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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

April 7, 2000

MEMORANDUM

SUBJECT: PP#7F04924. Clodinafop-propargyl on Wheat. Review of Analytical Methods and Residue Data. First Food Use Review.

DP Barcode:	D246730, D253344	PRAT Case:	289249
Submission No.:	S543995, S556842	Caswell No.:	None
Chemical #:	125203	Class:	Herbicide
Trade Name:	Discover™ Herbicide	EPA Reg. No.:	None
40 CFR:	None		

MRID Nos.: 44399190, 44399202, 44399203, 44399204, 44399205, 44399206, 44399207, 44399208, 44399209, 44399210, 44399211, 44399212, 44399213, 44399214, 44399215, 44399217, 44399218, 44399219, 44399220, 44399221, 44399222, 44399223, 44399224, 44399225, 44399226, 44399227, 44399228, 44399229, 44399230, 44399231, 44568401, 44568402, 44755301, 44755302, 44755303

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

THROUGH: Stephen Dapson, Branch Senior Scientist
Registration Action Branch 3
Health Effects Division (7509C)
04/10/2000

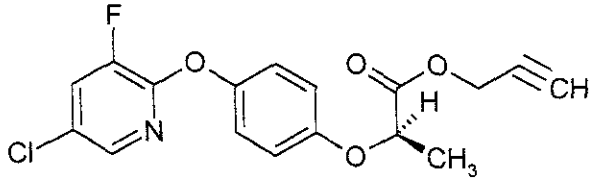
TO: Susan Stanton/Joanne Miller, PM Team #23
Herbicide-Fungicide Branch
Registration Division (7505C)

INTRODUCTION

Novartis Crop Protection, Inc. (formerly Ciba Crop Protection) has proposed establishment of tolerances for the herbicide clodinafop-propargyl (propanoic acid, 2-[4-[(5-chloro-3-fluoro-2-pyridinyl)oxy]phenoxy]-, 2-propynyl ester; CGA-184927) in or on wheat grain at 0.02 ppm and wheat straw at 0.05 ppm. (CGA-184927 is the "R" isomer.) Clodinafop-propargyl is a new active ingredient (ai) in the U.S., with no registered uses and no proposed non-food uses.

Clodinafop-propargyl is systemic, being absorbed by the leaves of weeds and rapidly transported to the growing point of leaves and stems.

The structure for clodinafop-propargyl is shown below:



clodinafop-propargyl
CGA-184927
("R" isomer)

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. The technical grade of the active ingredient is discussed in the following review: D255798, Shyam Mathur, 9/23/99.

OPPTS GLN 860.1200: PROPOSED USES

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 clodinafop-propargyl 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 [^{14}C-phenyl] CGA-178486 (racemic mixture) study:

a. Due to large amounts of the radioactivity being nonextractable with acetonitrile:water (8:2) and by Soxhlet extraction with methanol, only 21.6% TRR, 8.8%TRR, and 2.3%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. It would be preferable to use a formulation containing only the "R" enantiomer in the future study.

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 not adequately understood for the purposes of a permanent tolerance for the following reasons pertaining to the [2-^{14}C- pyridyl] CGA-184927 study:

a. Due to large amounts of the radioactivity being nonextractable with acetonitrile:water (8:2) and by Soxhlet extraction with methanol, only 17.2% TRR, 10.8% TRR, and 5.6 %TRR were identified in leaves (ear emergence), leaves (milky stage), and straw (mature), 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.

5. 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 (D263288, N. Dodd, 2/25/00) to be clodinafop-propargyl and its acid metabolite CGA-193469. HED may revisit the MARC after additional wheat metabolism data have been submitted.

OPPTS GLN 860.1300: NATURE OF THE RESIDUE IN LIVESTOCK

Ruminants

6. The nature of the residue in ruminants is not adequately understood for the purposes of a permanent tolerance for the following reason: The time from sampling to 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.

