHI, hay could be fed at a 30-day PHI, and grain and straw could be harvested at a 60-day PHI. Based on the available residue data, residues of parent or CGA-153433 were less than the limit of quantitation (LOQ) in the grain, forage, hay, and straw commodities which were analyzed in the US and Canada at these PHI's. (Straw in the US was not analyzed for CGA-153433. Hay was not analyzed in Canada. For US data, the limits of quantitation for parent were 0.02 ppm for grain and 0.05 ppm for forage, hay, and straw; the limit of quantitation for CGA-153433 was 0.05 ppm for grain, forage, and hay; straw was not analyzed for CGA-153433. For Canadian data, the limits of quantitation for parent were 0.02 ppm for grain and forage and 0.05 ppm for straw; the limits of quantitation for CGA-153433 were 0.02 or 0.05 ppm for grain, and 0.05 ppm for forage and straw.) However, the field trial residue data are not adequate to support a permanent tolerance for the following reasons:

a. Adequate geographic representation is not provided. (Wheat is not a minor crop, for which a regional registration would be accepted.) According to OPPTS 860.1500, a minimum of 20 field trials are needed to support a tolerance on wheat. The suggested distribution of wheat field trials is one in Region 2, one in Region 4, five in Region 5, one in Region 6, five in Region 7, six in Region 8, and 1 in Region 11. The US field trials were conducted in Region 5 (2 studies) and Region 7 (four studies), as defined in OPPTS 860.1500; however, these US studies did not determine CGA-153433 in straw. Of the 15 Canadian field trials, four studies were conducted in extended Zone 5, seven studies were conducted in extended Zone 7, and four studies were conducted in extended Zone 14; however, the Canadian field trials have deficiencies which are not upgradeable (see Conclusion 19 below). Additional field trial residue studies are needed to support a permanent tolerance. If residues of CGA-153433 in straw samples in the US can be reanalyzed by an adequate method and the reanalysis can be supported by storage stability data, the following additional field trial studies would be needed: For a 30-day PHI in forage, the additional studies would be one in Region 2, one in Region 4, three in Region 5, one in Region 6, one in Region 7, six in Region 8, and 1 in Region 11. (If a 7-day PHI in forage is desired, then the additional studies would be one in Region 2, one in Region 4, five in Region 5, one in Region 6, four in Region 7, six in Region 8, and one in Region 11.) Otherwise (without US residue data for CGA-153433 in straw), the following additional field trial studies would be needed: one in Region 2, one in Region 4, five in Region 5, one in Region 6, five in Region 7, six in Region 8, and one in Region 11. Each study should include PHI's of 30 (or 7) days for forage, 30 days for hay, and 60 days for grain and straw. Spring (including hard red spring, duram, and white spring) and winter (including hard red winter, soft red winter, and white winter) varieties of

wheat should be included in the studies. Each study should include DSV Adjuvant or similar adjuvant. Raw data and representative chromatograms of standards, controls, fortified samples, and treated samples should be included. Storage information including types of storage containers and dates of extraction (as well as dates of storage and analysis) should be included.

b. Only spring wheat was used in the US and Canadian studies. Winter wheat should be included in the residue studies.

c. Forage was sampled at the proposed preharvest interval (PHI) of 7 days in only one US study and three Canadian studies.

d. Based on the available residue data, the petitioner should submit a revised Section F which proposes tolerances of 0.10 ppm for the combined residues of cloquintocet-mexyl and its metabolite 5-chloro-8-quinolinoxyacetic acid on wheat grain, forage, hay, and straw. These levels were obtained by adding the limits of quantitation for CGA-185072 and CGA-153433.

19. For the Canadian field trial residue studies, the following data should have been included. (HED is not recommending that the petitioner attempt to upgrade these studies to an acceptable level.)

a. Grain, forage, hay, and straw should be analyzed in each of the wheat field trial residue studies. (For an early season use, data on aspirated grain fractions are not needed.) Of the 15 Canadian studies, only grain and straw were analyzed in most of the studies (i.e., in twelve studies for CGA-185072 and 9 studies for CGA-153433), and only forage was analyzed (for both CGA-185072 and CGA-153433) in three studies. Hay was not analyzed.

b. PHI's should reflect the proposed use. PHI's for grain and straw in the Canadian studies ranged from 55-105 days (with all but two studies with PHI's above 60 days) whereas the proposed PHI for grain and straw is 60 days.

c. Extraction dates were not provided for studies 44399217, 44399218, 44399219, 44399220, 44399221, 44399222, 44399223, 44399224, 44399225, 44399226, 44399227, and 44399231.

d. Storage containers were not described.

e. Raw data and representative chromatograms of standards, controls, fortified samples, and treated samples were not submitted.

OPPTS GLN 860.1520: MAGNITUDE OF THE RESIDUE IN PROCESSED FOOD/FEED

20. Pending submission of storage stability data on CGA-153433 in processed commodities (see storage stability section of this review), HED concludes that no concentration of CGA-185072 or CGA-153433 occurred on processing.

OPPTS GLN 860.1480: MAGNITUDE OF THE RESIDUE IN MEAT, MILK, POULTRY, AND EGGS

Ruminants

21. A ruminant feeding study is not needed and tolerances on milk and the meat, fat, liver, and kidney of cattle, goats, hogs, horses, and sheep are not needed because of the low residue levels found in milk, muscle, fat, liver, and kidney in the goat metabolism study and the corresponding low radioactive residues calculated for the 1X feeding level. This use falls under 40 CFR §180.6(a)(3) since no secondary residues are expected to occur in milk and in the meat, fat, liver, and kidney of cattle, goats, hogs, horses, and sheep.

Poultry

22. Because of the low residue levels found in muscle, fat, liver, and eggs in the poultry metabolism study and the corresponding low radioactive residues calculated for the 1X feeding level, a poultry feeding study is not needed and tolerances on poultry tissues and eggs are not needed. This use falls under 40 CFR §180.6(a)(3) since no secondary residues are expected to occur in poultry commodities.

OPPTS GLN 860.1850: CONFINED ACCUMULATION IN ROTATIONAL CROPS

23. The submitted confined rotational crop data are adequate for a permanent tolerance provided that rotational crop restrictions are placed on the formulation label of at least 85 days (or 3 months) for lettuce and other leafy vegetables, 146 days (or 5 months) for small grains (except wheat), and one year (or 12 months) for all other crops.

24. If the petitioner wants shorter rotational crop restrictions, then a confined rotational crop study conducted at the soil aging intervals of 1, 4, and 12 months would be needed for three rotated crops (a small grain, a leafy vegetable, and a root crop) reflecting one application at the maximum label rate of 0.02 lb CGA-185072 safener/A.

OPPTS GLN 860.1900: FIELD ACCUMULATION IN ROTATIONAL CROPS

25. No field accumulation in rotational crop study was submitted. Pending results from the confined rotational crop study which may be conducted if the petitioner wants shorter rotational crop restrictions, this study may be required.

CODEX

26. An International Residue Limits (IRL) Status sheet is attached (Attachment 4). Canada has recently reviewed a petition on wheat. At this time, there are no Codex, Canadian, or Mexican tolerances for cloquintocet-mexyl on wheat. Therefore, no compatibility questions exist with respect to Codex.

RECOMMENDATIONS

HED cannot recommend for the proposed permanent tolerances for cloquintocet-mexyl on wheat for reasons given in Conclusions #'s 2, 3 (a,b,c), 4, 5, 7, 9 (a,b), 10 (a,b,c,d), 11, 17 (a,b,c), 18 (a,b,c,d), 19 (a,b,c,d,e), 20, 23, 24, and 25 above.

Provided the petitioner submits a revised Section B/label and revised Section F and EPA's method validation is satisfactory (see Conclusions 2, 11, and 18d above), there will be no residue chemistry data requirements that would preclude the establishment of time-limited tolerances or a time-limited registration for the combined residues of cloquintocet-mexyl (acetic acid, [(5-chloro-8-quinolinyl)oxy]-, 1-methylhexyl ester) and its acid metabolite 5-chloro-8-quinolinoxyacetic acid in/on wheat grain, forage, hay, and straw at 0.10 ppm while the remaining concerns are addressed.

HED will now initiate a Human Health Risk Assessment for this use.

A DEEM Run can be conducted at this time.

DETAILED CONSIDERATIONS

See Attachment 1 for the chemical names and structures of the safener cloquintocet-mexyl and its metabolites which are discussed in this review. See Attachment 2 for the chemical names and structures of the active ingredient clodinafop-propargyl and the metabolites which are discussed in this review.

OPPTS GLN 830 SERIES: PRODUCT PROPERTIES

The product chemistry of the technical grade of the active ingredient and the formulated products are reviewed by Registration Division.

OPPTS GLN 860.1200: PROPOSED USES

Formulation

Discover™ Herbicide is an emulsifiable concentrate which contains 22.3% clodinafop-propargyl active ingredient (ai) and 77.7% inerts. (See the Confidential Appendix for the percentage and lbs ai/gal of cloquintocet-mexyl).

Wheat

Apply Discover™ Herbicide to all types of spring and winter wheat (including Durum) grown in Montana, Minnesota, North Dakota, and South Dakota. Apply Discover™ Herbicide postemergence to wheat from the 2-leaf stage to emergence of the 4th tiller. Always use DSV Adjuvant (included in the Discover case) with Discover™ Herbicide. Other adjuvants should not be used. The application rate is 3.2 - 4.0 fl oz Discover™ Herbicide/A with 10.2 - 12.8 oz/A of DSV Adjuvant, depending on the weed to be controlled (see the Confidential Appendix). Apply broadcast using ground equipment in at least 5 or 10 gal spray/A (use at least 10 gal spray/A under dry conditions and when treating Persian Darnel or Annual Ryegrass) or apply by aircraft in at least 3 or 5 gal spray/A (use at least 5 gal spray/A under dry conditions and when treating Persian Darnel or Annual Ryegrass). For aerial applications, do not apply DSV adjuvant at concentrations greater than 2% v/v in the spray mix as crop injury may result. Discover™ Herbicide can be tank mixed with the following tank mix partners: Ally®, Amber®, Banvel®, Banvel SGF®, Bronate®, Buctril®, Buctril + MCPA ester, Buctril® Gel, Buctril Gel + MCPA ester, Canvas™, Clarity®, Curtail™ M, 2,4-D Amine, Express®, Finesse®, Glean®, Harmony® Extra, Harmony® GT, Harmony GT MCPA ester, MCPA Amine, MCPA Ester, Peak®, Peak + MCPA ester, Starane™, Starane™ + Sword®, and Stinger™. Follow the directions/restrictions on the label of the tank mix partner. Do not use multiple tank-mix partners. Do not tank mix with any chemical additives, pesticides, or fertilizers that are not recommended on this label. Other herbicides may be applied sequentially, at least 4 days after application of Discover™. Do not treat wheat underseeded to forages. Do not apply to a crop that is stressed. Do not apply through any type of irrigation system. Do not graze livestock or feed forage from treated areas

for a minimum of 7 days following application. Do not feed hay for 30 days following application. Do not harvest wheat (grain and straw) for 60 days following application. Make only one application per crop season.

Conclusion

The Section B/label should be revised to change the feeding/grazing restriction on forage to 30 days since limited residue data are available at a 7-day PHI. Provided the above revision to the Section B/label is made, the proposed use of cloquintocet-mexyl on wheat will be adequately described. The proposed use directions will be adequate to allow an assessment of whether the residue data reflect the maximum residues likely to occur in food/feed.

OPPTS GLN 860.1300: NATURE OF THE RESIDUE IN PLANTS

Wheat (1990; MRID 44387457)

A wheat metabolism study was submitted (see citation below). The performing laboratory was Novartis Crop Protection AG, Basle, Switzerland (formerly Ciba-Geigy Limited).

MRID 44387457 Denzil, Dr. B. (1990) Penetration, Distribution and Degradation of CGA-185072 in Spring Wheat, Project 88BD15, Laboratory Project Report 24/90, Nexus Study Number 343-90, unpublished study sponsored by Novartis Crop Protection, Inc., 45 pp.

In-life phase

Ring labeled CGA-185072 (i.e., [3-^{14}C]5-chloro-8-quinolinoxyacetic acid, 1-methylhexyl ester) was applied post-emergently to spring wheat in a field (long term experiment) in Klus, Switzerland. The radiochemical purity of the test substance was 95.7%. The specific activity was 1.93 MBq/mg (52.1 μCi/mg). The application rate of CGA-185072 was 2X (see the Confidential Appendix). The application was made in 500 liters water/ha (53 gal water/A). The formulation was a 50 EC formulation which also contained clodinafop-propargyl.

Total Radioactive Residues

Total radioactivity was determined by combustion and liquid scintillation counting. Refer to Table 1 below.

Extraction and hydrolysis of residues

Samples were extracted with 80% aqueous acetonitrile. Samples were further extracted with 100% acetonitrile by Soxhlet extraction overnight. Nonextractable radioactivity was determined by combustion. Total radioactivity and extractable/nonextractable radioactivity are reported in Table 1 below.

Table 1. Radioactivity in Field Grown Wheat (2X)						
Time after Treatment	Plant Part	Total Residues (ppm)	Extractable (%)		Nonextractable (%)	Total Radioactivity[1] (%)
			Cold Extraction (%)	Soxhlet Extraction (%)		
1.5 hours	leaves	1.624	83.8	0.1	6.3	90.2
35 days (ear emergence)	ears	0.003	n.a.[2]			
	leaves	0.067	56.6	n.a.[2]	41.3	97.9
56 days (milky stage)	grains	0.002	n.a.[2]			
	husks	0.005	n.a.[2]			
	leaves	0.029	43.6	3.3	58.3	105.2
82 days (maturity)	grains	0.003	n.a.[2]			
	husks	0.003	n.a.[2]			
	straw	0.083	20.9	1.2	78.2	100.3

[1] percent of radioactivity determined by combustion
[2] not analyzed

Characterization/identification of residues

Extractable residues (20.9% of the TRR in straw) were partitioned with CH_2Cl_2/H_20 at pH 7. The resulting water phase (18.6% of the TRR in straw) was partitioned with CH_2Cl_2/H_20 at pH 3. The residues in the resulting water phase (13.6% of the TRR in straw) were cleaned up on an Amberlite XAD-4 column. The residues in the resulting CH_3CN eluate (containing 10.5% of the TRR in straw) were cleaved with cellulase. Residues were analyzed by thin layer chromatography (TLC) using multiple solvent systems and high pressure liquid chromatography (HPLC).

CGA-185072 was readily absorbed by the leaves and quickly degraded to the corresponding acid CGA-153433 (19.1% of the TRR in/on leaves at 1.5 hours after treatment). CGA-153433 further degraded, decreasing to 1.8% of the TRR in/on leaves by 35 days after treatment.

CGA-153433 (4.4% of the TRR) was identified in/on straw at 82 days after treatment. Residues in grains and husks (at 56 days and 82 days after treatment) were too low to identify.

Characterization/identification of residues is reported in Table 2 below.

Table 2. Characterization/Identification of Residues in Field Grown Wheat (2X)													
Time after Treatment	Plant Part	Total Residues (ppm)	I_1 (Start) %	CGA-153433		I_3 %	I_4 %	CGA-185072		II_3	Unre-solved %	Non-extract-able (%)	Total Radio-activity[a] (%)
				ppm	%			ppm	%				
1.5 hours	leaves	1.624	3.9		19.1	1.3	1.3	0.758	46.7	5.1	7.0	6.3	90.7
35 days	ears	0.003	n.a.[b]										
	leaves	0.067	45.4[c] 25.6[d]		1.8[c] 1.8[d]	9.7[d]	2.8[c] 2.8[b]	0.003	4.1[c] 14.2[d]	0.8[c] 0.8[d]	1.3[c] 1.3[d]	41.1[c] 41.1[d]	97.3[c] 97.3[d]
56 days	grains	0.002	n.a.[b]										
	husks	0.005	n.a.[b]										
	leaves	0.029	35.1%[c] 34.5%[d]				4.8[c] 4.8[d]		0.3[c] 0.9[d]		6.7[c] 6.7[d]	58.3[c] 58.3[d]	105.2[c] 105.2[d]
82 days	grains	0.003	n.a.[b]										
	husks	0.003	n.a.[b]										
	straw	0.083	14.3[c] 9.7[d]		4.4[c] 4.4[d]	4.6[d]	1.0[c] 1.0[d]	<0.001			2.3[c] 2.3[d]	78.2[c] 78.2[d]	100.2[c] 100.2[d]

[a] percent of radioactivity determined by combustion; [b] not analyzed;
[c] distribution before cellulase treatment; [d] distribution after cellulase treatment

Storage Stability

The field biological phase of the study was conducted between 4/18/88 and 8/15/88. The analytical phase was conducted between 5/25/88 and 3/29/89. The samples were stored frozen (-18°C) between sampling and analysis.

Summary

The fate of [3-^{14}C-quinoline]CGA-185072 (i.e., [3-^{14}C]5-chloro-8-quinolinoxyacetic acid, 1-methylhexyl ester) was studied in field grown spring wheat in Klus, Switzerland after postemergence foliar spray application at the 2X rate (see the Confidential Appendix). Samples were extracted with 80% aqueous acetonitrile. Samples were further extracted with 100% acetonitrile by Soxhlet extraction overnight. CGA-185072 was readily absorbed by the leaves and quickly degraded to the acid CGA-153433, which amounted to 19.1% of the TRR in/on leaves at 1.5 hours after treatment. CGA-153433 further degraded, decreasing to 1.8% of the TRR in/on leaves by 35 days after treatment. The only identified residues in leaves at ear emergence were CGA-185072 (14.2%) and CGA-153433 (1.8%). Nonextractable residues in leaves amounted to 41.1% and 58.3% of the TRR at 35 days and 56 days after treatment, respectively. An unknown (I_1) accounted for 25.6% of the TRR in leaves at 35 days. Total radioactive residues (expressed as parent equivalents) in field grown wheat at maturity (82 days after treatment) were 0.003 ppm in grains, 0.003 ppm in husks, and 0.083 ppm in straw. In straw, 78.2% remained as non-extractable radioactivity. The only identified residue in straw was CGA-153433 (4.4% of the TRR at 82 days after treatment). Residues in grains and husks (at 56 days and 82 days after treatment) were too low to identify.

A proposed plant metabolism scheme is outlined in Figure 1 (Attachment 3).