7. 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 residues in milk and tissues are hybrid acylglycerides (containing CGA-193469 as one component) and/or CGA-193469. The residues of concern in ruminants were determined by HED's Metabolism Assessment Review Committee on 2/15/00 (D263288, N. Dodd, 2/25/00) to be clodinafop-propargyl and its acid metabolite CGA-193469.

Poultry

8. The nature of the residue in poultry is not adequately understood for the purpose of a permanent tolerance for the following reason: The time from sampling to 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.

9. For this use on wheat, the nature of the residue in poultry is adequately understood for the purpose of a tolerance with an expiration date. The major residues in eggs, lean meat, and fat were CGA-193469 and/or hybrid acylglycerides which released CGA-193469 on hydrolysis. Metabolite 1E (38% TRR) and hybrid acylglycerides (29% TRR) were found in skin and attached fat. Small amounts of Metabolite 1E and traces of CGA-214111 were found in liver and kidney. In liver, 50% of the radioactivity remained unextracted. In kidney, 35% of the TRR was unextracted before acid and base hydrolysis. Upon acid and base hydrolysis, 50% of the TRR was identified as products which yield CGA-214111, leaving 50% unidentified including 12% unextracted. Due to the low residues expected in poultry tissues at the 1X feeding level of 0.05 ppm (as calculated in this review under OPPTS GLN 860.1480), additional metabolism data (beyond that required in Conclusion 8 above for a permanent tolerance) are not needed for this use on wheat. The residues of concern in poultry were determined by HED's Metabolism Assessment Review Committee on 2/15/00 (D263288, N. Dodd, 2/25/00) to be clodinafop-propargyl and its acid metabolite CGA-193469.

OPPTS GLN 860.1340: RESIDUE ANALYTICAL METHODS

Plants

10. 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. (Radiovalidation data and recovery data at the limit of quantitation would be needed for Methods REM 138.02 and 138.05 if they were used to collect residue data which are acceptable. Methods REM 138.02 and 138.05 were used only to collect the Canadian residue data. HED is not recommending that the petitioner attempt to upgrade the Canadian residue studies); b) Method REM 138.12 should be submitted.

11. 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 clodinafop-propargyl 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 Methods 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.

12. 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

13. 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 22 and 23 below).

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

14. Multiresidue method testing data for CGA-184927 and CGA-193469 in wheat grain have been submitted. CGA-184927 and CGA-193469 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-184927 was tested per Protocols C, D, and E. CGA-193469 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

15. 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-184927 and CGA-193469 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

16. Storage stability data were submitted for CGA-184927 in wheat grain and straw. CGA-184927 declined 7%, 11%, 23%, and 44% in wheat grain stored at -18°C for 85, 178, 372, and 728 days, respectively. CGA-184927 declined 28%, 36%, 37%, and 54% in wheat straw stored at -18°C for 85, 182, 380, and 731 days, respectively. The storage times for CGA-184927 in grain and straw in the storage stability studies are adequate to cover maximum storage times for CGA-184927 in grain and straw residue samples (62 days for grain and 70 days for straw in the US residue data and 580 days for grain and straw in the Canadian residue data). (Note: Since degradation was shown for CGA-184927 in wheat grain and straw, storage stability data will be required for any future uses on all crops/substrates for which tolerances are requested.)

17. Storage stability data were also submitted for CGA-193469 in wheat grain and straw. CGA-193469 is stable in wheat straw stored at -18°C for at least 380 days. Pending receipt of the additional information requested below for MRID 44399210, HED tentatively concludes that CGA-193469 is stable in wheat grain stored at -20°C for at least 727 days. The storage times for CGA-193469 in grain and straw in the storage stability studies are adequate to cover maximum storage times for CGA-193469 in grain and straw residue samples (i.e., 95 days for grain and 141 days for straw in US residue data and 458 days for grain in the Canadian residue data) except for some straw residue samples in Canada (which were stored up to 458 days).

18. 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-184927 and the 218-day storage interval for CGA-193469 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-184927 and CGA-193469 in the Canadian residue samples; however, HED is not recommending that the petitioner attempt to upgrade the Canadian residue studies to an acceptable level.

c. If Canadian studies could be used (i.e., upgraded to acceptable), storage stability data for CGA-193469 on straw for 458 days would be needed 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.

d. No storage stability data were submitted for wheat processed commodities. The storage time between processing and analysis was ≤25 days for CGA-184927; storage stability data are not needed for CGA-184927 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-193469 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-193469 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-193469 in wheat germ for 45 and 125 days.

OPPTS GLN 860.1500: MAGNITUDE OF THE RESIDUE IN PLANTS

19. 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-193469 were less than the limit of quantitation (LOQ) in grain, forage, and hay in the US and in grain and forage in Canada at these PHI's; for straw, residues of the parent were <LOQ but maximum residues of 0.21 ppm CGA-193469 were found in the US (MT; 57-day PHI) and maximum residues of 0.45 ppm CGA-193469 were found in Canada (Manitoba/1991 trials; 60-day PHI). (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-193469 was 0.05 ppm for grain, forage, hay, and straw. 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-193469 were 0.01 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. 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 20 below). Additional field trial residue studies are needed to support a permanent tolerance. 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.) 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 for the combined residues of clodinafop-propargyl (propanoic acid, (R)2-[4-[(5-chloro-3-fluoro-2-pyridinyl)oxy]phenoxy]-, 2-propynyl ester) and its metabolite (R)(2-[4-(5-chloro-3-fluoro-2-pyridinyloxy) phenoxy]-propanoic acid) at levels of 0.10 ppm for wheat grain, forage, and hay, and 0.50 ppm for wheat straw. These levels were obtained by adding the limits of quantitation and/or levels of residues for CGA-184927 and CGA-193469. (Note that an "(R)" is needed in the chemical name of the parent to designate the "R" isomer.)

20. 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 twelve studies and only forage was analyzed 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

21. Pending submission of storage stability data on CGA-193469 in processed commodities (see storage stability section of this review), HED concludes that no concentration of CGA-184927 or CGA-193469 occurred on processing.

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

Ruminants

22. 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

23. 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

24. The submitted confined rotational crop data are adequate for a permanent tolerance provided that a) rotational crop restrictions are placed on the label of 98 days (or 3 months) for lettuce and other leafy vegetables, 159 days (or 5 months) for small grains (except wheat), and one year (or 12 months) for all other crops; and b) the dates of harvest and/or analysis of ½ mature lettuce are corrected.

25. 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 0.06 lb CGA-184927 ai/A.

OPPTS GLN 860.1900: FIELD ACCUMULATION IN ROTATIONAL CROPS

26. 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

27. An International Residue Limits (IRL) Status sheet is attached (Attachment 5). Canada has recently reviewed a petition on wheat. At this time, Canada has a default MRL of 0.1 mg/kg for clodinafop-propargyl on wheat. A Mexican limit exists for clodinafop-propargyl on wheat at 0.050 ppm. There are no Codex tolerances for clodinafop-propargyl on wheat. Therefore, no compatibility questions exist with respect to Codex.

RECOMMENDATIONS

HED cannot recommend for the proposed permanent tolerances for clodinafop-propargyl on wheat for reasons given in Conclusions #'s 2, 3 (a,b,c), 4 (a,b,c), 5, 6, 8, 10 (a,b), 11 (a,b,c,d), 12, 18 (a,b,c,d), 19 (a,b,c,d), 20 (a,b,c,d,e), 21, 24 (a,b), 25, and 26 above.