Conclusion

The nature of the residue in wheat is not adequately understood for the purposes of a permanent tolerance for the following reasons pertaining to the [3-^{14}C-quinoline]CGA-185072 study:

a.. Due to large amounts of the radioactivity being nonextractable with 80% aqueous acetonitrile and by Soxhlet extraction with 100% acetonitrile, only 16.0%, 0.9%, and 4.4%TRR were identified in leaves (ear emergence), leaves (milky stage), and straw (maturity), respectively. The petitioner should have attempted to extract more of the radioactivity using acid, base, and enzymes and then characterized/identified the residues.

b. Residues in grain were not identified in the field study. The identity of residues in grain resulting from application to the plant in a manner simulating expected field use are needed. The study should be conducted at a higher rate than the 2X study which was submitted.

c. The time from sampling to final analysis should be clarified for the wheat samples. If the time between sampling and final analysis of the field samples exceeded 6 months, evidence should be provided that the identity of residues did not change during the period between collection and final analysis. Such evidence would be analyses of representative substrates early in the study and at its completion. To be acceptable, such analyses should show that the basic profile of radiolabeled residues has not changed during that time.

The nature of the residue in wheat is adequately understood for the purposes of a tolerance with an expiration date. The residues of concern in wheat were determined by HED's Metabolism Assessment Review Committee (MARC) on 2/15/00 (D263289, N. Dodd, 2/25/00) to be CGA-185072 and its acid metabolite CGA-153433. HED may revisit the MARC after additional wheat metabolism data have been submitted.

OPPTS GLN 860.1300: NATURE OF THE RESIDUE IN LIVESTOCK

RUMINANTS

(1990; MRID 44387458)

A study on the metabolism of CGA-185072 in the goat was submitted (see citation below). The performing laboratory was Hazleton UK, North Yorkshire, England.

44387458 Powles, P. (1990) CGA-185072: Absorption, Distribution, and Excretion in the Lactating Goat After Multiple Oral Administration, Laboratory Project No. 6193-380/161, Nexus Study Number 349-90, unpublished study sponsored by Novartis Crop Protection, Inc. (formerly Ciba Crop Protection), 59 pp.

In-life phase

A lactating goat was orally fed doses of (3-^{14}C)quinoline-labeled cloquintocet-mexyl in a daily capsule for ten days. The daily dose level was 5 ppm (i.e., 0.158 mg/kg bw/day, based on an average daily feed of 1.56 kg/day and an average body weight of 49.5 kg). (The feeding level of 5 ppm is 18X the maximum theoretical residue level in the diet of cattle, as calculated in this review under OPPTS GLN 860.1480.) The radiochemical purity of the test substance was 96 or 97%. The specific activity was 1.91 MBq/mg (51.6 μCi/mg). Urine, feces, and milk were collected before each daily dose. An additional milk collection was made 7 hours after dosing. Tissue samples were taken at ca. 24 hours after the last dose. Muscle (tenderloin, hindquarter, forequarter), fat (omental, kidney fat, subcutaneous), liver, and kidney were sampled.

Total Radioactive Residues

The total radioactivity levels in feces, tissues, and milk were determined by combustion (of solid samples) and liquid scintillation counting. The total radioactivity in urine was determined by liquid scintillation counting without combustion.

The majority of the administered radioactivity was eliminated in urine (62%) and feces (21%).

Total radioactivity levels in muscle, fat, kidney, and liver are reported in Table 3 below.

Table 3. Total Radioactivity in Tissues of a Goat after Ten Daily Doses of ^{14}C-CGA-185072 at a Level of 5 ppm (18X)

Matrix	CGA-185072 Equivalents (ppm)
muscle	
forequarter	<LOD[1]
hindquarter	0.002
tenderloin	0.003
fat	
kidney	<LOD[1]
subcutaneous	0.001
omental	<LOD[1]
kidney	0.024
liver	0.010

[1] LOD = limit of detection (0.001 ppm)

Total radioactivity in milk during the study is reported in Table 4 below:

Table 4. Total Radioactivity in Whole Milk of a Goat after Ten Daily Doses of ^{14}C-CGA-185072 at a Level of 5 ppm (18X)	
Sampling Time in 10-Day Study (hours)	CGA-185072 Equivalents (ppm)
0-24	0.084
24-48	0.015
48-72	0.007
72-96	0.007
96-120	0.009
120-144	0.009
144-168	0.008
168-192	0.007
192-216	0.008
216-240	0.007

Storage Stability

The samples were homogenized mechanically prior to storage and stored on solid carbon dioxide for shipment to the analytical laboratory.

The experimental part of the study was conducted June-August, 1989. Radioactivity in all matrices was determined May 4-8, 1990.

Summary

Radioactivity levels in tissues and milk resulting from a feeding level of 5 ppm (3-^{14}C)quinoline-labeled CGA-185072 for 10 days were low. The highest concentrations (expressed as CGA-185072 equivalents) were found in kidney (0.024 ppm) and liver (0.010 ppm). Residues were $\leq$0.003 ppm in muscle and $\leq$0.001 ppm in fat. Residues in milk peaked during the first day of the dosing period at 0.084 ppm but declined to 0.015 ppm by the second day and further declined

to 0.008 ± 0.001 ppm for the remainder of the study. The majority of the radioactivity administered to the lactating goat was eliminated in urine (62%) and feces (21%).

(1992; MRID 44387460)

A study on the metabolism of CGA-185072 in the goat was submitted (see citation below). The performing laboratory was Novartis Crop Protection AG, Basle, Switzerland.

44387460 Müller, Dr. T. (1992) CGA-185072: The Nature of the Metabolites in Milk, Tissues and Excreta of a Goat after Multiple Oral Administration of [3-^{14}C]Quinoline CGA-185072, Laboratory Project Number 5/92, Nexus Study Number 499-92, unpublished study sponsored by Novartis Crop Protection AG (formerly Ciba-Geigy Limited), 46 pp.

In-life phase

The urine, tissues, and milk used in this study were obtained from study MRID 44387458, which is discussed above.

Total Radioactive Residues

The tissue and milk samples obtained from MRID 44387458 contained the following radioactivity:

Table 5. Total Radioactivity in Tissues and Milk of a Goat after Ten Daily Doses of ^{14}C-CGA-185072 at a Level of 5 ppm (18X)

Matrix		CGA-185072 Equivalents (ppm)
muscle[1]		
	forequarter	<LOD[2]
	hindquarter	0.002
	tenderloin	0.003
	average	0.002
kidney		0.024
liver		0.010
milk	(day 5)	0.009

[1] Equal amounts of forequarter, hindquarter, and tenderloin were pooled to obtain a mean value of 0.002 ppm.
[2] LOD = limit of detection (0.001 ppm)

Extraction and hydrolysis of residues

Urine: Residues in urine were purified by liquid chromatography and HPLC to isolate a fraction containing 34.3% TRR.

Milk: Milk (containing 0.009 ppm radioactivity) was extracted with acetonitrile to precipitate proteins, lipoproteins, and other lipophilic components. The acetonitrile extract (87% TRR) was extracted with hexane. The aqueous layer (80.4% TRR) was acidified to pH 4 with formic acid and extracted with ethyl acetate. The ethyl acetate phase (71.3% TRR) was subjected to HPLC to obtain a methanol fraction (55.9% TRR).

Muscle: Muscle (hindquarter, forequarter, and tenderloin) containing 0.002 ppm radioactive residues was extracted with acetonitrile. The acetonitrile extract (60.5% TRR) was cleaned up by LC and preparative TLC to obtain a fraction containing 34.7% of the TRR.

Kidney: Kidney was extracted with acetonitrile. The acetonitrile extract (74.2% TRR) was cleaned up by LC and preparative TLC to obtain a fraction containing 68.5% TRR.

Liver: Liver was extracted with acetonitrile by sonication and in an homogenizer. The extract (53.6% TRR) was purified by LC and preparative TLC to obtain a fraction containing 36.2% TRR.

Other extraction procedures were conducted on liver :

Biphasic Extraction: Three liver subsamples (ca. 25 g each) were extracted under acidic (pH 4, with formic acid), basic (pH 9, with 25% ammonia/water), and neutral conditions. The appropriate aqueous suspension was mixed with 25 mL chloroform and 50 mL methanol followed by shaking for 15 minutes. Twenty-five mL chloroform were added and shaking continued for 15 minutes. Then 25 mL water were added and shaking continued for 15 minutes. After filtration, the extracts were put in a separatory funnel containing 100 mL chloroform, 100 mL methanol, and 90 mL water. Radioactivity was determined in the solids and in the organic and aqueous layers which were taken from a separatory funnel as shown in Table 6 below:

Table 6. Radioactive Residues in Chloroform and Aqueous Phases and Solid Phase			
Phase	pH of the Aqueous Phase		
	9	7	4
chloroform	29%	21%	17%
aqueous	22%	23%	35%
solid	49%	56%	48%
experimental recovery	87%	95%	103%

Enzymatic digestion: A subsample of liver was enzymatically digested with subtilisin from Bacillus licheniformis by incubation at 55°C for 1 hour. The filtrate was adjusted to pH 3 with formic acid and extracted with methylene chloride. Radioactivity was determined in the aqueous phase (31% TRR) and organic phase (46% TRR).

Characterization/identification of residues

Residues were identified by one- and two-dimensional thin layer chromatography, liquid chromatography, high performance liquid chromatography (HPLC), and high voltage electrophoresis (HVE).

Urine: HPLC indicated the presence of several radioactive metabolites. The major metabolite (23% TRR) was identified by two-dimensional TLC cochromatography and high voltage electrophoresis (HVE) as CGA-153433. (HVE elicited an amphoteric character confirming the identity of CGA-153433: Under acidic conditions (pH 2), the radioactive zone moved to the cathode indicating a protonated molecule; under neutral (pH 7) or basic (pH 10) conditions, the radioactive zone moved to the anode.) Other metabolites comprised 4%, 2%, 1%, 1%, and 0.7% of the TRR.

Milk: HPLC and two-dimensional TLC cochromatography identified CGA-153433 as the major residue in milk.

Muscle: Metabolites in muscle could not be identified by HPLC and two-dimensional TLC cochromatography. The TLC radiochromatogram exhibited undefinable zones which could not be assigned to any reference compound. Because of low radioactivity, further purification steps were not possible.

Kidney: Two-dimensional TLC showed one major metabolite in kidney, which was identified by TLC cochromatography as CGA-153433.

Liver: Metabolites in liver could not be identified by two-dimensional TLC because of interfering components and low radioactivity.

Storage Stability

In MRID 44387458, the experimental part of the study was started 6/17/89 and terminated 8/14/89. In MRID 44387460, the experimental part of the study was started 10/31/89 and terminated on 12/19/90. Samples were stored frozen until shipment, shipped in dry ice, and stored frozen at the laboratory in Basle until analysis.

Summary

A lactating goat was fed 5 ppm (3-^{14}C)quinoline-labeled cloquintocet-mexyl for ten days. (This is 18X the maximum theoretical residues in the diet of cattle as calculated in section 860.1480 of this review.) Residues were identified by one- and two-dimensional thin layer chromatography, liquid chromatography, high performance liquid chromatography (HPLC), and high voltage electrophoresis (HVE). The major residue in urine, milk, and kidney was CGA-153433. Residues in muscle and liver were not determined because of interferences and low radioactivity. No attempt was made to identify residues in fat because of low radioactivity (≤0.001 ppm).

The proposed ruminant metabolic pathway of 3-^{14}C-quinoline CGA-185072 is outlined in Figure 1 (Attachment 3).

Conclusion

The nature of the residue in ruminants is not adequately understood for the purpose of a permanent tolerance for the following reason: The time between sampling and final analysis should be clarified for milk and tissues. If the time between sampling and final analysis of the samples exceeded 6 months, evidence should be provided that the identity of residues did not change during the period between collection and final analysis. Such evidence would be analyses of representative substrates early in the study and at its completion. To be acceptable, such analyses would show that the basic profile of radiolabeled residues has not changed during that time.

For this use on wheat, the nature of the residue in ruminants is adequately understood for the purposes of a tolerance with an expiration date. The major residue in urine, milk, and kidney was CGA-153433. Residues in muscle and liver were not determined because of interferences and low radioactivity. No attempt was made to identify residues in fat because of low radioactivity (≤0.001 ppm). The residues of concern in ruminants were determined by HED's

Metabolism Assessment Review Committee on 2/15/00 (D263289, N. Dodd, 2/25/00) to be CGA-185072 and its acid metabolite CGA-153433.

POULTRY

(1991; MRID 44387459)

A study on metabolism of CGA-185072 in laying hens was submitted (see citation below). The performing laboratory was Hazleton UK, North Yorkshire, England.

44387459 Stewart, F.P. (1991) [3-^{14}C]Quinoline CGA-185072: Distribution and Excretion in the Laying Hen after Multiple Oral Administration, Laboratory Project No. 6356-380/164, Nexus Study Number 379-91, unpublished study sponsored by Novartis Crop Protection, Inc. (formerly Ciba Crop Protection), 90 pp.

In-life phase

Three hens were orally fed doses of (3-^{14}C)quinoline-labeled cloquintocet-mexyl in a daily capsule for fourteen days. The daily dose level was 5 ppm. (The feeding level of 5 ppm is 50X the maximum theoretical residue level in the diet of poultry, as calculated in this review under OPPTS GLN 860.1480.) The radiochemical purity of the test substance was 96 or 97%. The specific activity was 1.91 MBq/mg (51.62 μCi/mg). Excreta were collected just after dosing. Eggs were collected in the afternoon after dosing and the following morning before dosing. Tissue samples were taken at ca. 12 hours after the last dose. Muscle (mixture of lean meat from leg, thigh, and breast), skin (including attached fat), peritoneal fat, liver, and kidney were sampled.

Total Radioactive Residues

The total radioactivity levels (as ppm equivalents of [3-^{14}C]quinoline CGA-185072) in egg yolk, egg white, abdominal fat, kidney, liver, skin, and lean meat were determined by combustion (of solid samples) and liquid scintillation counting.

The majority of the administered radioactivity was eliminated in the excreta (84%).

Total radioactivity levels in abdominal fat, kidney, liver, skin, and lean meat are reported in Table 7 below.

Table 7. Total Radioactivity in Tissues of Hens after Fourteen Daily Doses of ^{14}C-CGA-185072 at a Level of 5 ppm (50X)				
Matrix	CGA-185072 Equivalents (ppm)			
	Hen 304F	Hen 103F	Hen 108F	Mean
abdominal fat	ND[1]	ND[1]	ND[1]	ND[1]
kidney	0.0066	0.0102	0.0361	0.0176
liver	0.0031	0.0062	0.0101	0.0065
skin	ND[1]	ND[1]	ND[1]	ND[1]
lean meat	ND[1]	ND[1]	ND[1]	ND[1]

ND[1] = Not detected (<0.002 ppm in fat, liver, and kidney; <0.001 ppm in lean meat and skin)

Total radioactivity in egg yolk during the study is reported in Table 8 below:

Table 8. Total Radioactivity in Egg Yolk of Three Hens after Fourteen Daily Doses of ^{14}C-CGA-185072 at a Level of 5 ppm (50X)

Time (hours)	CGA-185072 Equivalents (ppm)			
	Hen 304F	Hen 103F	Hen 108F	Mean
24	ND[1]	ND[1]	ND[1]	ND[1]
48	ND[1]	ND[1]	ND[1]	ND[1]
72	ND[1]	ND[1]	ND[1]	ND[1]
96	NS[2]	0.0010	0.0016	0.0013
120	0.0013	0.0014	NS[2]	0.0014
144	0.0016	0.0019	ND[1]	0.0012
168	0.0028	0.0019	0.0030	0.0026
192	0.0025	NS[2]	0.0034	0.0030
216	0.0021	0.0020	0.0038	0.0026
240	0.0020	NS[2]	NS[2]	0.0020
264	0.0023	0.0021	0.0025	0.0023
288	0.0017	0.0021	ND[1]	0.0013
312	0.0022	0.0021	0.0040	0.0028
324	NS[2]	0.0023	NS[2]	0.0023

ND[1] = Not detected (≤0.002 ppm)
NS[2] = No sample

Total radioactivity in egg white during the study is reported in Table 9 below:

Table 9. Total Radioactivity in Egg White of Three Hens after Fourteen Daily Doses of ^{14}C-CGA-185072 at a Level of 5 ppm (50X)

Time (hours)	CGA-185072 Equivalents (ppm)			
	Hen 304F	Hen 103F	Hen 108F	Mean
24	ND[1]	ND[1]	ND[1]	ND[1]
48	ND[1]	ND[1]	0.0013	0.0004
72	ND[1]	ND[1]	ND[1]	ND[1]
96	NS[2]	ND[1]	ND[1]	ND[1]
120	ND[1]	ND[1]	NS[2]	ND[1]
144	ND[1]	ND[1]	0.0014	0.0005
168	ND[1]	ND[1]	ND[1]	ND[1]
192	ND[1]	NS[2]	0.0013	0.0007
216	ND[1]	ND[1]	ND[1]	ND[1]
240	ND[1]	NS[2]	NS[2]	ND[1]
264	ND[1]	ND[1]	ND[1]	ND[1]
288	ND[1]	ND[1]	0.0029	0.0010
312	ND[1]	ND[1]	0.0071	0.0024
324	NS[2]	ND[1]	NS[2]	ND[1]

ND[1] = Not detected (≤0.002 ppm)
NS[2] = No sample

Storage stability

Muscle (mixture of lean meat from leg, thigh, and breast), skin (including attached fat), peritoneal fat, liver, and kidney were homogenized mechanically before storage at ≤20°C.

Summary

Three hens were orally fed 5 ppm of (3-^{14}C)quinoline-labeled cloquintocet-mexyl in a daily capsule for fourteen days. (This is 50X the maximum theoretical residues in the diet of poultry

as calculated in section 860.1480 of this review.) Total radioactivity (in ppm CGA-185072 equivalents) were determined in egg white (≤0.007 ppm), egg yolk (≤0.004 ppm), muscle (<0.001 ppm, i.e., <LOD), peritoneal fat (<0.002, i.e., <LOD), liver (≤0.01 ppm), and kidney (≤0.04 ppm).

(1992; MRID 44387461)

A study on the metabolism of CGA-185072 in poultry was submitted (see citation below). The performing laboratory was Novartis Crop Protection AG, Basle, Switzerland.

44387461 Müller, Dr. T. (1992) CGA-185072: The Nature of the Metabolites in Eggs, Tissues and Excreta of Hens after Multiple Oral Administration of [3-^{14}C]Quinoline CGA-185072, Laboratory Project Number 6/92, Nexus Study Number 501-92, unpublished study sponsored by Novartis Crop Protection, Inc. (formerly Ciba Crop Protection), 43 pp.

In-life phase

The tissues and eggs used in this study were obtained from study MRID 44387459, which is discussed above.