Provided the petitioner submits a revised Section B/label and revised Section F and EPA's method validation is satisfactory (see Conclusions 2, 12, and 19d 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 clodinafop-propargyl (propanoic acid, (R)2-[4-[(5-chloro-3-fluoro-2-pyridinyl)oxy]phenoxy]-, 2-propynyl ester) and its acid metabolite (R)(2-[4-(5-chloro-3-fluoro-2-pyridinyloxy) phenoxy]-propanoic acid) in/on wheat grain, forage, and hay at 0.10 ppm and wheat straw at 0.50 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 active ingredient clodinafop-propargyl and its 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. The technical grade of the active ingredient is discussed in the following review: D255798, Shyam Mathur, 9/23/99. The impurities present in the technical are not expected to be of concern.

OPPTS GLN 860.1200: PROPOSED USES

Formulation

Discover™ Herbicide is an emulsifiable concentrate containing 22.3% clodinafop-propargyl active ingredient (ai) and 77.7% inerts. The formulation contains 2 lb ai/gal.

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 fl oz Discover™ Herbicide/A (23 g ai/A; 0.05 lb ai/A) with 10.2 oz/A of DSV Adjuvant or 4.0 fl oz Discover™ Herbicide/A (28 g ai/A; 0.06 lb ai/A) with 12.8 oz/A of DSV Adjuvant, depending on the weed to be controlled. 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 clodinafop-propargyl 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

1989: MRID 44399203

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

MRID 44399203 Stingelin, Dr. J. (1989) Penetration, Distribution, and Degradation of ^{14}C-Phenyl CGA-178486 in the Field Spring Wheat, Project No. 86JS08, Laboratory Project Report 31/89, Nexus Study Number 330-89, unpublished study sponsored by Novartis Crop Protection, Inc., 59 pp.

In-life phase

The fate of CGA-178486 [(R,S) 2-[4-(5-chloro-3-fluoro-2-pyridinyloxy)phenoxy]-propanoic acid, 2-propynyl ester] was studied in field grown spring wheat in St. Aubin, Switzerland after post-emergence foliar spray application of an emulsifiable concentrate formulation containing [^{14}C-phenyl] CGA-178486. [Note: CGA-178486 contains both the "R" and "S" isomers whereas CGA-184927 contains only the "R" isomer.] The radiochemical purity of the test substance was >98%; the specific radioactivity was 1.71 MBq/mg (46.2 μCi/mg). The application rate was 125 g CGA-178486 ai/hectare (0.11 lb ai/A), approximately 2X the proposed maximum label rate. Samples were harvested at 41 days (ear emergence stage), 61 days (milky stage), and 82 days (mature stage) after treatment.

Total radioactive residues (TRR)

Total radioactive residues in field grown spring wheat were determined by combustion and liquid scintillation counting. As reported in Table 1 below, the total radioactive residues were determined in ears, leaves (at ear emergence and milky stages), grain, husks, and straw.

Table 1. *Distribution of* Total Radioactive Residues of [^{14}C-Phenyl]CGA-178486 in Field Grown Spring Wheat

PHI	Plant Parts	CGA-178486 Equivalents (ppm)
41 days (ear emergence)	Ears Leaves	0.006 0.068
61 days (milky stage)	Grain Husks Leaves	0.005 0.008 0.046
82 days (maturity)	Grain Husks Straw	0.009 0.012 0.081

Extraction and hydrolysis of residues

Residues in plant samples were extracted with acetonitrile:water (8:2) and Soxhlet extracted with methanol. Only leaves (41-day PHI and 61-day PHI) and straw (82-day PHI) were extracted; extraction of grain in this study is not required since the TRR in grain was <10 ppb. As reported in Table 2 below, the non-extractable radioactivity was 32.5% TRR in leaves (41-day PHI; ear emergence), 70.2% TRR in leaves (61-day PHI; milky stage), and 83.8% TRR in mature straw (82-day PHI).

Table 2. Extraction of TRR of [^{14}C-Phenyl]CGA-178486 in Field Grown Spring Wheat						
PHI	Plant Parts	TRR (ppm)[1]	Extracted Radioactivity (%TRR)		Non-extracted Radioactivity (%TRR)	Sum of Extracted and Non-extracted Radioactivity (%TRR)
			Cold Extract	Soxhlet Extract		
41 days (ear emergence)	Leaves	0.068	49.5	4.9	32.5	86.9
61 days (milky stage)	Leaves	0.046	33.0	6.4	70.2	109.6
82 days (maturity)	Straw	0.081	13.7	6.3	83.8	103.8

[1] in equivalents of CGA-178486

Partitioning of the cold extract with dichloromethane (CH_2Cl_2) at pH 3 yields an organosoluble phase and a water soluble phase. Table 3 gives the distribution of the radioactivity in the organosoluble and water soluble phases.

Table 3. Distribution of Radioactivity in the Organosoluble and Water Soluble Phases after Partitioning of the Cold Extract at pH 3				
PHI	Plant Parts	Extractable Radioactivity in the Cold Extract (%TRR)	CH_2Cl_2 Phase (%TRR)	Water Phase (%TRR)
41 days (ear emergence)	Leaves	49.5	9.0	40.5
61 days (milky stage)	Leaves	33.0	12.2	18.3
82 days (maturity)	Straw	13.7	6.3	4.5

Conjugates were cleaved with the enzyme cellulase and by hydrolysis with hydrochloric acid (0.1 N and 3.0 N HCl).

Characterization/identification of residues

Only the residues in leaves (41-day and 61-day PHI's) and straw (82-day PHI) were identified. Metabolites were identified by thin layer chromatography (TLC) and high performance liquid chromatography (HPLC). The structures of the metabolites were confirmed by mass spectroscopy (MS). The structure of metabolite II_2 [(R,S) (2-[4-(6-hydroxy-5-chloro-3-fluoro-2-pyridinyloxy)phenoxy]-propanoic acid)] was also confirmed by ^{1}H-NMR. Residues in the CH_2Cl_2 phase and acid hydrolyzed water phase are reported in Tables 4 and 5 below. Amounts of aglycones released by cellulase treatment of various water phases are reported in Table 6 below.

Table 4. Characterization/Identification of Residues of [^{14}C-Phenyl]CGA-178486 in the CH_2Cl_2 Phase and Acid Hydrolyzed Water Phase in Spring Wheat

Plant Part-PHI	TRR (ppm)	CGA-178486 (%TRR)	CGA-193468 (%TRR)	CGA-144462 (%TRR)	II_2[2] (%TRR)	CGA-146445 (%TRR)	II_0[3] (%TRR)	Origin (%TRR)	Unresolved (%TRR)
Leaves-41 days (ear emergence)	0.068	nd[1]	0.7	7.6	3.0	10.3	3.3	8.5	8.4
Leaves-61 days (milky stage)	0.046	nd	0.2	4.4	nd	4.2	nd	4.2	1.9
Straw-82 days (maturity)	0.081	nd	0.2	0.3	nd	1.8	nd	1.9	0.9

[1] nd = not detected (The limit of detection is 0.001 ppm in leaves and 0.0005 ppm in straw.)

[2] II_2 = (R,S) (2-[4-(6-hydroxy-5-chloro-3-fluoro-2-pyridinyloxy)phenoxy]-propanoic acid)

[3] not identified

Table 5. Identification of Residues of [^{14}C-Phenyl]CGA-178486 in the CH_2Cl_2 Phase and Acid Hydrolyzed Water Phase in Spring Wheat

Plant Part-PHI	TRR (ppm)	CGA-178486		CGA- 193468		CGA-144462		II_2[3]		CGA-146445		Total Identified (%TRR)
		% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	
Leaves-41 days (ear emergence)	0.068	nd[1]	<0.001[2]	0.7	0.05	7.6	0.5	3.0	0.2	10.3	0.7	21.6
Leaves-61 days (milky stage)	0.046	nd	<0.001[2]	0.2	0.009	4.4	0.2	nd	nd	4.2	0.19	8.8
Straw-82 days (maturity)	0.081	nd	<0.0005[2]	0.2	0.02	0.3	0.02	nd	nd	1.8	0.15	2.3

[1] nd = not detected

[2] The limit of detection is 0.001 ppm in leaves and 0.0005 ppm in straw.