Total Radioactive Residues

The tissue and egg samples obtained from MRID 44387459 contained the following radioactivity:

Table 10. Total Radioactivity in Tissues and Eggs of Hens after Fourteen Daily Doses of ^{14}C-CGA-185072 at a Level of 5 ppm

Matrix	CGA-185072 Equivalents[1] (ppm)
liver	0.007
kidney	0.018
egg yolk	0.002
egg white	<0.001

[1] The residue levels in Table 10 are a result of pooling 3 liver samples, 3 kidney samples, 35 egg whites, and 35 egg yolks from MRID 44387459.

Extraction and hydrolysis of residues

Liver: Liver containing 0.007 ppm radioactive residues was extracted with acetonitrile. The acetonitrile extract (57.5% TRR) was cleaned up by liquid chromatography to obtain a methanol eluate (53.1% TRR).

Kidney: Kidney containing 0.018 ppm radioactive residues was extracted with acetonitrile. The acetonitrile extract (74.2% TRR) was cleaned up by liquid chromatography to yield a methanol eluate (72.3% TRR).

Egg White: Egg white containing <0.001 ppm radioactive residues was extracted with acetonitrile. The acetonitrile extract (77.7% TRR) was subjected to liquid chromatography, which yielded a methanol eluate (36.1% TRR) and an ammonium formate buffer eluate (41.5% TRR). The ammonium formate buffer eluate was cleaned up by liquid chromatography to yield a methanol eluate (36.4%TRR). The two methanol eluates were combined (72.5% TRR) and cleaned up again by liquid chromatography, yielding a methanol eluate containing 71.3% TRR.

Egg Yolk: Egg yolk containing 0.002 ppm radioactive residues was extracted with acetonitrile, yielding an acetonitrile extract (21.4% TRR) and solids (78.6% TRR). The solids were extracted with acidified acetonitrile (pH 4.5) containing 1% water/formic acid (1:1, v:v). The resulting acetonitrile extract contained 38.9% TRR. The combined acetonitrile extracts contained 60.3% TRR. Further purification was not possible due to low radioactivity.

Characterization/identification of residues

The major metabolite in liver, kidney, and egg white was identified by two-dimensional thin layer chromatography (TLC) and cochromatography as CGA-153433. Residues in egg yolk could not be identified due to low radioactivity. Because no detectable residues were found in lean meat (<0.001 ppm) and fat (<0.002 ppm), characterization/identification of residues in lean meat and fat was not attempted.

Storage stability

In MRID 44387459, the experimental part of the study was started 8/3/89 and terminated 7/3/90. In MRID 44387461, the experimental part of the study was started 2/16/90 and terminated 12/28/90. Samples were stored frozen until shipment, shipped in dry ice, and stored frozen at the laboratory until analysis.

Summary

The major metabolite in liver, kidney, and egg white was identified by two-dimensional TLC and cochromatography as CGA-153433. Residues in egg yolk could not be identified due to low

radioactivity. Because no detectable residues were found in lean meat (<0.001 ppm) and fat (<0.002 ppm), characterization/identification of residues in lean meat and fat was not attempted.

The proposed poultry metabolic pathway of 3-^{14}C-quinoline CGA-185072 is outlined in Figure 1 (Attachment 3).

Conclusion

The nature of the residue in poultry is not adequately understood for the purpose of a permanent tolerance for the following reason: The time between sampling and final analysis should be clarified for eggs and tissues. If the time between sampling and final analysis of the samples exceeded 6 months, evidence should be provided that the identity of residues did not change during the period between collection and final analysis. Such evidence would be analyses of representative substrates early in the study and at its completion. To be acceptable, such analyses would show that the basic profile of radiolabeled residues has not changed during that time.

For this use on wheat, the nature of the residue in poultry is adequately understood for the purposes of a tolerance with an expiration date. The major metabolite in liver, kidney, and egg white was identified by two-dimensional TLC and cochromatography as CGA-153433. Residues in egg yolk could not be identified due to low radioactivity. Because no detectable residues were found in lean meat (<0.001 ppm) and fat (<0.002 ppm), characterization/identification of residues in lean meat and fat was not attempted. The residues of concern in ruminants were determined by HED's Metabolism Assessment Review Committee on 2/15/00 (D263289, N. Dodd, 2/25/00) to be CGA-185072 and its acid metabolite CGA-153433.

OPPTS GLN 860.1340: RESIDUE ANALYTICAL METHODS

PLANTS

Method REM 138.01 (1990; MRID 44399211)

Method REM 138.01 was used to determine CGA-185072 in wheat in all of the residue/processing samples in the US and Canada and in some of the storage stability samples (see citation below). The performing laboratory was Novartis Crop Protection AG, Basle, Switzerland.

MRID 44399211 Altenburger, Dr. E. (1990) Determination of Residues of Parent Compounds By Liquid Chromatography (HPLC) [Wheat], Analytical Method REM 138.01, Nexus Study Number 357-90, unpublished study sponsored by Novartis Crop Protection, Inc., 24 pp.

CGA-185072 and CGA-184927 are extracted from homogenized plant samples with acetonitrile. The extract is cleaned up by partitioning fatty coextracts into hexane. The analytes are then cleaned up by solid phase extraction on a C-18 cartridge, reextraction into hexane-diethyl ether, and a second solid phase extraction on a silica cartridge. CGA-184927 and CGA-185072 are eluted in separate fractions and determined separately on a 2-column switching high performance liquid chromatographic (HPLC) system with UV-detection. The limits of quantitation of the method for CGA-185072 are 0.02 ppm for grain and 0.05 ppm for wheat forage and straw.

Extraction efficiency

Recoveries were determined in the independent laboratory method validation discussed below. Recoveries obtained at the time of residue data analyses (concurrent recoveries) are included in the section "OPPTS GLN 860.1500: Magnitude of the Residue in Plants."

Radiovalidation

Radiovalidation data were not submitted. Radiovalidation data are needed to demonstrate the efficiency of the proposed enforcement method in extracting and quantifying residues in aged samples.

Interference study

An interference study was not submitted. Either an interference study must be submitted which determines whether other pesticides registered on wheat will interfere with the analysis of cloquintocet-mexyl residues by the enforcement method or a specific confirmatory method such as mass spectroscopy is needed as discussed in OPPTS GLN 860.1340. Provided that a specific confirmatory method is made available, the Agency will not require that an interference study be conducted.

Confirmatory method

Independent laboratory method validation of proposed enforcement method (1998; MRID 44568401)

The petitioner submitted an independent laboratory method validation for Method REM 138.01 for determination of CGA-185072 in wheat (see citation below). The performing laboratory was Novartis Crop Protection, Inc., Greensboro, NC.

44568401 Joseph, T.A. (1998) Method Validation Ruggedness Trial for the Determination of CGA-184927 and CGA-185072 in Wheat and Soil Using Method REM 138.01, "Determination of Residues of Parent Compound by Liquid Chromatography," Project Number 173001, Laboratory Project Number ABR-98016, Novartis Number 179-98, unpublished study submitted by Novartis Crop Protection, Inc., 75 pp.

Samples of wheat grain, forage, and straw were fortified with CGA-185072. Wheat grain was fortified at levels of 0.02, 0.04, and 0.10 ppm. Wheat forage and straw were fortified at levels of 0.05, 0.10, and 0.20 ppm. The limits of quantitation of the method for CGA-185072 are 0.02 ppm for grain and 0.05 ppm for wheat forage and straw.

Three trials were conducted to obtain satisfactory results on all substrates. Satisfactory results were obtained for CGA-185072 in the first trial for wheat forage and straw and in the third trial for wheat grain. Problems encountered were as follows: 1) In the analyses of CGA-185072 in wheat grain, interfering peaks in chromatograms were believed to be caused by allowing the C-18 cartridge to dry under vacuum in the elution step; 2) In all three analyses of CGA-185072 in wheat grain, one in five of the fortification samples (i.e., fortifications of 0.02 ppm in the first analysis and 0.04 ppm in the second and third analyses) had a recovery >120% for an unknown reason. Critical steps were as follows: 1) In the C-18 elution step, the cartridge must not be allowed to run dry; 2) The mobile phases must be degassed by sparging before use. Sparging with helium for approximately one minute was sufficient.

Results of the independent method validation are presented in Table 11 below. All of the control samples were free of quantifiable residues (<0.02 ppm for wheat grain and <0.05 ppm for wheat forage and straw). Representative chromatograms were provided for controls, recoveries, reagent blanks, and CGA-185072 standards. The independent laboratory indicates that a set of seven to thirteen samples can be prepared for analysis by HPLC in one working day. Automated HPLC chromatographic analysis can be performed overnight.

Table 11. Independent Laboratory Method Validation Results

Commodity[1]	Chemical Added	PPM Added	PPM Found	% Recovery
wheat grain	CGA-185072	0.00	<0.02	--
		0.00	<0.02	--
		0.02	0.02	109
		0.02	0.03	136
		0.04	0.05	113
		0.04	0.05	112
		0.10	0.12	120
wheat forage	CGA-185072	0.00	<0.05	--
		0.00	<0.05	--
		0.05	0.05	102
		0.05	0.04	74
		0.10	0.09	86
		0.10	0.10	101
		0.20	0.20	101
wheat straw	CGA-185072	0.00	<0.05	--
		0.00	<0.05	--
		0.05	0.06	113
		0.05	0.05	101
		0.10	0.09	91
		0.10	0.10	96
		0.20	0.17	85

[1] Results are reported from the successful trials only: Trial # 3 for wheat grain and Trial #1 for wheat forage and straw.

Method REM 138.06 (1991; MRID 44399213)

Method REM 138.06 was used to determine CGA-153433 in wheat in all of the residue studies in Canada and in some storage stability samples (see citation below). The performing laboratory was Novartis Crop Protection AG, Basle, Switzerland.

MRID 44399213 Altenburger, Dr. E. (1991) Determination of Residues of Metabolites CGA 153433 and CGA 193469 By Liquid Chromatography (HPLC) [Wheat], Analytical Method REM 138.06, Nexus Study Number 404-91, unpublished study sponsored by Novartis Crop Protection, Inc., 16 pp.

CGA-153433 and CGA-193469 are extracted from homogenized crop samples with an acetone-buffer pH 3 mixture. [The buffer pH 3 (citrate-hydrochloric acid) is a mixture of citric acid monohydrate, sodium chloride, sodium hydroxide, and water.] After evaporation of the organic solvent, CGA-193469 is extracted into hexane-diethyl ether at acidic pH; CGA-153433 is afterwards extracted into diethyl ether-dichloromethane from the same aqueous extract after adding 1 mL of saturated NaCl solution. The two organic solutions are evaporated, separately taken up in ion pair reagent solution, and cleaned up by extraction with hexane. The metabolites are then independently determined by reversed phase high performance liquid chromatography (HPLC) on a two column switching system with UV-detection. The limit of quantitation of the method for CGA-153433 is 0.05 ppm for wheat forage, grain, and straw.

Extraction efficiency

Recoveries were determined in the independent laboratory method validation discussed below. Recoveries obtained at the time of residue data analyses (concurrent recoveries) are included in the section "OPPTS GLN 860.1500: Magnitude of the Residue in Plants."

Radiovalidation

Radiovalidation data were not submitted. Radiovalidation data are needed to demonstrate the efficiency of the proposed enforcement method in extracting and quantifying residues in aged samples.

Interference study

An interference study was not submitted. Either an interference study must be submitted which determines whether other pesticides registered on wheat will interfere with the analysis of cloquintocet-mexyl residues by the enforcement method or a specific confirmatory method such as mass spectroscopy is needed as discussed in OPPTS GLN 860.1340. Provided that a specific confirmatory method is made available, the Agency will not require that an interference study be conducted.

Confirmatory method

A confirmatory method is not available. A confirmatory method is needed.

Independent laboratory method validation of proposed enforcement method (1998; MRID 44568402)

The petitioner submitted an independent laboratory method validation for Method REM 138.06 for determination of CGA-153433 in wheat (see citation below). The performing laboratory was Novartis Crop Protection, Inc., Greensboro, NC.

44568402 Joseph, T.A. (1998) Method Validation Ruggedness Trial for the Determination of Metabolites of CGA-184927 and CGA-185072 in Wheat Using Method REM 138.06, "Determination of Residues of Metabolites CGA-153433 and CGA-193469 by Liquid Chromatography (HPLC)," Project Number 173001, Laboratory Project Number ABR-98017, Novartis Number 180-98, unpublished study submitted by Novartis Crop Protection, Inc., 72 pp.

Samples of wheat grain, forage, and straw were fortified with CGA-153433 at levels of 0.05, 0.10, and 0.20 ppm. The limit of quantitation (LOQ) of the method for CGA-153433 is 0.05 ppm for wheat forage, grain, and straw.

Three trials were conducted to obtain satisfactory results on all substrates. Satisfactory results for CGA-153433 were obtained in the third trial for wheat forage, grain, and straw. Novartis Crop Protection, Basil, Switzerland, was contacted because of a stability problem with CGA-153433 in acetonitrile solution in the wheat straw analyses. The stock and fortification standards were then made up in ethanol to achieve a satisfactory recovery.

Results of the independent laboratory validation are presented in Table 12 below. All of the control samples were free of quantifiable residues (<0.05 ppm). Representative chromatograms were provided for controls, recoveries, reagent blanks, and the CGA-153433 standard. The independent laboratory indicates that a set of seven samples can be worked up for both analytes in one eight-hour day. Automated HPLC chromatographic analysis can be performed overnight.

Table 12. Independent Laboratory Method Validation Results

Commodity[1]	Chemical Added	PPM Added	PPM Found	% Recovery
wheat forage	CGA-153433	0.00	<0.05	--
		0.00	<0.05	--
		0.05	0.03	64
		0.05	0.04	70
		0.10	0.07	67
		0.10	0.07	70
		0.20	0.14	67
wheat straw	CGA-153433	0.00	<0.05	--
		0.00	<0.05	--
		0.05	lost	lost
		0.05	0.03	59
		0.10	0.06	58
		0.10	0.09	85
		0.20	0.14	68
wheat grain	CGA-153433	0.00	<0.05	--
		0.00	<0.05	--
		0.05	0.04	71
		0.05	0.04	82
		0.10	0.07	72
		0.10	0.07	74
		0.20	0.15	75

[1] Results are reported from the successful trials only: Trial # 3 for wheat forage, grain and straw.

Method REM 138.10 (1993; MRID 44755302)

Method REM 138.10 was used to determine CGA-153433 in wheat in some storage stability samples and in all of the residue/processing studies in the US (see citation below). The performing laboratory was Novartis Crop Protection AG, Basle, Switzerland.

MRID 44755302 Mair, P. (1993) Determination of CGA-193469 and CGA-153433 by HPLC, Analytical Method REM 138.10, Nexus Study Number 599-99, unpublished study sponsored by Novartis Crop Protection, Inc., 24 pp.

CGA-153433 and CGA-193469 are extracted from homogenized wheat substrates with an acetone:citrate buffer (8:2, v:v) (pH 3) solution. (The acetone:citrate buffer solution is made from citric acid monohydrate, sodium chloride, sodium hydroxide, and water.) The citrate solution is partitioned with hexane:diethyl ether (8:2, v:v). The organic phase contains CGA-193469 while the aqueous phase contains CGA-153433. After the organic phase is dried, CGA-193469 is redissolved in a buffer solution (pH 7) and cleaned up by partitioning with hexane. CGA-153433 is partitioned into ethyl acetate. The ethyl acetate is dried, and CGA-153433 is dissolved in a buffer solution (pH 7). The analytes are cleaned up on C-18 solid phase extraction cartridges. (Note: The CGA-193469 method was modified for forage, hay, and straw samples by adding a silica column cleanup step prior to the C-18 step). CGA-193469 and CGA-153433 are separately determined by reversed-phase HPLC on a two column switching system with UV-detection. (Note: CGA-193469 residue determinations on grain were performed without column switching.) The limits of quantitation for CGA-153433 are 0.02 ppm for wheat grain and 0.05 ppm for forage, hay, and straw. The petitioner indicated that a series of 10 specimens can be processed during two working days and that automated HPLC chromatographic analysis can be performed overnight.

Extraction Efficiency

Recoveries were reported in MRID 44755302 for wheat grain, straw, and green plant material as follows:

Table 13. Recoveries of CGA-153433 in Wheat Straw, Grain, and Whole Plant		
Crop Matrix	Fortification Level (ppm)	Recoveries (%) (average, n=8)
wheat grain	0.05	63, 58, 67, 62, 67, 68, 69, 63 (average 65)
	0.5	64, 65, 66, 65, 66, 68, 66, 67 (average 66)
wheat straw	0.05	68, 71, 54, 54, 65, 73, 72, 69 (average 66)
	0.5	53, 63, 60, 74, 59, 64, 61, 65 (average 62)
green plant material	0.05	81, 80, 69, 71, 64, 72, 86, 74 (average 75)
	0.5	67, 76, 76, 76, 74, 79, 75, 82 (average 76)

Recoveries obtained at the time of residue data analyses (concurrent recoveries) are included in the section "OPPTS GLN 860.1500: Magnitude of the Residue in Plants."

Radiovalidation

Radiovalidation data were not submitted. Radiovalidation data are needed to demonstrate the efficiency of the proposed enforcement method in extracting and quantifying residues in aged samples.

Interference study

An interference study which determines whether other pesticides registered on wheat will interfere with the analysis of cloquintocet-mexyl residues by the enforcement method was not submitted; however, a specific confirmatory method (GC/MS or LC/MS) is available. Since a specific confirmatory method (GC/MS) is available, the Agency will not require that an interference study be conducted, as stated in OPPTS GLN 860.1340.

Confirmatory method

Method REM 138.10 (MRID 44755302) indicates that a confirmatory method is GC/MS after derivatization with diazomethane. EPA considers diazomethane as a methylating agent to be a hazardous reagent. The petitioner should investigate whether another methylating agent could be substituted for diazomethane. If an alternative methylating agent is not available, then EPA requires that justification for use of diazomethane be provided.

An alternative confirmatory method for CGA-153433 would be LC/MS. Selected residue samples (in MRID 44755303) were analyzed for CGA-153433 by HPLC with mass spectrometric detection (LC/MS) after extraction and cleanup as described in Method REM 138.10.

REM 138.12

REM 138.12 is a minor improvement of REM 183.01. REM 138.12 was used to determine CGA-185072 in some wheat straw storage stability samples (MRID 44399209). In MRID 44399209, Method REM 138.12 is described as "essentially identical" to REM 138.01. The petitioner also states that "REM 138.12 was issued to account for a validation and for minor improvements introduced during the live time of REM 138.01".

The following reference was not submitted to EPA: REM 138.12, "Determination of Parent Compounds by HPLC in Wheat Grain, Straw, Green Plant and Soil", Dr. Peter Mair, Ciba Plant Protection, 1993.

Method REM 138.12 should be submitted.