[3] II_2 = (R,S) (2-[4-(6-hydroxy-5-chloro-3-fluoro-2-pyridinyloxy)phenoxy]-propanoic acid)

Table 6. Aglycones Released by Cellulase Treatment of Various Water Phases										
PHI	Plant Part	TRR (ppm)	CGA-193468		CGA-144462		H_2		CGA-146445	
			%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
41 days	Leaves	0.068	0.8	0.0005	2.6	0.0018	4.9	0.0033	7.0	0.0048
61 days	Leaves	0.046	0.2	0.00009	0.5	0.0002	0.9	0.0004	1.0	0.00046
82 days	Straw	0.081	0.04	0.00003	0.2	0.0002	0.3	0.0002	0.4	0.0003

The following wheat metabolism pathway for CGA-178486 is proposed as outlined in Figure 1 (Attachment 2): 1) the parent (an ester) is hydrolyzed to form the acid CGA-144462 with subsequent sugar conjugation of the acid; 2) CGA-144462 is hydroxylated at the 6-position of the pyridyl ring to form II_2 [(R,S) (2-[4-(6-hydroxy-5-chloro-3-fluoro-2-pyridinyloxy)phenoxy]-propanoic acid)] with subsequent sugar conjugation of II_2; 3) the pyridinyloxy-phenoxy ether bridge of CGA-144462 is cleaved to form CGA-146445 with subsequent sugar conjugation of CGA-146445; and 4) CGA-144462 is cleaved at the phenoxy-propanoic acid ether bridge to form CGA-193468.

Storage stability

The field biological phase of the study was conducted between 4/17/86 and 8/6/86. The analytical phase was conducted between 4/15/86 and 12/31/87. Samples were stored frozen (-18°C).

Summary

The fate of [^{14}C-phenyl]CGA-178486 [(R,S) 2-[4-(5-chloro-3-fluoro-2-pyridinyloxy)phenoxy]-propanoic acid, 2-propynyl ester] was studied in field grown spring wheat in St. Aubin, Switzerland after post-emergence foliar spray application of [^{14}C-phenyl] CGA-178486 at 2X. Grain was not extracted from the field study; extraction of grain in this study is not required since the TRR in grain was <10 ppb. Leaves harvested at 41 days (ear emergence stage) and 61 days (milky stage) after treatment and straw harvested at 82 days (mature stage) after treatment were extracted. The non-extractable radioactivity was 32.5% TRR in leaves (41-day PHI; ear emergence), 70.2% TRR in leaves (61-day PHI; milky stage), and 83.8% TRR in mature straw (82-day PHI). Metabolites were identified by thin layer chromatography (TLC) and high performance liquid chromatography (HPLC). The structures of the metabolites were confirmed by mass spectroscopy (MS). The structure of metabolite II_2 [(R,S) (2-[4-(6-hydroxy-5-chloro-3-fluoro-2-pyridinyloxy)phenoxy]-propanoic acid)] was also confirmed by ^{1}H-NMR. Residues identified in the extractable residues from leaves and straw were CGA-193468, CGA-144462, metabolite II_2 [(R,S) (2-[4-(6-hydroxy-5-chloro-3-fluoro-2-pyridinyloxy)phenoxy]-propanoic acid)], and CGA-146445. No parent was found in leaves or straw. All identified metabolites were <10% TRR except CGA-146445 (10.3% TRR) in leaves (ear emergence; 41-days PHI).