Summary

Analytical Method REM 138.01 was used to determine CGA-185072 in wheat in all of the residue/processing samples in the US and Canada and in some of the storage stability samples. CGA-185072 and CGA-184927 are determined separately by high performance liquid chromatography (HPLC) with UV-detection. The limits of quantitation of the method for CGA-185072 are 0.02 ppm for grain and 0.05 ppm for wheat forage and straw. A successful independent laboratory method validation was conducted for Method REM 138.01 on wheat grain, forage, and straw. An EPA method validation of Method REM 138.01 has been requested (D254000, PP#7F04924, N. Dodd, 4/27/99). The method validation was requested for CGA-185072 on wheat grain, forage, and straw.

Analytical method REM 138.06 was used to determine CGA-153433 in wheat in all of the residue studies in Canada and in some storage stability samples. CGA-153433 and CGA-193469 are independently determined by high performance liquid chromatography (HPLC) with UV-detection. The limit of quantitation of the method for CGA-153433 is 0.05 ppm for wheat

forage, grain, and straw. A successful independent laboratory method validation was conducted for Method REM 138.06 on wheat grain, forage, and straw. An EPA method validation of Method REM 138.06 has been requested (D254000, PP#7F04924, N. Dodd, 4/27/99). The method validation was requested for CGA-153433 on wheat grain, forage, and straw.

Analytical method REM 138.10 was used to determine CGA-153433 in wheat in some storage stability samples and in all the residue/processing studies in the US. CGA-193469 and CGA-153433 are separately determined by HPLC with UV-detection. The limits of quantitation for CGA-153433 are 0.02 ppm for wheat grain and 0.05 ppm for forage, hay, and straw. An EPA method validation of Method REM 138.10 has been requested (D254000, PP#7F04924, N. Dodd, 4/27/99). The method validation was requested for CGA-153433 on wheat grain, forage, and straw.

Analytical method REM 138.12, a minor improvement of REM 183.01, was used to determine CGA-185072 in some wheat storage stability samples. Method REM 138.12 should be submitted to EPA.

Conclusions

To establish a permanent tolerance, the following additional information is needed regarding the analytical methods used to obtain the storage stability and residue data: a) Radiovalidation data for Methods REM 138.01, 138.06, 138.10, and 138.12 are needed to demonstrate the efficiency of the methods in extracting and quantifying aged or bound residues in samples; b) Method REM 138.12 should be submitted.

Before EPA can determine whether adequate analytical methods are available for enforcement of permanent tolerances on wheat, the following additional information is needed for the proposed enforcement methods: a) For REM 138.01 and REM 138.06, either an interference study must be submitted which determines whether other pesticides registered on wheat will interfere with the analysis of cloquintocet-mexyl residues by the enforcement method or a specific confirmatory method such as mass spectroscopy is needed as discussed in OPPTS GLN 860.1340. Provided that a specific confirmatory method is available, the Agency will not require that an interference study be conducted; b) Confirmatory methods are needed for REM 138.01 and 138.06; c) The GC/MS confirmatory method in Method REM 138.10 includes derivatization with diazomethane. The petitioner should investigate whether another methylating agent could be substituted for diazomethane. If an alternative methylating agent is not available, EPA requires that justification for the use of diazomethane be provided. An alternative confirmatory method for REM 138.10 would be LC/MS. REM 138.10 could be rewritten to include LC/MS as the confirmatory method instead of GC/MS; d) Adequate EPA petition method validations are needed for the proposed enforcement methods. RAB3 has requested EPA petition method validations for REM 138.01, 138.06, and 138.10. These EPA petition method validations are underway. Adequate independent laboratory validations have been provided for methods REM 138.01 and 138.06.

Provided that the petition method validations which are being conducted by EPA are successful, adequate enforcement methods (MRID #'s 44399211, 44399213, and 44755302) are available to enforce tolerances with an expiration date on wheat.

ANIMALS

Analytical/enforcement methods for animal commodities are not needed since tolerances on animal commodities are not needed for this use on wheat. (See Section OPPTS GLN 860.1480 in this review.)

OPPTS GLN 860.1360: MULTIRESIDUE METHODS (1998: MRID 44755301)

Multiresidue method testing data for CGA-185072 and CGA-153433 in wheat grain have been submitted (see citation below). The performing laboratory was Novartis Crop Protection, Inc., Greensboro, NC.

MRID 44755301 Lin, Kaijun (1998), Determination of CGA-184927, CGA-185072, CGA-153433 and CGA-193469 by the U.S. Food and Drug Administration Multiresidue Methods, Project Number 173001, Laboratory Project Number ABR-98093, Novartis Number 480-98, unpublished study submitted by Novartis Crop Protection, Inc., 133 pp.

CGA-185072 and CGA-153433 in wheat grain were tested through the FDA multiresidue methods according to the decision tree and protocols in the Pesticide Analytical Manual, Volume I (PAM I), Appendix II, Transmittal 96-1 (1/96). CGA-185072 was tested per Protocols C, D, and E. CGA-153433 were tested per Protocols B and C.

CGA-185072

Protocol C: CGA-185072 yielded adequate detector responses to Section 302 DG5, DG13, and DG18 gas-liquid chromatography (GLC) systems.

Protocol D: CGA-185072 was completely recovered through the complete method without Florisil cleanup (Section 302 E4), and no interference was observed. CGA-185072 was not recovered through Florisil cleanup (Section 302 C1) or the complete method with Florisil cleanup (Section 302 E4/C1).

Protocol E: CGA-185072 was not recovered through Section 303 C1 Florisil cleanup, partially (7%) recovered through Section 303 C2 Florisil cleanup, and not recovered through the complete method (Section 303 E3/C1 and E3/C2).

CGA-153433

Protocol C: CGA-153433 did not yield adequate detector responses to any of the Section 302 DG5, DG13, and DG18 systems; however, the methyl ester of CGA-153433 yielded adequate responses to the gas-liquid chromatography (GLC) systems.

Protocol B: The methyl ester of CGA-153433 was not recovered through Florisil cleanup (Section 402 C1c).

Conclusion

Multiresidue method testing data for CGA-185072 and CGA-153433 in wheat grain have been submitted. CGA-185072 and CGA-153433 were tested through the FDA multiresidue methods according to the decision tree and protocols in the Pesticide Analytical Manual, Volume I (PAM I), Appendix II, Transmittal 96-1 (1/96). CGA-185072 was tested per Protocols C, D, and E. CGA-153433 was tested per Protocols B and C. RAB3 (D255566, N. Dodd, 5/12/99) has forwarded the submitted multiresidue methods data to FDA for review to determine sufficiency.

OPPTS 860.1650: SUBMITTAL OF ANALYTICAL REFERENCE STANDARDS

The petitioner was requested (via memos from Susan Stanton, RD, to Karen Stumpf on 4/5/99 and 4/6/99) to send the analytical reference standards and Material Safety Data Sheets for CGA-185072 and CGA-153433 to US EPA, National Pesticide Standards Repository/Analytical Chemistry Branch/OPP, 710 Mapes Road, Fort George G. Meade, MD 20755-5350. The petitioner indicated to Susan Stanton, Registration Division/EPA, in April 1999 that the reference standards and Material Safety Data Sheets were sent. The EPA petition method validations are underway.

OPPTS GLN 860.1380: STORAGE STABILITY DATA

PLANTS

Storage conditions and intervals of samples

US Samples (1999; MRID 44755303)

Wheat residue samples in the US were frozen after collection and shipped via freezer truck or overnight courier with dry ice to the performing laboratory where they were stored frozen (-20°C). Before storage at the performing lab, the samples were prepared as follows: forage, hay (excluding grain), and straw (excluding grain) were cut into approximately two-inch pieces and ground with dry ice. Grain was ground after removal of chaff. The samples were stored frozen in polyethylene bags or bottles until analysis. The maximum storage interval for wheat

samples from sampling to analysis for CGA-185072 was 105 days (approx. 3 ½ months); the maximum time between extraction and analysis was 21 days. The maximum storage interval from sampling to analysis for wheat samples analyzed for CGA-153433 was 231 days (approx. 8 months); the maximum time between extraction and analysis was 48 days. Wheat processed commodities were stored frozen (-20°C) at the analytical laboratory until analysis. Processed grain samples were either ground or used as received. The samples were stored frozen in polyethylene bags or bottles until analysis. The maximum storage time between sampling of grain and analysis of the processed commodities was 52 days for CGA-185072 and 152 days for CGA-153433; the maximum time between extraction and analysis was 7 days for CGA-185072 and 10 days for CGA-153433. The storage time between processing and analysis of the processed commodities was ≤25 days for CGA-185072. The storage time between processing and analysis for CGA-153433 was 51 days for aspirated grain, 45 and 125 days for germ, 45 days for bran, 42 days for middlings and shorts, and 37 days for low grade flour and patent flour.

Storage intervals for specific wheat commodities are tabulated below for CGA-185072 and CGA-153433:

Table 14. Storage Intervals for Wheat Commodities

Matrix	CGA-185072		CGA-153433	
	Sampling to Analysis (Days)	Extraction to Analysis (Days)	Sampling to Analysis (Days)	Extraction to Analysis (Days)
grain	20-62	0-13	54-95	0-12
forage	54-105	1-21	129-218	1-48[1]
hay	42-93	1-20	129-231	0-25
straw	15-70	1-11	104-141	3-38[2]
processed commodities[3]	48-52	0-7	64-152	2-10

[1] 1-30 days except for one 44-day interval and one 48-day interval

[2] 3-31 days except for one 38-day interval

[3] The storage time between processing and analysis was ≤25 days for CGA-185072, and ≤51 days for CGA-153433 except for germ (125 days).

Canadian Samples (1997; MRID 44399216; and 1991-1993; MRID's 44399217, 44399218, 44399219, 44399220, 44399221, 44399222, 44399223, 44399224, 44399225, 44399226, 44399227, 44399228, 44399229, 44399230, 44399231)

Wheat residue samples in Canada were grain and straw in 12 studies and forage in 3 studies. Of the 12 grain/straw studies, the samples were threshed in the field to separate grain and straw

except in one study (MRID 44399218) in which no field treatment occurred. In the 3 forage studies (MRID 44399222, 44399223, and 44399224), no field treatment occurred. Samples were stored frozen (at -10°C to -30°C) until shipment, shipped frozen, and then stored frozen (at -20°C) until analysis. Samples were prepared for analysis by grinding or milling grain and by cutting straw or forage into pieces and milling or homogenizing the forage/straw. Samples were prepared for analysis 0-5 months before analysis except possibly in MRID's 44399228, 44399229, and 44399230, in which preparation dates were not given. In MRID's 44399228, 44399229, and 44399230, samples were extracted 7-12 days before analysis. The other studies do not give extraction dates. Storage containers were not described. The storage time between sampling and analysis of grain and straw ranged from 55 to 574 days for CGA-185072 and 98 to 341 days for CGA-153433. The storage time between sampling and analysis of forage for CGA-185072 and CGA-153433 ranged from 412-434 days.

Storage stability data (MRID 44399207, 44399208, 44399209, and 44399210)

1994; MRID 44399207

A storage stability study for CGA-153433 on wheat straw was submitted (see citation below). The performing laboratory was Novartis Crop Protection AG, Basle, Switzerland.

MRID 44399207 Mair, Dr. P. (1994) Special Study 119/92: Interim Report, Residue Stability Study for CGA-193469 and CGA-153433 in Wheat Straw under Freezer Storage Conditions, Laboratory Project Number 119/92, Nexus Study Number 493-94, unpublished study sponsored by Novartis Crop Protection, Inc., 17 pp.

Wheat straw which had been cut into small pieces in a cutting mill was treated with a methanolic solution of CGA-193469 and CGA-153433, milled in a cross beater mill with dry ice, placed in double layered polyethylene plastic bags, and stored frozen (-18°C) for one year. (This report is an interim report of a two-year storage stability study.) CGA-153433 was extracted from samples on days 0, 50, 92, 184, and 380. Analytical methods for CGA-153433 were REM 138.06 (for days 0-50 of the study) and REM 138.10 (for the rest of the study). At each analysis interval, five samples of stored fortified material, one untreated control, and two fresh fortification samples were analyzed. Storage stability samples were fortified with CGA-153433 at approximately 1 ppm. Fresh fortification samples were fortified at 0.5 ppm. Representative chromatograms of standards, controls, freshly fortified samples, and stored samples for CGA-153433 were submitted. Storage stability fortification recovery data for CGA-153433 in wheat straw are reported in Table 15 below.

Table 15. Storage Stability Fortification Recovery Data for CGA-153433 in Wheat Straw							
Commodity	Analyte	Residue Level Added (ppm)	Storage Period[1] (days)	Residue Level Found, Uncorrected[2] (ppm)	Fresh Fortification Recovery[3] (%)	Apparent Recovery[4] in Stored Sample (%)	Corrected Recovery[5] in Stored Sample (%)
wheat straw	CGA-153433	1.1	0	0.89, 0.77, 0.99, 0.96, 0.95 (av 0.91)	64, 61 (av 62)	100	100
			50	0.84, 0.88, 0.83, 0.77, 0.86 (av 0.84)	56, 56 (av 56)	92	102
			92	0.94, 0.97, 0.95, 0.99, 1.02 (av 0.97)	72, 83 (av 78)	107	85
			184	0.95, 0.94, 1.01, 0.91, 0.97 (av 0.96)	70, 72 (av 71)	105	92
			380	1.05, 1.09, 0.97, 0.90, 0.72 (av 0.95)	65, 57 (av 61)	104	106

[1] Samples were extracted and analyzed at these storage periods.

[2] Residue levels found in stored samples were not corrected for controls or fresh fortification recoveries.

[3] Fresh fortification recovery samples were fortified at 0.5 ppm. Results were not corrected for controls.

[4] based on 0-day residues being 100%

[5] Average residue levels found were corrected for average recoveries of freshly fortified wheat straw and expressed as a percentage of residues at day 0 (see Equation 1 below).

Equation 1:

$$R_t^{sto} = \frac{(\sum r_t^{sto} / n_t^{sto}) / (\sum R_t^{fr} / n_t^{fr})}{(\sum r_0^{sto} / n_0^{sto}) / (\sum R_0^{fr} / n_0^{fr})}$$

R_t^{sto} : average recovery of stored samples corrected for average recovery of freshly fortified specimen at sampling date t

r_t^{sto} : residue found in stored specimen at sampling date t

R_t^{fr} : recovery of freshly fortified specimen at sampling date t

n_t^{sto} : number of replicates of stored specimen at date t

n_t^{fr} : number of replicates of freshly fortified specimen

subscript 0: respective values from day 0

Summary

Residues of CGA-153433 were stable in wheat straw stored at -18°C for 380 days.

1995; MRID 44399208

A storage stability study for CGA-185072 on wheat grain has been submitted (see citation below). The performing laboratory was Novartis Crop Protection AG, Basle, Switzerland.

MRID 44399208 Mair, Dr. P. (1995) Report on Special Study 119/93: Residue Stability Study for CGA-184927 and CGA-185072 in Wheat (Grain) Under Freezer Storage Conditions, Laboratory Project Number 119/93, Nexus Study Number 747-95, unpublished study sponsored by Novartis Crop Protection, Inc., 20 pp.

Wheat grain was treated with a methanolic solution of CGA-184927 and CGA-185072, milled in a cross beater mill with dry ice, placed in polyethylene plastic bags, and stored frozen (-18°C) for two years. CGA-185072 was extracted from samples on days 0, 14, 30, 85, 178, 372, and 728. Analytical methods for CGA-185072 were REM 138.01 (for days 0-178) and REM 138.12 (for the rest of the study) (REM 138.12 is a minor improvement over REM 138.01.) At each analysis interval, five samples of stored fortified material, one untreated control, and two fresh fortification samples were analyzed. Storage stability samples were fortified with CGA-185072 at approximately 0.1 ppm. Fresh fortification recovery samples were fortified with CGA-185072 at 0.2 ppm except at 728 days (0.05 ppm). Representative chromatograms of standards, controls, freshly fortified samples, and stored samples for CGA-185072 were submitted. Storage

stability fortification recovery data for CGA-185072 in wheat germ are reported in Table 16 below.

Table 16. Storage Stability Fortification Recovery Data for CGA-185072 in Wheat Grain							
Commodity	Analyte	Residue Level Added (ppm)	Storage Period[1] (days)	Residue Level Found, Uncorrected [2] (ppm)	Fresh Fortification Recovery[3] (%)	Apparent Recovery[4] in Stored Sample (%)	Corrected Recovery[5] in Stored Sample (%)
wheat grain	CGA-185072	0.15	0	0.13, 0.13, 0.13, 0.14, 0.14 (av 0.13)	79, 81 (av 80)	100	100
			14	0.13, 0.14, 0.13, 0.14, 0.13 (av 0.13)	82, 82 (av 82)	100	98
			30	0.13, 0.12, 0.13, 0.11, 0.12 (av 0.12)	74, 77 (av 76)	92	97
			85	0.13, 0.13, 0.13, 0.13, 0.13 (av 0.13)	78, 80 (av 79)	100	101
			178	0.12, 0.11, 0.11, 0.10, 0.10 (av 0.11)	73, 75 (av 74)	85	91
			372	0.10, 0.10, 0.08, 0.08, 0.08 (av 0.09)	65, 69 (av 67)	69	83
			728	0.10, 0.11, 0.10, 0.10, 0.11 (av 0.10)	71, 77 (av 74)	77	83

[1] Samples were extracted and analyzed at these storage intervals.

[2] Residue levels found were not corrected for controls or fresh fortification recoveries.

[3] Fresh fortification recovery samples were fortified at 0.2 ppm except for CGA-185072 at 728 days (0.05 ppm). Results were not corrected for controls.

[4] based on 0-day residues being 100%

[5] Average residue levels found were corrected for average recoveries of freshly fortified wheat straw and expressed as a percentage of residues at day 0 (see prior Equation 1).

Summary

CGA-185072 declined 17% in wheat grain stored at -18°C for 728 days.

MRID 44399209

A storage stability study for CGA-185072 on wheat straw has been submitted (see citation below). The performing laboratory was Novartis Crop Protection AG, Basle, Switzerland.

MRID 44399209 Mair, Dr. P. (1995) Residue Stability Study for CGA-184927 and CGA-185072 in Wheat (Straw) under Freezer Storage Conditions, Laboratory Project Number 120/93, Nexus Study Number 748-95, unpublished study submitted by Novartis Crop Protection, Inc., 21 pp.

Wheat straw was cut in a cutting mill and homogenized in a cross beater mill with dry ice. The straw was treated with a methanolic solution of CGA-184927 and CGA-185072 and placed into double layered polyethylene plastic bags for storage at -18°C for two years. Stored samples were analyzed for CGA-185072 after 0, 15, 29, 85, 182, 380, and 731 days of storage. Stored samples were analyzed for CGA-153433 after 759 days storage. Analytical methods REM 138.01 and REM 138.12 were used to determine residues of CGA-185072 in stored straw. Analytical method REM 138.10 was used to determine residues of CGA-153433 in stored straw. At each analysis interval, five samples of stored fortified material, one untreated control, and two fresh fortification samples were analyzed. The residue level added to the storage stability samples was not stated. Fresh fortification recovery samples were fortified at 0.5 ppm, 0.2 ppm (sampling times 182 and 380 days), or 0.1 ppm (sampling times 731 and 759 days). Representative chromatograms of standards, controls, freshly fortified samples, and stored samples for CGA-185072 were submitted. Storage stability fortification recovery data for CGA-185072 in wheat straw are reported in Table 17 below. As shown in Table 18 below, residues of the metabolite CGA-153433 were not found after 759 days frozen storage of CGA-185072 fortified samples.

Table 17. Storage Stability Fortification Recovery Data for CGA-185072 in Wheat Straw							
Commodity	Analyte	Residue Level Added (ppm)	Storage Period[1] (days)	Residue Level Found, Uncorrected[2] (ppm)	Fresh Fortification Recovery[3] (%)	Apparent Recovery in Stored Sample[4] (%)	Corrected Recovery[5] in Stored Sample (%)
wheat straw	CGA-185072	0.4	0	0.35, 0.36, 0.35, 0.35, 0.36 (av 0.35)	81, 78 (av 80)	100	100
			15	0.39, 0.39, 0.39, 0.38, 0.38 (av 0.39)	82, 81 (av 82)	111	109
			29	0.39, 0.37, 0.37, 0.39, 0.40 (av 0.38)	82, 82 (av 82)	109	106
			85	0.36, 0.36, 0.36, 0.36, 0.36 (av 0.36)	78, 80 (av 79)	103	104
			182	0.34, 0.34, 0.36, 0.36, 0.34 (av 0.35)	80, 78 (av 79)	100	101
			380	0.33, 0.30, 0.30, 0.28, 0.29 (av 0.30)	72, 71 (av 72)	86	95
			731	0.28, 0.29, 0.27, 0.32, 0.29 (av 0.29)	99, 94 (av 96)	83	69

[1] Samples were extracted and analyzed at these storage periods.

[2] Residue levels found were not corrected for controls or fresh fortification recoveries.

[3] Fresh fortification recovery samples were fortified at 0.5 ppm, 0.2 ppm (sampling times 182 and 380 days), or 0.1 ppm (sampling time 731 days). Results were not corrected for controls.

[4] based on 0-day residues being 100%
[5] Average residue levels found were corrected for average recoveries of freshly fortified wheat straw and expressed as a percentage of residues at day 0 (see prior Equation 1).

Table 18. Residues of the Metabolite CGA-153433 in Wheat Straw after Frozen Storage of CGA-185072 Fortified Samples

Commodity	Analyte	Storage Period (days)	Residue Level Found, Uncorrected [1] (ppm)	Fresh Fortification Recovery[2] (%)
wheat straw	CGA-153433	759	<0.10, <0.10, <0.10, <0.10, <0.10	70, 70

[1] Residue levels found were not corrected for controls or fresh fortification recoveries.
[2] Fresh fortification recovery samples were fortified at 0.1 ppm. Results were not corrected for controls.

Summary

CGA-185072 declined 31% in wheat straw stored at -18°C for 731 days.

MRID 443992-10

A storage stability study for CGA-153433 on wheat grain has been submitted (see citation below). The performing laboratory was Novartis Crop Protection AG, Basle, Switzerland.

MRID 44399210 Mair, Dr. P. (1993) Two-Year Residue Stability Study of Metabolites CGA-193469 and CGA-153433 (Grain) under Freezer Conditions [Wheat], Laboratory Project Number 300/91 (Final Report), Nexus Study Number 521-92, unpublished study submitted by Novartis Crop Protection, Inc., 7 pp.

Homogenized wheat grain was fortified with both CGA-193469 and CGA-153433 at 1 ppm and stored at -20°C for two years. Stored samples were analyzed for CGA-153433 after 0, 14, 28, 91, 184, 365, and 727 days of storage. The analytical method was "Method for Determination of CGA-193469 and CGA-153433 in Cereals - For Use in Storage Stability Studies". The method involves extraction with acetone/buffer (pH = 3), extraction of analytes into dichloromethane, and analysis of CGA-193469 and CGA-153433 separately by HPLC with UV detection. Storage stability fortification recovery data for CGA-153433 in wheat grain are reported in Table 19 below.

Table 19. Storage Stability Fortification Recovery Data for CGA-153433 in Wheat Grain						
Commodity	Analyte	Residue Level Added (ppm)	Storage Period[1] (days)	Residue Level Found, Uncorrected (ppm)	Fresh Fortification Recovery[2] (%)	Corrected Recovery[3] in Stored Sample (%)
wheat grain	CGA-153433	1.0 ppm	0	not reported	77, 76	101, 92
			14		72, 73	109, 112
			28		72, 76	114, 111
			91		74, 78	86, 101
			184		69, 74	105, 95
			365		84, 84	98, 99
			727		84, 82	97, 101

[1] Samples were extracted and analyzed at these storage periods.
[2] Results were not corrected for controls.
[3] For each storage period after day 0, average residue levels found were corrected for average recoveries of freshly fortified wheat straw and expressed as a percentage of residues at day 0.

Summary

Additional data are needed for Study 300/91 (MRID 44399210). Raw data, including residues (ppm) found and representative chromatograms (for standards, controls, freshly fortified samples, and stored samples) should be submitted. Storage containers should be described. The method used to analyze the storage stability samples should be submitted or identified by number as a submitted method. Pending receipt of the additional information, the submitted data indicate that CGA-153433 in wheat grain stored at -20°C is stable for 727 days.

Conclusion

Storage stability data were submitted for CGA-185072 in wheat grain and straw. CGA-185072 declined 17% in wheat grain stored at -18°C for 728 days. CGA-185072 declined 31% in wheat straw stored at -18°C for 731 days. The storage times for CGA-185072 in grain and straw in the storage stability studies are adequate to cover maximum storage times for CGA-185072 in grain and straw residue samples (62 days for grain and 70 days for straw in the US residue data and 574 days for grain and straw in the Canadian residue data). (Note: Since degradation was shown for CGA-185072 in wheat grain and straw, storage stability data will be required for any future uses on all crops/substrates for which tolerances are requested.)

Storage stability data were also submitted for CGA-153433 in wheat grain and straw. Residues of CGA-153433 were stable in wheat straw stored at -18°C for 380 days. Pending receipt of the additional information requested below for MRID 44399210, HED tentatively concludes that CGA-153433 is stable in wheat grain stored at -20°C for 727 days. The storage times for CGA-153433 in grain and straw in the storage stability studies are adequate to cover maximum storage times for CGA-153433 in grain and straw residue samples (i.e., 95 days for grain and 141 days for straw in US residue data and 341 days for grain and straw in the Canadian residue data).

Adequate storage stability data have not been submitted. The following additional storage stability data are needed:

a. Additional data are needed for Study 300/91 (MRID 44399210). Raw data, including residues (ppm) found and representative chromatograms (for standards, controls, freshly fortified samples, and stored samples) should be submitted. Storage containers should be described. The method used to analyze the storage stability samples should be submitted or identified by number as a submitted method.

b. No storage stability data were submitted for forage. Storage stability data for forage are needed for the 105-day storage interval for CGA-185072 and the 218-day storage interval for CGA-153433 in US residue samples. If the Canadian residue studies could be used (i.e., upgraded to acceptable), storage stability data for forage would be needed for the 434-day storage interval for CGA-185072 and CGA-153433 in the Canadian residue samples so that the tolerance can be adjusted for any storage degradation; however, HED is not recommending that the petitioner attempt to upgrade the Canadian residue studies to an acceptable level.

c. No storage stability data were submitted for wheat processed commodities. The storage time between processing and analysis was ≤25 days for CGA-185072; storage stability data are not needed for CGA-185072 in processed commodities since they were analyzed within 30 days of their production (OPPTS 860.1520). The storage time between processing and analysis for CGA-153433 was 51 days for aspirated grain, 45 and 125 days for germ, 45 days for bran, 42 days for middlings and shorts, and 37 days for low grade flour and patent flour. Storage stability data for

CGA-153433 in aspirated grain fractions are not needed since this is an early season use and residues are not expected to occur in aspirated grain fractions. Storage stability data are not needed for bran, flour, middlings, and shorts since these matrices are similar to grain and can be covered by the storage stability data on grain. Storage stability data are needed for CGA-153433 in wheat germ for 45 and 125 days.

OPPTS GLN 860.1500: MAGNITUDE OF THE RESIDUE IN PLANTS

WHEAT (1999; MRID 44755303)

A report on residues in spring wheat from six field trials in the U.S. was submitted (see citation below). The performing laboratory was Novartis Crop Protection, Inc., Greensboro, NC.

MRID 44755303 Boyette, S.E. (1999) CGA-184927 and CGA-185072 - Magnitude of the Residues in or on Wheat, Novartis Number 127-98, unpublished study sponsored by Novartis Crop Protection, Inc., 474 pp.

Six field trials on spring wheat to determine residues of CGA-185072 and CGA-153433 were conducted in the four states of ND (2), MN (1), MT (2), and SD(1) in crop year 1998. These states represent the spring wheat growing areas of the U.S. which border the spring wheat producing provinces of Canada. (Results of winter wheat field trials were to be reported later.) The US field trials were conducted in Region 5 (2 studies) and Region 7 (four studies), as defined in OPPTS 860.1500. The regions were Region 5 (Grand Forks County near Larimore, ND; OW-HR-210-98), Region 5 (Polk County near Crookston, MN; OW-HR-211-98), Region 7 (McHenry County near Velva, ND; OW-HR-212-98), Region 7 (Sheridan County near Plentywood, MT; OW-HR-213-98), Region 7 (Fergus County near Lewiston, MT; OW-HR-214-98), and Region 7 (Charles Mix County near Pickstown, SD; OW-HR-215-98).

A single foliar application of the CGA-184927/CGA-185072 240 EC formulation (DISCOVER™) was applied with ground equipment. The test material was applied to spring wheat at the 1X rate (see the Confidential Appendix). A 5X rate was also applied in one study (OW-HR-210-98/ND). All applications were made in 5 gallons spray per acre, except for one spring wheat field trial (OW-HR-213-98/MT) in which applications were made using approximately 2 gallons spray per acre to simulate aerial application. Score, an adjuvant, was used at a concentration of 1% (v/v). Wheat forage (0-day and 30-day PHI), hay (30-day PHI), straw (60-day PHI), and grain (60-day PHI) were sampled. The effect of PHI on residue levels was investigated in one study in which forage and hay were collected at 0, 7, 14, 21, 30, and 37 days after application and straw and grain samples were collected at 46, 53, 60, and 67 days after application. Samples were frozen after collection and shipped via freezer truck or overnight courier with dry ice to the performing laboratory: Human Safety Department, Novartis Crop Protection, Inc., Greensboro, NC 27419. At the laboratory, the samples were stored frozen (-20°C) until analysis. The samples were prepared for analysis as follows: forage, hay (excluding grain), and straw (excluding grain) were cut into approximately two-inch pieces and ground with

dry ice. Grain was ground after removal of chaff. After preparation, samples were stored frozen in polyethylene bags or bottles until analysis. The maximum storage interval for wheat samples from sampling to analysis for CGA-185072 was 105 days (approx. 3 ½ months); the maximum time between extraction and analysis was 21 days. The maximum storage interval from sampling to analysis for wheat samples analyzed for CGA-153433 was 231 days (approx. 8 months); the maximum time between extraction and analysis was 48 days.

Analytical method REM 138.01, with modifications for some substrates, was used to determine residues of CGA-185072. (The modifications, made to minimize interfering peaks and obtain acceptable recoveries, are listed in Table 3 of MRID 44755303.) CGA-185072 was extracted from wheat substrates with acetonitrile and cleaned up by solvent partition and solid phase extraction. CGA-185072 was determined by HPLC with ultraviolet detection. The limit of quantitation (based on the lowest acceptable recovery level) was 0.02 ppm for grain and 0.05 ppm for forage, hay, and straw. Recoveries of CGA-185072 were 65-129% (average 93%, n=10) for forage, 62-105% (average 78%, n=6) for hay, and 62-104% (average 81%, n= 6) for straw at fortifications of 0.05 ppm. Recoveries of CGA-185072 were 94-133% (average 107%, n=9) for grain at fortifications of 0.02 ppm. Recoveries for CGA-185072 are tabulated in Table 20 below.

Table 20. Procedural Recoveries for CGA-185072 in Wheat Grain, Forage, Hay, and Straw Using Method REM 138.01

Study #	Commodity	PPM Added	% Recovery
OW-HR-210-98/ND	forage	0.05	121
	hay	0.05	65
	straw	0.05	69
		0.50	105
	grain	0.02	98
		0.20	121
OW-HR-211-98/MN	forage	0.05	110
		0.10	125
	hay	0.20	68
	straw	1.00	122
	grain	0.02	133
		0.10	130
OW-HR-212-98/ND	forage	0.05	65, 100
		0.10	105, 130
		0.50	100
	hay	0.05	62, 87, 105
		0.20	63
		0.50	108
	straw	0.05	69, 87, 95
		0.20	126
		0.50	87
		1.00	101
	grain	0.02	94, 102, 112
		0.05	128
		0.50	119

Table 20. Procedural Recoveries for CGA-185072 in Wheat Grain, Forage, Hay, and Straw Using Method REM 138.01			
Study #	Commodity	PPM Added	% Recovery
OW-HR-213-98/MT	forage	0.05	70, 96
		0.20	96, 103
	hay	0.05	82
		0.50	103
	straw	0.05	104
		0.10	127
	grain	0.02	116
OW-HR-214-98/MT	forage	0.05	65, 82
		0.10	62
		0.20	80
	hay	0.50	114
	straw	0.05	62
		0.20	115
	grain	0.02	99
OW-HR-215-98/SD	forage	0.05	94, 129
		0.10	127
		0.50	89
	hay	0.05	65
	straw	5.00	106
	grain	0.02	107
		0.10	91

Analytical method REM 138.10, with modifications, was used to determine the metabolite CGA-153433. (The modifications, made to minimize interfering peaks and obtain acceptable recoveries, are listed in Table 3 of MRID 44755303.) CGA-153433 was extracted from wheat substrates with an 80:20 acetone:citrate buffer (pH 3) solution, and cleaned up by solvent partition and solid phase extraction. CGA-153433 was determined by HPLC with UV detection. The limit of quantitation (based on the lowest acceptable recovery level) was 0.05 ppm for forage, hay, straw, and grain. Recoveries of CGA-153433 were for 56-99% (average 73%, n= 13) for forage,

61-111% (average 86%, n=2) for hay, and 59-94% (average 67%, n=9) for grain at fortifications of 0.05 ppm; straw recoveries were not available. Recoveries for CGA-153433 are tabulated in Table 21 below.

Table 21. Procedural Recoveries for CGA-153433 in Wheat Grain, Forage, and Hay[1] Using Method REM 138.10

Study #	Commodity	PPM Added	% Recovery
OW-HR-210-98/ND	forage	0.05	59, 85
	hay	0.05	111
	grain	0.05	64
		0.20	75
OW-HR-211-98/MN	forage	0.05	58, 65
		0.10	57, 68
	hay	0.20	62
	grain	0.05	60
OW-HR-212-98/ND	forage	0.05	73, 75
		0.10	65
		0.50	62
	hay	0.05	53[2]
		0.20	52[2]
		0.50	62
	grain	0.05	65, 66, 66
		0.50	68, 70
OW-HR-213-98/MT	forage	0.05	69, 99
		0.20	73, 73
	hay	0.50	62
	grain	0.05	61
OW-HR-214-98/MT	forage	0.05	68, 88
		0.10	66
		0.20	75
	hay	0.50	56

Table 21. Procedural Recoveries for CGA-153433 in Wheat Grain, Forage, and Hay[1] Using Method REM 138.10

Study #	Commodity	PPM Added	% Recovery
	grain	0.05	70
OW-HR-215-98/SD	forage	0.05	56, 72
		0.10	71
		0.50	74
	hay	0.05	61
	grain	0.05	59
		0.10	72

[1] CGA-153433 in straw could not be determined using current methodology.
[2] analyzed for CGA-153433 by HPLC with mass spectrometric detection (LC/MS) after extraction and cleanup as described above

Residues of CGA-185072 and CGA-153433 were determined in spring wheat from all field trials including the aerial study and the residue decline study. Residues of CGA-185072 and CGA-153433 are reported in Tables 22-26 below. Controls for CGA-185072 were <0.02 ppm for wheat grain and <0.05 ppm for forage, hay, and straw. Controls for CGA-153433 were <0.05 ppm for wheat grain, forage, hay, and straw. Representative chromatograms of standards, controls, fortified samples (forage, hay, and grain), and treated samples (forage, hay, and grain) were submitted for CGA-185072 and CGA-153433. Residues reported in Tables 22-26 are corrected for recoveries. Residues which are uncorrected for recoveries are reported in the raw data (MRID 44755303) and are footnoted in Tables 22-26 when >LOQ. Values reported in the tables as <LOQ were also <LOQ before correction for recoveries.

Table 22. Residues of CGA-185072 and its Metabolite CGA-153433 in Wheat Forage at 1X			
Study #/State	PHI (days)	CGA-185072 (ppm)	CGA-153433 (ppm)
OW-HR-210-98/ND	0	1.68, 1.17 [1]	0.46, 0.39 [2]
OW-HR-211-98/MN		1.19, 1.15 [1]	0.40, 0.60 [3]
OW-HR-212-98/ND		0.22, 0.24 [4]	0.27, 0.25 [5]
OW-HR-213-98/MT		0.60, 0.58 [6]	0.20, 0.34 [7]
OW-HR-214-98/MT		1.26, 1.07 [8]	0.56, 0.61 [9]
OW-HR-215-98/SD		0.16, 0.16 [1]	0.29, 0.27 [10]
OW-HR-212-98/ND	7	<0.05, <0.05	<0.05, <0.05
OW-HR-212-98/ND	14	<0.05, <0.05	<0.05, <0.05
OW-HR-212-98/ND	21	<0.05, <0.05	<0.05, <0.05
OW-HR-211-98/MN	29	<0.05, <0.05	<0.05, <0.05
OW-HR-212-98/ND	30	<0.05, <0.05	<0.05, <0.05
OW-HR-213-98/MT	30	<0.05, <0.05	<0.05, <0.05
OW-HR-214-98/MT	30	<0.05, <0.05	<0.05, <0.05
OW-HR-215-98/SD	30	<0.05, <0.05	<0.05, <0.05
OW-HR-210-98/ND	32	<0.05, <0.05	<0.05, <0.05
OW-HR-212-98/ND	37	<0.05, <0.05	<0.05, <0.05

[1] 100% recovery used for recoveries over 100%
[2] uncorrected 0.315, 0.264 ppm with 68.45% recovery
[3] uncorrected 0.252, 0.377 ppm with 62.92% recovery
[4] uncorrected 0.142, 0.156 ppm with 65.34% recovery
[5] uncorrected 0.198, 0.182 ppm with 72.61% recovery
[6] uncorrected 0.598, 0.578 ppm with 99.40% recovery
[7] uncorrected 0.139, 0.241 ppm with 70.71% recovery
[8] uncorrected 0.797, 0.679 ppm with 63.40% recovery
[9] uncorrected 0.375, 0.407 ppm with 66.83% recovery
[10] uncorrected 0.209, 0.193 ppm with 71.75% recovery

Table 23. Residues of CGA-185072 and its Metabolite CGA-153433 in Wheat Hay at 1X			
Study #/State	PHI (days)	CGA-185072 (ppm)	CGA-153433 (ppm)
OW-HR-212-98/ND	0	0.27, 0.29 [1]	0.42 [2, 3], 0.42 [2, 3]
OW-HR-212-98/ND	7	<0.05, <0.05	<0.05 [2], <0.05 [2]
OW-HR-212-98/ND	14	<0.05, <0.05	<0.05, <0.05
OW-HR-212-98/ND	21	<0.05, <0.05	<0.05, <0.05
OW-HR-211-98/MN	29	<0.05, <0.05	<0.05, <0.05
OW-HR-212-98/ND	30	<0.05, <0.05	<0.05, <0.05
OW-HR-213-98/MT	30	<0.05, <0.05	<0.05, <0.05
OW-HR-215-98/SD	30	<0.05, <0.05	<0.05, <0.05
OW-HR-210-98/ND	32	<0.05, <0.05	<0.05, <0.05
OW-HR-212-98/ND	37	<0.05, <0.05	<0.05, <0.05
OW-HR-214-98/MT	51	<0.05, <0.05	<0.05, <0.05

[1] uncorrected 0.165, 0.179 with 62.29% recovery

[2] analyzed by LC/MS

[3] uncorrected 0.223, 0.224 ppm with 52.80% recovery

Table 24. Residues of CGA-185072 and its Metabolite CGA-153433 in Wheat Straw at 1X			
Study #/State	PHI (days)	CGA-185072 (ppm)	CGA-153433 (ppm)
OW-HR-212-98/ND)	46	<0.05, <0.05	NA[3]
OW-HR-212-98/ND)	53	<0.05, <0.05	NA[3]
OW-HR-214-98/MT	57	<0.05, <0.05	NA[3]
OW-HR-211-98/MN	58	<0.05, <0.05	NA[3]
OW-HR-212-98/ND	60	<0.05, <0.05	NA[3]
OW-HR-213-98/MT	60	<0.05, <0.05	NA[3]
OW-HR-215-98/SD	60	<0.05, <0.05	NA[3]
OW-HR-210-98/ND[1]	61	<0.05, <0.05	NA[2]
OW-HR-212-98/ND)	67	<0.05, <0.05	NA[3]

[1] Residues of CGA-185072 in wheat straw at 5X were <0.05 ppm.
[2] Not available at 1X or 5X because results for this sample could not be obtained with the methodology used.
[3] Not available because results for this sample could not be obtained with the methodology used.

Table 25. Residues of CGA-185072 and its Metabolite CGA-153433 in Wheat Grain at 1X			
Study #/State	PHI (days)	CGA-185072 (ppm)	CGA-153433 (ppm)
OW-HR-212-98/ND	46	<0.02, <0.02	<0.05, <0.05
OW-HR-212-98/ND	53	<0.02, <0.02	<0.05, <0.05
OW-HR-214-98/MT	57	<0.02, <0.02	<0.05, <0.05
OW-HR-211-98/MN	58	<0.02, <0.02	<0.05, <0.05
OW-HR-212-98/ND	60	<0.02, <0.02	<0.05, <0.05
OW-HR-213-98/MT	60	<0.02, <0.02	<0.05, <0.05
OW-HR-215-98/SD	60	<0.02, <0.02	<0.05, <0.05
OW-HR-210-98/ND[1,2]	61	<0.02, <0.02	<0.05, <0.05
OW-HR-212-98/ND	67	<0.02, <0.02	<0.05, <0.05

[1] Residues of CGA-185072 in wheat grain at 5X were <0.02 ppm.
[2] Residues of CGA-153433 in wheat grain at 5X were <0.05 ppm.

Table 26. Residues of CGA-185072 and its Metabolite CGA-153433 in Wheat Grain and Straw at 5X (Study OW-HR-210-98/ND)			
commodity	PHI (days)	CGA-185072 (ppm)	CGA-153433 (ppm)
wheat grain	61	<0.02	<0.05
wheat straw	61	<0.05	na[1]

[1] Data could not be obtained using current methodology.

According to OPPTS 860.1500, 20 field trials are needed to support a tolerance on wheat. According to HED SOP 98.2, HED reviewers should consider field trials conducted in the Canadian portions of the extended zones as acceptable in support of domestic uses provided such trials meet the other criteria in Guideline 860.1500.

Reports on residues in wheat from fifteen field trials in Canada were submitted (see citations below). The performing laboratory was Novartis Crop Protection AG, Basle, Switzerland.

MRID 44399216 Williams, Robert K. (1997) Summary of Residue Trials for CGA-185072 on Spring Wheat in Canada, Laboratory Project No. ABR-97083, Study Number 489-97, unpublished study sponsored by Novartis Crop Protection, Inc., 12 pp.

MRID 44399217 Mair, Dr. P. (1993) Determination of Residues of CGA-184927, CGA-185072, and Metabolites CGA-193469 and CGA-153433 in Wheat Grain and Straw - Field Trial [Crossfield, Alberta], Laboratory Project No. 3083/92, Nexus Study Number 619-93, unpublished study sponsored by Novartis Crop Protection, Inc., 9 pp.

MRID 44399218 Mair, Dr. P. (1993) Determination of Residues of CGA-184927, CGA-185072 and Metabolites CGA-193469 and CGA-153433 in Wheat Grain and Straw - Field Trial [Crossfield, Alberta], Laboratory Project No. 3082/92, Nexus Study Number 617-93, unpublished study sponsored by Novartis Crop Protection, Inc., 9 pp.

MRID 44399219 Mair, Dr. P. (1993) Determination of Residues of CGA-184927, CGA-185072 and Metabolites CGA-193469 and CGA-153433 in Wheat Grain and Straw - Field Trial [Vibank, Saskatchewan], Laboratory Project No. 3084/92, Nexus Study Number 620-93, unpublished study sponsored by Novartis Crop Protection, Inc., 9 pp.

MRID 44399220 Mair, Dr. P. (1992) Determination of Residues of CGA-184927, CGA-185072 and Metabolites CGA-193469 and CGA-153433 in Wheat Grain and Straw - Field Trial [Vibank, Saskatchewan], Laboratory Project No. 3055/91, Nexus Study Number 622-93, unpublished study sponsored by Novartis Crop Protection, Inc., 9 pp.

MRID 44399221 Mair, Dr. P. (1992) Determination of Parent Compounds and Metabolites CGA-193469 and CGA-153433 in Wheat Grain and Straw - Field Trial [Albertina Farms, Okotoks, Alberta], Laboratory Project No. 3050/91, Nexus Study Number 621-93, unpublished study sponsored by Novartis Crop Protection, Inc., 9 pp.

MRID 44399222 Mair, Dr. P. (1992) Determination of Parent Compounds and Metabolites CGA-193469 and CGA-153433 in Wheat (Green Forage)- Field Trial [Olds College, Olds], Laboratory Project No. 3052/91, Nexus Study Number 519-92, unpublished study sponsored by Novartis Crop Protection, Inc., 9 pp.

MRID 44399223 Mair, Dr. P. (1992) Determination of Parent Compounds and Metabolites CGA-193469 and CGA-153433 in Wheat (Green Forage)- Field Trial [Gray, Saskatchewan], Laboratory Project No. 3056/91, Nexus Study Number 520-92, unpublished study sponsored by Novartis Crop Protection, Inc., 9 pp.

MRID 44399224 Mair, Dr. P. (1992) Determination of CGA-184927, CGA-185072 and Metabolites CGA-193469 and CGA-153433 in Wheat (Green Forage)- Field Trial [Elm River Research Farm, Portage La Prairie, Manitoba], Laboratory Project No. 3054/91, Nexus Study Number 623-93, unpublished study sponsored by Novartis Crop Protection, Inc., 9 pp.

MRID 44399225 Mair, Dr. P. (1992) Determination of Parent Compounds and Metabolites CGA-193469 and CGA-153433 in Wheat Grain and Straw - Field Trial [Portage La Prairie, Manitoba], Laboratory Project No. 3051/91, Nexus Study Number 518-92, unpublished study sponsored by Novartis Crop Protection, Inc., 9 pp.

MRID 44399226 Mair, Dr. P. (1991) Determination of Residues of CGA-184927, CGA-185072 and Metabolites CGA-193469 and CGA-153433 in Wheat Grain and Straw - Field Trial [Strathmore, Saskatchewan], Laboratory Project No. 3064/90, Nexus Study Number 394-91, unpublished study sponsored by Novartis Crop Protection, Inc., 8 pp.

MRID 44399227 Mair, Dr. P. (1991) Determination of Residues of CGA-184927, CGA-185072 and Metabolites CGA-193469 and CGA-153433 in Wheat Grain and Straw - Field Trial [Regina, Saskatchewan], Laboratory Project No. 3068/90, Nexus Study Number 396-91, unpublished study sponsored by Novartis Crop Protection, Inc., 8 pp.

MRID 44399228 Altenburger, Dr. E. (1991) Determination of Residues of CGA-184927 and CGA-185072 in Wheat after Single Application of 100 EC [Teulow, Manitoba], Laboratory Project No. 3079/89, Nexus Study Number 397-91, unpublished study sponsored by Novartis Crop Protection, Inc., 17 pp.

MRID 44399229 Altenburger, Dr. E. (1991) Determination of Residues of CGA-184927 and CGA-185072 in Wheat after Single Application of 100 EC [Indian Head, Saskatchewan], Laboratory Project No. 3077/89, Nexus Study Number 398-91, unpublished study sponsored by Novartis Crop Protection, Inc., 17 pp.

MRID 44399230 Altenburger, Dr. E. (1991) Determination of Residues of CGA-184927 and CGA-185072 in Wheat after Single Application of 100 EC [Davin, Saskatchewan], Laboratory Project No. 3078/89, Nexus Study Number 401-91, unpublished study sponsored by Novartis Crop Protection, Inc., 17 pp.

MRID 44399231 Mair, Dr. P. (1991) Determination of Residues of Parent Compounds and Metabolites CGA-193469 and CGA-153433 in Wheat (Grain and Straw) - Field Trial [Portage La Prairie, Manitoba], Laboratory Project No. 3066/90, Nexus Study Number 395-91, unpublished study sponsored by Novartis Crop Protection, Inc., 8 pp.

Fifteen field trials on wheat were conducted in Canada in 1989 (3), 1990 (3), 1991 (6), and 1992 (3). In the summary report MRID 44399216, the locations of the 15 Canadian field trials relative to the overlapping US-Canadian zones defined in HED SOP 98.2 were reported. Four studies were conducted in extended Zone 5, seven studies were conducted in extended Zone 7, and four studies were conducted in extended Zone 14. Hard red spring wheat was used in ten studies. Duram spring wheat was used in MRID's 44399220, 44399223, and 44399227. Columbus variety spring wheat was used in MRID's 44399229 and 44399230. An EC (emulsifiable concentrate) formulation of clodinafop-propargyl (CGA-184927) and the safener cloquintocet-mexyl (CGA-

185072) was applied. CGA-185072 was applied at the 1X rate (see the Confidential Appendix). The application was made in 100 liters spray solution/ha (10.7 gal/A). In each study, one postemergence foliar application was made to each of 3 or 4 plots. Assist (1%, vol/vol) was included in 8 of the studies. The application was made by bicycle sprayer in all of the studies except MRID 44399228 (small plot sprayer). Samples were stored at -10 to -30°C until shipment, shipped frozen, and then stored at -20°C until analysis. The analytical methods were REM 138.01 for CGA-185072 and REM 138.06 for CGA-153433. In MRID's 44399328, 44399329, and 44399330, CGA-153433 in grain and straw was not determined. The limits of quantitation were 0.02 ppm for CGA-185072 in grain and forage, 0.05 ppm for CGA-185072 in straw, 0.02 or 0.05 ppm for CGA-153433 in grain, and 0.05 ppm for CGA-153433 in forage and straw. Procedural recoveries are reported in Tables 27-28 below. Residues in grain and straw are reported in Table 29 below. Residue results were not corrected for controls or recoveries.

Table 27. Procedural Recoveries for CGA-185072 in Wheat Grain, Straw, and Forage Using Method REM 138.01

MRID #	Commodity	PPM Added	% Recovery
44399217 44399218 44399219	wheat grain	0.04 0.2 0.4	88 86 87
	wheat straw	0.1 0.5 1.0	93 88 87
44399220 44399221 44399225	wheat grain	0.04 0.4	85 76
	wheat straw	0.1 1.0	85 87
44399222	wheat forage	0.04 0.2 0.4	70 66 66
44399223	wheat forage	0.04 0.2 0.4	92 90 85
44399224	wheat forage	0.04 0.2 0.4	85 89 87
44399226 44399227 44399231	wheat grain	0.04 0.4	117 128
	wheat straw	0.1 1.0	104 89
44399228 44399229 44399230	wheat grain	0.04 0.4	91 84
	wheat straw	0.1 1.0	84 77

Table 28. Procedural Recoveries for CGA-153433 in Wheat Grain, Straw, and Forage Using Method REM 138.06[1]			
MRID #	Commodity	PPM Added	% Recovery
44399217 44399218 44399219	wheat grain	0.04 0.2 0.4	66 66 69
	wheat straw	0.1 0.5 1.0	88 83 76
44399220 44399221 44399225	wheat grain	0.1 1.0	84 78
	wheat straw	0.1 1.0	65 74
44399222	wheat forage	0.1 0.5 1.0	73 75 73
44399223	wheat forage	0.1 0.5 1.0	78 81 78
44399224	wheat forage	0.1 0.5 1.0	79 71 72
44399226 44399227 44399231	wheat grain	0.1 1.0	69 68
	wheat straw	0.1 1.0	71[2] 62[2]

[1] CGA-153433 was not determined in MRID's 44399228, 44399229, and 44399230.

[2] Recoveries of CGA-153433 in straw were corrected for control.

Table 29. Residues of the Safener CGA-185072 and its Metabolite CGA-153433 in Wheat Grain, Straw, and Forage after One Application at a Rate of 20 g Safener/ha (0.02 lb Safener/A)

MRID #	Formulation/ Harvest Date	Location	Commodity	PHI (days)	CGA-185072 (ppm)	CGA-153433 (ppm)
44399217[1, 2, 6]	240 EC Oct/92	Estlin, Saskatchewan (Zone 7)	grain straw	105 105	<0.02 (n=4) <0.05 (n=4)	<0.02 (n=4) <0.05 (n=4)
44399218[1, 2]	240 EC Sept/92	Crossfield, Alberta (Zone 14)	grain straw	88 88	<0.02 (n=4) <0.05 (n=4)	<0.02 (n=4) <0.05 (n=4)
44399219[1, 2]	240 EC Oct/92	Vibank, Saskatchewan (Zone 7)	grain straw	97 97	<0.02 (n=4) <0.05 (n=4)	<0.02 (n=4) <0.05 (n=4)
44399220[1, 3]	240 EC Sept/91	Vibank, Saskatchewan (Zone 7)	grain straw	71 71	<0.02 (n=4) <0.05 (n=4)	<0.05 (n=4) <0.05 (n=4)
44399221[3]	240 EC Sept/91	Okotoks, Alberta (Zone 14)	grain straw	91 91	<0.02 (n=4) <0.05 (n=4)	<0.05 (n=4) <0.05 (n=4)
44399222[4]	240 EC June-July/91	Olds, Alberta (Zone 14)	forage	3 7 14 28	<0.02 (n=3) <0.02 (n=3) <0.02 (n=3) <0.02 (n=3)	<0.05 (n=3) <0.05 (n=3) <0.05 (n=3) <0.05 (n=3)
44399223[1, 4]	240 EC July/91	Gray, Saskatchewan (Zone 7)	forage	3 7 14 28	<0.02 (n=3) <0.02 (n=3) <0.02 (n=3) <0.02 (n=3)	<0.05 (n=3) <0.05 (n=3) <0.05 (n=3) <0.05 (n=3)
44399224[4]	240 EC June-July/91	Portage La Prairie, Manitoba (Zone 5)	forage	3 8 14 28	<0.02 (n=3) <0.02 (n=3) <0.02 (n=3) <0.02 (n=3)	<0.05 (n=3) <0.05 (n=3) <0.05 (n=3) <0.05 (n=3)

44399225[3]	240 EC Sept/91	Portage La Prairie, Manitoba (Zone 5)	grain straw	60 60	<0.02 (n=4) <0.05 (n=4)	<0.05 (n=4) <0.05 (n=4)
44399226[1, 3, 7]	100 EC Sept/90	Strathmore, Alberta (Zone 14)	grain straw	77 77	<0.02 (n=4) <0.05 (n=4)	<0.05 (n=4) <0.05 (n=4)
44399227[1, 3]	100 EC Aug/90	Regina, Saskatchewan (Zone 7)	grain straw	84 84	<0.02 (n=4) <0.05 (n=4)	<0.05 (n=4) <0.05 (n=4)
44399228[5]	100 EC Aug/89	Teulow, Manitoba (Zone 5)	grain straw	69 69	<0.02 (n=3) <0.05 (n=3)	NA[8]
44399229[5]	100 EC Aug/89	Indian Head, Saskatchewan (Zone 7)	grain straw	55 55	<0.02 (n=3) <0.05 (n=3)	NA[8]
44399230[5]	100 EC Aug/89	Davin, Saskatchewan (Zone 7)	grain straw	86 86	<0.02 (n=3) <0.05 (n=3)	NA[8]
44399231[1, 3]	100 EC Aug/90	Portage La Prairie, Manitoba (Zone 5)	grain straw	66 66	<0.02 (n=4) <0.05 (n=4)	<0.05 (n=4) <0.05 (n=4)

[1] Application was made in 1% Assist (vol/vol).
[2] Controls were <0.02 ppm CGA-185072 and <0.02 ppm CGA-153433 in grain, and <0.05 ppm CGA-185072 and <0.05 ppm CGA-153433 in straw.
[3] Controls were <0.02 ppm CGA-185072 and <0.05 ppm CGA-153433 in grain, and <0.05 ppm CGA-185072 and <0.05 ppm CGA-153433 in straw.
[4] Controls were <0.02 ppm CGA-185072 and <0.05 ppm CGA-153433 in forage.
[5] Controls were <0.02 ppm CGA-185072 in grain and <0.05 ppm CGA-185072 in straw.
[6] Although the title indicates that the field trial was conducted in Crossfield, Alberta, the data indicate that the location was Estlin, Saskatchewan.
[7] Although the title indicates that the field trial was conducted in Strathmore, Saskatchewan, the data indicate that the location was Strathmore, Alberta.
[8] not available

Summary

In the US, six field trials on spring wheat to determine residues of CGA-185072 and CGA-153433 were conducted in the four states of ND (2), MN (1), MT (2), and SD(1) in crop year 1998. The US field trials were conducted in Region 5 (2 studies) and Region 7 (four studies), as defined in OPPTS 860.1500. A single foliar application of the CGA-184927/CGA-185072 240 EC formulation (DISCOVER™) was applied. CGA-185072 was applied at the 1X rate (see the Confidential Appendix). The application was made with ground equipment. A 5X rate was also applied in one study (OW-HR-210-98/ND). Score, an adjuvant, was used at a concentration of 1% (v/v). Samples were frozen after collection, shipped frozen, and stored frozen (-20°C) at the analytical laboratory. Analytical Method REM 138.01, with modifications for some substrates, was used to determine residues of CGA-185072 by HPLC with ultraviolet detection. The limit of quantitation (based on the lowest acceptable recovery level) was 0.02 ppm for grain and 0.05 ppm for forage, hay, and straw. Recoveries of CGA-185072 were 65-129% (average 93%, n=10) for forage, 62-105% (average 78%, n=6) for hay, and 62-104% (average 81%, n= 6) for straw at fortifications of 0.05 ppm. Recoveries of CGA-185072 were 94-133% (average 107%, n=9) for grain at fortifications of 0.02 ppm. Analytical Method REM 138.10, with modifications, was used to determine the metabolite CGA-153433 by HPLC with UV detection. The limit of quantitation for CGA-153433 (based on the lowest acceptable recovery level) was 0.05 ppm for forage, hay, straw, and grain. Recoveries of CGA-153433 were for 56-99% (average 73%, n= 13) for forage, 61-111% (average 86%, n=2) for hay, and 59-94% (average 67%, n=9) for grain at fortifications of 0.05 ppm; straw recoveries were not available. Selected samples were analyzed for CGA-153433 by HPLC with mass spectrometric detection (LC/MS). Residues in the US studies at 1X were <0.05 ppm CGA-185072 + <0.05 ppm CGA-153433 in wheat forage at a 7-day PHI (one study) and a 29-32 day PHI (6 studies); <0.05 ppm CGA-185072 + <0.05 ppm CGA-153433 in wheat hay at a 30-day PHI; <0.05 ppm CGA-185072 in wheat straw at a 60-day PHI; and <0.02 ppm CGA-185072 + <0.05 ppm CGA-153433 in wheat grain at a 60-day PHI. Residues at 5X and a 61-day PHI were <0.02 ppm CGA-185072 and <0.05 ppm CGA-153433 in wheat grain and <0.05 ppm CGA-185072 in wheat straw. Residues of CGA-153433 in wheat straw at 1X and 5X were not determined.

In Canada, fifteen field trials on spring wheat (hard red spring wheat and duram spring wheat) were conducted in Canada in 1989 (3), 1990 (3), 1991 (6), and 1992 (3). The locations of the 15 Canadian field trials relative to the overlapping US-Canadian zones defined in HED SOP 98.2 were reported. Four studies were conducted in extended Zone 5, seven studies were conducted in extended Zone 7, and four studies were conducted in extended Zone 14. An EC (emulsifiable concentrate) formulation of clodinafop-propargyl (CGA-184927) and the safener cloquintocet-mexyl (CGA-185072) was applied. CGA-185072 was applied at the 1X rate (see the Confidential Appendix). The application was made in 100 liters spray solution/ha (10.7 gal/A). In each study, one postemergence foliar application was made to each of 3 or 4 plots. Assist (1%, vol/vol) was included in 8 of the studies. The application was made by bicycle sprayer in all of the studies except MRID 44399228 (small plot sprayer). Samples were stored frozen until shipment, shipped frozen, and then stored frozen (at -20°C) in the laboratory until analysis. The analytical methods

were REM 138.01 for CGA-185072 and REM 138.06 for CGA-153433. In MRID's 44399328, 44399329, and 44399330, CGA-153433 in grain and straw was not determined. The limits of quantitation were 0.02 ppm for CGA-185072 in grain and forage, 0.05 ppm for CGA-185072 in straw, 0.02 or 0.05 ppm for CGA-153433 in grain, and 0.05 ppm for CGA-153433 in forage and straw. Recoveries for CGA-185072 using REM 138.01 were 85-117% (average 95%, n=4) in wheat grain and 70-92% (average 82%, n=3) in wheat forage at a fortification level of 0.04 ppm, and 84-104% (average 92%, n=4) in wheat straw at a fortification level of 0.1 ppm. Recoveries for CGA-153433 at a fortification level of 0.1 ppm using REM 138.06 were 69-84% (average 76%, n=2) in wheat grain, 73-79% (average 77%, n=3) in wheat forage, and 65-88% (average 75%, n=3) in wheat straw. Residues in Canada were <0.02 ppm CGA-185072 + <0.05 ppm CGA-153433 in wheat grain at PHI's ranging from 60-105 days, <0.05 ppm CGA-185072 + <0.05 ppm CGA-153433 in straw at PHI's ranging from 60-105 days, and <0.02 ppm CGA-185072 + <0.05 ppm CGA-153433 in forage at PHI's ranging from 3 to 28 days.

Conclusion

The proposed use indicates that forage could be fed/grazed at a 7-day PHI, hay could be fed at a 30-day PHI, and grain and straw could be harvested at a 60-day PHI. Based on the available residue data, residues of parent or CGA-153433 were less than the limit of quantitation (LOQ) in the grain, forage, hay, and straw commodities which were analyzed in the US and Canada at these PHI's. (Straw in the US was not analyzed for CGA-153433. Hay was not analyzed in Canada. For US data, the limits of quantitation for parent were 0.02 ppm for grain and 0.05 ppm for forage, hay, and straw; the limit of quantitation for CGA-153433 was 0.05 ppm for grain, forage, and hay; straw was not analyzed for CGA-153433. For Canadian data, the limits of quantitation for parent were 0.02 ppm for grain and forage and 0.05 ppm for straw; the limits of quantitation for CGA-153433 were 0.02 or 0.05 ppm for grain, and 0.05 ppm for forage and straw.) However, the field trial residue data are not adequate to support a permanent tolerance for the following reasons:

a. Adequate geographic representation is not provided. (Wheat is not a minor crop, for which a regional registration would be accepted.) According to OPPTS 860.1500, a minimum of 20 field trials are needed to support a tolerance on wheat. The suggested distribution of wheat field trials is one in Region 2, one in Region 4, five in Region 5, one in Region 6, five in Region 7, six in Region 8, and 1 in Region 11. The US field trials were conducted in Region 5 (2 studies) and Region 7 (four studies), as defined in OPPTS 860.1500; however, these US studies did not determine CGA-153433 in straw. Of the 15 Canadian field trials, four studies were conducted in extended Zone 5, seven studies were conducted in extended Zone 7, and four studies were conducted in extended Zone 14; however, the Canadian field trials have deficiencies which are not upgradeable (see below). Additional field trial residue studies are needed to support a permanent tolerance. If residues of CGA-153433 in straw samples in the US can be reanalyzed by an adequate method and the reanalysis can be supported by storage stability data, the following additional field trial studies would be needed: For a 30-day PHI in forage, the additional studies would be one in Region 2, one in Region 4, three in Region 5, one in Region 6, one in Region 7, six in Region 8, and 1 in Region 11. (If a 7-day PHI in forage is desired, then the additional

studies would be one in Region 2, one in Region 4, five in Region 5, one in Region 6, four in Region 7, six in Region 8, and one in Region 11.) Otherwise (without US residue data for CGA-153433 in straw), the following additional field trial studies would be needed: one in Region 2, one in Region 4, five in Region 5, one in Region 6, five in Region 7, six in Region 8, and one in Region 11. Each study should include PHI's of 30 (or 7) days for forage, 30 days for hay, and 60 days for grain and straw. Spring (including hard red spring, duram, and white spring) and winter (including hard red winter, soft red winter, and white winter) varieties of wheat should be included in the studies. Each study should include DSV Adjuvant or similar adjuvant. Raw data and representative chromatograms of standards, controls, fortified samples, and treated samples should be included. Storage information including types of storage containers and dates of extraction (as well as dates of storage and analysis) should be included.

b. Only spring wheat was used in the US and Canadian studies. Winter wheat should be included in the residue studies.

c. Forage was sampled at the proposed preharvest interval (PHI) of 7 days in only one US study and three Canadian studies.

d. Based on the available residue data, the petitioner should submit a revised Section F which proposes tolerances of 0.10 ppm for the combined residues of cloquintocet-mexyl and its metabolite 5-chloro-8-quinolinoxyacetic acid on wheat grain, forage, hay, and straw. These levels were obtained by adding the limits of quantitation for CGA-185072 and CGA-153433.

For the Canadian field trial residue studies, the following data should have been included. (HED is not recommending that the petitioner attempt to upgrade these studies to an acceptable level.)

a. Grain, forage, hay, and straw should be analyzed in each of the wheat field trial residue studies. (For an early season use, data on aspirated grain fractions are not needed.) Of the 15 Canadian studies, only grain and straw were analyzed in most of the studies (i.e., in twelve studies for CGA-185072 and 9 studies for CGA-153433), and only forage was analyzed (for both CGA-185072 and CGA-153433) in three studies. Hay was not analyzed.

b. PHI's should reflect the proposed use. PHI's for grain and straw in the Canadian studies ranged from 55-105 days (with all but two studies with PHI's above 60 days) whereas the proposed PHI for grain and straw is 60 days.

c. Extraction dates were not provided for studies 44399217, 44399218, 44399219, 44399220, 44399221, 44399222, 44399223, 44399224, 44399225, 44399226, 44399227, and 44399231.

d. Storage containers were not described.

e. Raw data and representative chromatograms of standards, controls, fortified samples, and treated samples were not submitted.

OPPTS GLN 860.1520: MAGNITUDE OF THE RESIDUE IN PROCESSED FOOD/FEED

WHEAT (1999: MRID 44755303)

A wheat processing study was submitted (see citation below). The performing laboratory was Novartis Crop Protection, Inc., Greensboro, NC.

MRID 44755303 Boyette, S.E. (1999) CGA-184927 and CGA-185072 - Magnitude of the Residues in or on Wheat, Novartis Number 127-98, unpublished study sponsored by Novartis Crop Protection, Inc., 474 pp.

Wheat grain samples were obtained from one study in ND (OW-HR-210-98), in which a single foliar application of the CGA-184927/CGA-185072 240 EC formulation (DISCOVER™) was applied to spring wheat at the rates of 1X and 5X (see the Confidential Appendix). The samples were processed under simulated commercial practices into aspirated grain fractions, germ, bran, middlings, shorts, low grade flour, and patent flour at Texas A&M University, Riverside Campus, Food Protein Center, Bryan TX 77801. All processed samples were shipped frozen via freezer truck or overnight courier with dry ice to the Human Safety Department, Novartis Crop Protection, Inc., Greensboro, NC 27419 for analysis. At Novartis, the samples were stored frozen (-20°C) until analysis. Processed grain samples were either ground or used as received. The samples were stored frozen in polyethylene bags or bottles until analysis. Storage time between sampling of grain to be processed and analysis of the grain and its processing fractions was 48-52 days; the time between extraction and analysis was 0-7 days. The storage time between processing and analysis of the processed commodities was ≤25 days for CGA-185072 and ≤51 days (except for 125 days for germ) for CGA-153433.

Analytical Method REM 138.01, with modifications, was used to determine residues of CGA-185072. CGA-185072 was extracted from wheat grain and processed grain fractions with acetonitrile and cleaned up by solvent partition and solid phase extraction. CGA-185072 was determined by HPLC with column switching (from a 250 mm Nucleosil amino column to a 250 mm Nucleosil silica column) with ultraviolet detection. The limit of quantitation (based on the lowest acceptable recovery level) was 0.02 ppm for grain and processed grain commodities. Procedural recoveries for the processing study were reported in Table 30 below.

Table 30. Procedural Recoveries of CGA-185072 from Grain and its Processed Commodities		
Matrix	Fortification Level (ppm)	% Recovery
grain	0.02	104
aspirated grain	0.10	129
germ	0.02	83
bran	0.20	93
middlings	0.02	107
shorts	0.50	134
low grade flour	0.02	126
patent flour	1.00	136

Analytical Method REM 138.10, with modifications, was used to determine the metabolite CGA-153433. CGA-153433 was extracted from wheat grain and processed grain fractions with an 80:20 acetone:citrate buffer (pH 3) solution, cleaned up by solvent partition and solid phase extraction, and determined by HPLC with UV detection. The limit of quantitation (based on the lowest acceptable recovery level) was 0.05 ppm for grain and processed grain commodities. Procedural recoveries for the processing study were reported in Table 31 below.

Table 31. Procedural Recoveries of CGA-153433 from Grain and its Processed Commodities		
Matrix	Fortification Level (ppm)	% Recovery
grain	0.05	94
aspirated grain	1.00	90
	5.00	65
germ	0.05	66
bran	0.20	64
middlings	0.05	62
shorts	0.50	58
low grade flour	0.05	60
patent flour	1.00	67

[1] analyzed for CGA-153433 by HPLC with mass spectrometric detection (LC/MS) after extraction and cleanup as described above

Results of the wheat grain processing study are tabulated in Table 32 below. Controls for CGA-185072 were <0.02 ppm for grain and the processed commodities. Controls for CGA-153433 were <0.05 ppm for grain and processed commodities. Representative chromatograms of standards, controls, fortified samples (aspirated grain fractions, germ, bran, middlings, shorts, and flour), and treated samples (aspirated grain fractions, germ, bran, middlings, shorts, and flour) were submitted for CGA-184927 and CGA-153433. Residues in treated samples were not corrected for controls. Residues reported in Table 32 are corrected for recoveries. Values reported in the table as <LOQ were also <LOQ before correction for recoveries.

Table 32. Residues of CGA-185072 and its Metabolite CGA-153433 in Processed Commodities from Wheat Grain from OW-HR-210-98/ND, Treated at 1X[1] and 5X and Harvested at a 61-day PHI				
Substrate	CGA-185072 (ppm)		CGA-153433 (ppm)	
	1X	5X	1X	5X
grain	<0.02	<0.02	<0.05	<0.05
aspirated grain fractions	<0.02	<0.02	<0.05	<0.05
germ	<0.02	<0.02	<0.05	<0.05
bran	<0.02	<0.02	<0.05	<0.05
middlings	<0.02	<0.02	<0.05	<0.05
shorts	<0.02	<0.02	<0.05	<0.05
low grade flour	<0.02	<0.02	<0.05	<0.05
patent flour	<0.02	<0.02	<0.05	<0.05

[1] The 1X rate is given in the Confidential Appendix.

Summary

Wheat grain treated with a 240 EC formulation of CGA-184927 and CGA-185072 (Discover™) at 1X and 5X (see the Confidential Appedix) was processed. Residues of CGA-185072 and its metabolite CGA-153433 were <0.02 ppm and <0.05 ppm, respectively, in wheat grain and the following processed commodities: aspirated grain fractions, germ, bran, middlings, shorts, low grade flour, and patent flour.

Conclusion

Pending submission of storage stability data on CGA-153433 in processed commodities (see storage stability section of this review), HED concludes that no concentration of CGA-185072 or CGA-153433 occurred on processing.

OPPTS GLN 860.1480: MAGNITUDE OF THE RESIDUE IN MEAT, MILK, POULTRY, AND EGGS

Dairy Cattle Feeding Study

No ruminant feeding study was conducted. In the goat metabolism study (MRID's 44387458 and 44387460), a lactating goat was dosed with (3-^{14}C)quinoline-labeled cloquintocet-mexyl for ten

consecutive days at a dose level of 5.0 ppm. Maximum total radioactive residues found at the 5.0 ppm dose level were 0.084 ppm in milk, 0.003 ppm in muscle, 0.001 ppm in fat, 0.010 ppm in liver, and 0.024 ppm in kidney.

Cattle feedstuffs from wheat are grain, forage, hay, straw, aspirated grain fractions, and milled byproducts. The maximum theoretical residues in the diets of beef and dairy cattle can be calculated as shown in Tables 33 and 34 below.

Table 33. Maximum Theoretical Residues in the Diet of Beef Cattle

Feedstuff	% of Diet	% Dry Matter	Tolerance (ppm)	Dietary Burden (ppm)
wheat forage	25	25	0.10	0.10
wheat hay	25	88	0.10	0.03
wheat straw	10	88	0.10	0.01
aspirated grain fractions	20	85	0.10	0.02
wheat milled byproducts	20	88	0.10	0.02
Total	100			0.18

Table 34. Maximum Theoretical Residues in the Diet of Dairy Cattle

Feedstuff	% of Diet	% Dry Matter	Tolerance (ppm)	Dietary Burden (ppm)
wheat forage	60	25	0.10	0.24
wheat hay	40	88	0.10	0.04
Total	100			0.28

Residues found in milk, muscle, fat, kidney, and liver in the goat metabolism study at the 5.0 ppm dose level and extrapolated to a 1X (0.28 ppm) dose level are tabulated below:

Table 35. Total Radioactive Residues (TRR) in a Goat from a 5.0 ppm Dosing Level and Extrapolated to 1X (0.28 ppm)		
Cattle Substrates	TRR from 5 ppm Dosing Level (ppm)	TRR Extrapolated to 1X (ppm)
milk (maximum)	0.084	0.005
muscle (tenderloin)	0.003	0.0002
fat (subcutaneous)	0.001	0.00006
kidney	0.024	0.001
liver	0.010	0.0006

Summary

Based on the goat metabolism study and the maximum theoretical dietary burden, maximum radioactive residues in goat tissues and milk resulting from the proposed use on wheat would be 0.005 ppm in milk, 0.0002 ppm in muscle, 0.00006 ppm in fat, 0.001 ppm in kidney, and 0.0006 ppm in liver.

Conclusion

A ruminant feeding study is not needed and tolerances on milk and the meat, fat, liver, and kidney of cattle, goats, hogs, horses, and sheep are not needed because of the low residue levels found in milk, muscle, fat, liver, and kidney in the goat metabolism study and the corresponding low radioactive residues calculated for the 1X feeding level. This use falls under 40 CFR §180.6(a)(3) since no secondary residues are expected to occur in milk and in the meat, fat, liver, and kidney of cattle, goats, hogs, horses, and sheep.

Poultry Feeding Study

No poultry feeding study was conducted. In the poultry metabolism study (MRID's 44387459 and 44387461), three laying hens were dosed with (3-^{14}C)quinoline-labeled cloquintocet-mexyl for fourteen consecutive days at a dose level of 5 ppm. Maximum total radioactive residues found in muscle, fat, liver, and eggs at the 5 ppm dose were nondetectable (<0.001 ppm) in muscle, nondetectable (<0.002 ppm) in fat, 0.01 ppm in liver, and 0.006 ppm in eggs.

Poultry feedstuffs from wheat are grain and milled byproducts. No detectable residues (<0.02 ppm CGA-185072 and <0.05 ppm CGA-153433) were found in wheat grain and its processed

commodities. The maximum theoretical residues in the diet of poultry can be calculated using the tolerance level of 0.10 ppm for grain and wheat milled byproducts as shown in Table 36 below.

Table 36. Maximum Theoretical Residues in the Diet of Poultry

Feedstuff	% of Diet	Proposed Tolerance (ppm)	Dietary Burden (ppm)
wheat grain	80	0.10	0.08
wheat milled byproducts	20	0.10	0.02
Total	100		0.10

Residues found in muscle, fat, liver, and eggs in the poultry metabolism study at the 5 ppm dose level and extrapolated to a 1X (0.10 ppm) dose level are tabulated in Table 37 below.

Table 37. Total Radioactive Residue in Hens from a 5 ppm Dosing Level and Extrapolated to 1X (0.10 ppm)

Commodity	Maximum TRR from 5 ppm Dose Level (ppm)	TRR Extrapolated to 1X (ppm)
muscle	ND (<0.001)	<0.000020
fat	ND (<0.002)	<0.000040
liver	0.01	0.00020
eggs	0.006[1]	0.00012

[1] Maximum residue, found in egg from Hen 108F at 312 hrs (30% of 0.0040 ppm in yolk + 70% of 0.0071 ppm in white)

Summary

Based on the poultry metabolism study and the maximum theoretical dietary burden, maximum radioactive residues in poultry tissues and eggs resulting from the proposed use on wheat would be <0.000020 ppm in muscle, <0.000040 ppm in fat, 0.00020 ppm in liver, and 0.00012 ppm in eggs.

Conclusion

Because of the low residue levels found in muscle, fat, liver, and eggs in the poultry metabolism study and the corresponding low radioactive residues calculated for the 1X feeding level, a poultry

feeding study is not needed and tolerances on poultry tissues and eggs are not needed. This use falls under 40 CFR §180.6(a)(3) since no secondary residues are expected to occur in poultry commodities.

OPPTS GLN 860.1850: CONFINED ACCUMULATION IN ROTATIONAL CROPS

Confined Accumulation in Rotational Crops (1993; MRID 44387454)

A rotational crop study for cloquintocet-mexyl was submitted (see citation below). The performing laboratory was Novartis Crop Protection, Inc., Basle, Switzerland.

MRID 44387454 Denzil, Dr. B. (1993) Outdoor Confined Accumulation Study on Rotational Crops after Application of [3-^{14}C] Quinoline CGA-185072, Project 88BD16, Laboratory Project Number 1/93, Nexus Study Number 610-93, unpublished study sponsored by Novartis Crop Protection, Inc. (formerly Ciba Crop Protection), 41 pp.

In-life phase

[3-^{14}C]Quinoline CGA-185072, formulated as an emulsifiable concentrate (EC 50), was applied to two field plots of wheat in sandy loam soil in Klus, Switzerland in 1988. The radiochemical purity was 95.7%. The specific activity was 1.93 MBq/mg (52.1 μCi/mg). CGA-185072 was applied at the rate of 2X (see the Confidential Appendix) to two plots: plot 4A (6 m^2) and plot 4B (4 m^2). One application was made to each plot with ground equipment in 500 liters spray/ha (53 gal spray/A). The timing was early postemergence on plot 4A and pre-emergence on plot 4B. The treated wheat on plot 4A was used for a metabolism study before the rotational crops (winter wheat, sugar beets, and corn) were each planted on 1 m^2 of the plot. Lettuce seedlings (ca. 4 weeks old) were planted on Plot 4B. The times between application of CGA-185072 and planting of the rotational crops were 85 days for lettuce, 146 days for winter wheat, 321 days for sugar beets, and 351 days for corn.

Total radioactive residue (TRR)

Total radioactive residues were determined by combustion and liquid scintillation counting. The total radioactive residues of CGA-185072 in rotational crops after application to spring wheat are reported in Table 38 below.

Table 38. Total Radioactive Residues in Rotational Crops after Application of ^{14}C-CGA-185072 to Spring Wheat				
Crop/Plant Part	Days between Application of the Safener and Planting of the Rotational Crops	Days between Planting of the Rotational Crops and Harvest	Days from Harvest to Analysis of Rotational Crop Samples	CGA-185072 Equivalents (ppm)
Lettuce, ½ mature heads	85	28	14	<0.001
Lettuce, mature heads	85	49	1	<0.001
Winter wheat, ¼ mature whole tops	146	188	134	<0.001
Winter wheat, ½ mature (milky stage) whole tops	146	240	82	<0.001
Winter wheat, mature stalks husks grains	146	 289 289 289	18	 <0.001 0.001 0.001
Sugar Beets, ¼ mature tops roots	321	 77 77	69	 <0.001 0.001

Crop/Plant Part	Days between Application of the Safener and Planting of the Rotational Crops	Days between Planting of the Rotational Crops and Harvest	Days from Harvest to Analysis of Rotational Crop Samples	CGA-185072 Equivalents (ppm)
Sugar Beets, ½ mature	321		1	
tops		114		<0.001
roots		114		<0.001
Sugar Beets, mature	321		1	
tops		203		<0.001
roots		203		<0.001
Corn, ¼ mature				
whole tops	351	47	69	<0.001
Corn, ½ mature				
whole tops	351	84	1	<0.001
Corn, mature	351		6	
stalks		173		<0.001
cobs		173		<0.001
grains		173		<0.001

[1] limit of detection = 0.001 ppm

Extraction and Hydrolysis of Residues

Plant samples were not extracted because of low radioactivity (≤0.001 ppm) in the rotational crops (lettuce, winter wheat, corn, and sugar beets).

Characterization/Identification

Because of low radioactivity (≤0.001 ppm) in the rotational crops (lettuce, winter wheat, corn, and sugar beets), no attempt was made to characterize/identify the residues.

Storage Stability

At harvest, all rotational crop samples were placed in plastic bags. Samples which were not analyzed on the day of harvest were stored frozen (at -18°C) until analysis. Times from harvest to analysis of rotational crop samples are reported in Table 38 above.

Summary

Following one application of [3-^{14}C]quinoline CGA-185072 to spring wheat at the 2X rate (see the Confidential Appendix), radioactivity levels in each of the rotational crops (lettuce, winter wheat, sugar beets, and corn) were ≤0.001 ppm at the rotational crop intervals tested (i.e., days between application of CGA-185072 and planting of the rotational crops: 85 days for lettuce, 146 days for winter wheat, 321 days for sugar beets, and 351 days for corn).

Conclusion

The submitted confined rotational crop data are adequate for a permanent tolerance provided that rotational crop restrictions are placed on the formulation label of at least 85 days (or 3 months) for lettuce and other leafy vegetables, 146 days (or 5 months) for small grains (except wheat), and one year (or 12 months) for all other crops.

If the petitioner wants shorter rotational crop restrictions, then a confined rotational crop study conducted at the soil aging intervals of 1, 4, and 12 months would be needed for three rotated crops (a small grain, a leafy vegetable, and a root crop) reflecting one application of CGA-185072 at the maximum label rate (1X).

OPPTS GLN 860.1900: FIELD ACCUMULATION IN ROTATIONAL CROPS

No field accumulation in rotational crop study was submitted. Pending results from the confined rotational crop study which may be conducted if the petitioner wants shorter rotational crop restrictions, this study may be required.

OTHER CONSIDERATIONS

CODEX

An International Residue Limits (IRL) Status sheet is attached (Attachment 4). Canada has recently reviewed a petition on wheat. At this time, there are no Codex, Canadian, or Mexican tolerances for cloquintocet-mexyl on wheat. Therefore, no compatibility questions exist with respect to Codex.

DEEM RUN

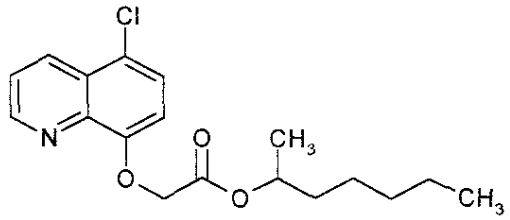
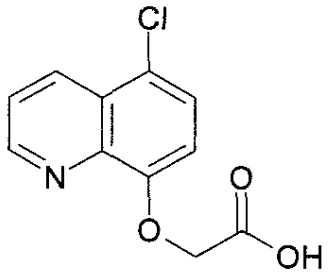
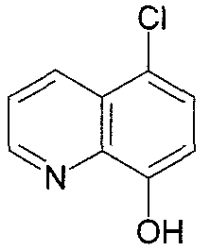
A DEEM Run can be conducted at this time.

Attachment 1: Table of Names and Structures of Cloquintocet-mexyl and its Metabolites
Attachment 2: Table of Names and Structures of Clodinafop-propargyl and its Metabolites
Attachment 3: Proposed Wheat, Goat, and Hen Metabolism Pathway of Cloquintocet-mexyl (CGA-185072)
Attachment 4: International Residue Limit Status Sheet
Attachment 5: Confidential Appendix

cc: RF, SF, N. Dodd (810C), PM# 5, PP#7F04920, A. Lowit (810J)

RDI:Chem Team:2/29/00:ChemSac:3/22/00:S. Dapson:4/6/00
7509C:RAB3:CM#2:Rm810C:305-5681:N. Dodd:nd:4/7/00

ATTACHMENT 1

Table 39. Names and Structures of Cloquintocet-mexyl and its Metabolites	
cloquintocet-mexyl CGA-185072 acetic acid, [(5-chloro-8-quinolinyl)oxy]-, 1-methylhexyl ester	
5-chloro-8-quinolinoxyacetic acid CGA-153433	
C18469	

ATTACHMENT 2

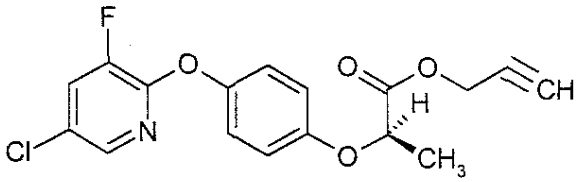
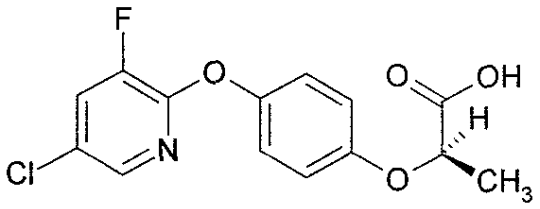
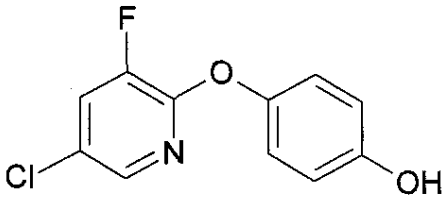
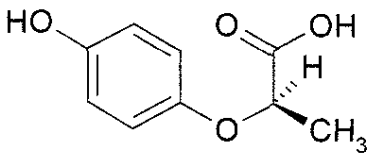
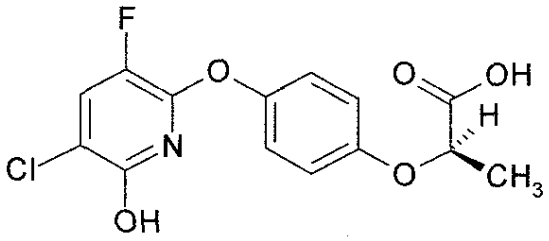
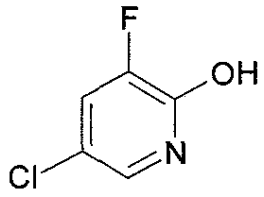
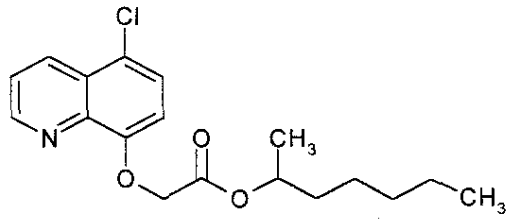
Table 40. Names and Structures of Clodinafop-propargyl and its Metabolites	
clodinafop-propargyl CGA-184927 (R) (2-[4-[(5-chloro-3-fluoro-2-pyridinyl)oxy]phenoxy]-propanoic acid, 2-propynyl ester) and CGA-178486 (R,S) (2-[4-[(5-chloro-3-fluoro-2-pyridinyl)oxy]phenoxy]-propanoic acid, 2-propynyl ester)	
CGA-193469 (R) (2-[4-(5-chloro-3-fluoro-2-pyridinyloxy) phenoxy]-propanoic acid) and CGA-144462 Metabolite II_4 (R,S) (2-[4-(5-chloro-3-fluoro-2-pyridinyloxy) phenoxy]-propanoic acid)	
CGA-193468 Metabolite II_5 4-(5-chloro-3-fluoro-2-pyridinyloxy)-phenol	

Table 40. Names and Structures of Clodinafop-propargyl and its Metabolites	
CGA-214111 (R) (2-(4-hydroxy-phenoxy)-propanoic acid) and CGA-146445 Metabolite II_3 / Metabolite II_1 (R,S) (2-(4-hydroxy-phenoxy)-propanoic acid)	
Metabolite II_2 (R,S) (2-[4-(6-hydroxy-5-chloro-3-fluoro-2-pyridinyloxy)phenoxy]-propanoic acid) and Metabolite 1E 2-[4-(6-hydroxy-5-chloro-3-fluoro-2-pyridinyloxy)phenoxy]-propanoic acid	
Metabolite IV_2 2-hydroxy-3-fluoro-5-chloro-pyridine	

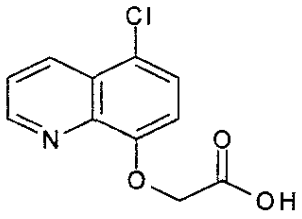
ATTACHMENT 3

Figure 1. Proposed Wheat, Goat, and Hen Metabolism Pathway of Cloquintocet-mexyl



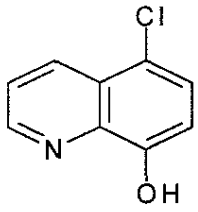
CGA-185072

↓



CGA-153433

↓



C18469
(hypothetical metabolite)

ATTACHMENT 4

INTERNATIONAL RESIDUE LIMIT STATUS

Chemical Name:	Common Name:	☒ Proposed tolerance ☐ Reevaluated tolerance ☐ Other	Date:3/3/00
acetic acid, [(5-chloro-8-quinolinyl)oxy]-, 1-methylhexyl ester	cloquintocet-mexyl		

Codex Status (Maximum Residue Limits)	U. S. Tolerances
☐ No Codex proposal step 6 or above ☒ No Codex proposal step 6 or above for the crops requested	Petition Number: 7F04920 DP Barcode:D257181 Other Identifier:
Residue definition (step 8/CXL):	Reviewer/Branch: Nancy Dodd, RAB3
	Residue definition: cloquintocet-mexyl and its acid metabolite 5-chloro-8-quinolinoxyacetic acid

Crop (s)	MRL (mg/kg)	Crop(s)	Tolerance (ppm)
		wheat grain	0.10
		wheat forage	0.10
		wheat hay	0.10
		wheat straw	0.10

Limits for Canada	Limits for Mexico
☐ No Limits ☒ No Limits for the crops requested	☐ No Limits ☒ No Limits for the crops requested
Residue definition:	Residue definition:

Crop(s)	MRL (mg/kg)	Crop(s)	MRL (mg/kg)

Notes/Special Instructions:

Rev. 1998

~~CONFIDENTIAL APPENDIX to D257181~~

Formulation

Discover™ Herbicide is an emulsifiable concentrate containing 5.6% cloquintocet-mexyl safener, 22.3% clodinafop-propargyl active ingredient (ai), and 72.1% inerts. The formulation contains 0.5 lb/gal of the cloquintocet-mexyl safener and 2 lb/gal of clodinafop-propargyl ai.

Proposed Use on Wheat

The application rate is 3.2 - 4.0 fl oz Discover™ Herbicide/A (0.01-0.02 lb CGA-185072 safener/A) with 10.2 - 12.8 oz/A of DSV Adjuvant, depending on the weed to be controlled.

Nature of the Residue in Plants

MRID 44387457: The application rate was 48.5 g CGA-185072/ha (0.04 lb safener/A; 2X) in 500 liters water/ha (53 gal water/A). The formulation was a 50 EC formulation containing clodinafop-propargyl at approximately twice the concentration of CGA-185072.

Magnitude of the Residue

US studies (MRID 44755303): The 1X rate is 28.33 g CGA-184927/A (0.06 lb ai/A) and 7.1 g CGA-185072/A (0.02 lb safener/A).

Canadian studies: The application rate was 80 g CGA-184927/ha (0.07 lb ai/A; 1.2X) and 20 g CGA-185072/ha (0.02 lb safener/A; 1X).

Processing Studies

MRID 44755303: The 1X rate is 28.33 g CGA-184927/A (0.06 lb ai/A) and 7.1 g CGA-185072/A (0.02 lb safener/A).

Rotational Crops

MRID 44387454: The application rate was 48.5 g CGA-185072/ha (0.04 lb safener/A; 2X) to plot 4A (6 m^2) and 47.3 g CGA-185072/ha (0.04 lb safener/A) to plot 4B (4 m^2).

13544

004134

Chemical:	**Inert ingredient undetermined**
PC Code:	**999999**
HED File Code	**11000 Chemistry Reviews**
Memo Date:	**04/07/2000**
File ID:	**DPD257181**
Accession Number:	***412-01-0056***

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