Based on the structures identified, the following pathway of [^{14}C-phenyl] labeled CGA-178486/CGA-184927 in wheat is proposed: 1) hydrolysis of the parent ester molecule CGA-178486/CGA-184927 to form the acid CGA-144462/CGA-193469, and subsequent sugar conjugation of the acid; 2) hydroxylation of the 6-position of the pyridyl ring in CGA-144462/CGA-193469 to form metabolite II_2 and subsequent sugar conjugation; 3) cleavage of the ether bridge between the pyridinyl and phenyl rings in CGA-144462/CGA-193469, yielding CGA-146445/CGA-214111 and its corresponding sugar conjugate; and 4) cleavage of CGA-144462/CGA-193469 at the phenoxy-propanoic acid ether bridge to form CGA-193468.

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 [^{14}C-phenyl] CGA-178486 (racemic mixture) study:

a. Due to large amounts of the radioactivity being nonextractable with acetonitrile:water (8:2) and by Soxhlet extraction with methanol, only 21.6% TRR, 8.8%TRR, and 2.3%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. It would be preferable to use a formulation containing only the "R" enantiomer in the future study.

c. The time from sampling to final analysis should be clarified for 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.

1990; MRID 44399202

A second wheat metabolism study was submitted (see citation below). The performing laboratory was Novartis Crop Protection AG, Basle, Switzerland.

MRID 44399202 Stingelin, Dr. J. (1990) Distribution and Degradation of [2-^{14}C-Pyridyl] CGA-184927 in Field Grown Spring Wheat, Report No. 87JS10, Laboratory Project Report 27/90, Nexus Study Number 342-90, unpublished study sponsored by Novartis Crop Protection, Inc., 50 pp.

In-life phase

The fate of [2-^{14}C-pyridyl] CGA-184927 [(R) (2-[4-(5-chloro-3-fluoro-2-pyridinyloxy)phenoxy]-propanoic acid, 2-propynyl ester)] was studied in field grown spring wheat in St. Aubin, Switzerland after post-emergence foliar spray application of an emulsifiable concentrate formulation containing [2-^{14}C- pyridyl] CGA-184927. The radiochemical purity of the test substance was >98%; the specific activity was 1.647 MBq/mg (44.5 μCi/mg). The application rate was 125 g CGA-184927 ai/hectare (0.11 lb ai/A), approximately 2X the proposed maximum

label rate. Samples were harvested at 49 days (ear emergence stage), 68 days (milky stage), and 91 days (mature stage) after treatment.

Total radioactive residues (TRR)

Total radioactive residues in field grown spring wheat were determined by combustion and liquid scintillation counting. As reported in Table 7 below, the total radioactive residues were determined in ears, leaves (at ear emergence and milky stages), grain, husks, and straw. The total radioactive residues in grains and husks were higher by a factor of about 1.6 and 2, compared to the results found for [^{14}C-phenyl]CGA-178486.

Table 7. Distribution of Total Radioactive Residues of [2-^{14}C-Pyridyl]CGA-184927 in Field Grown Spring Wheat

PHI	Plant Parts	CGA-184927 Equivalents (ppm)
49 days (ear emergence)	Ears	0.007
	Leaves	0.019
68 days (milky stage)	Grain	0.007
	Husks	0.012
	Leaves	0.024
91 days (maturity)	Grain	0.014
	Husks	0.024
	Straw	0.067

Extraction and hydrolysis of residues

Residues in plant samples were extracted with acetonitrile:water (8:2) and Soxhlet extracted with methanol. Leaves (49-day PHI; ear emergence), husks and leaves (68-day PHI; milky stage), and mature grain, husks, and straw (91-day PHI) were extracted. As reported in Table 8 below, the non-extractable radioactivity in leaves was 41.5% TRR at ear emergence and 51.4% TRR at the milky stage; the non-extractable radioactivity in mature grain, husks, and straw accounted for 76.9%, 71.0%, and 73.7% TRR, respectively.

Table 8. Extraction of TRR of [2-^{14}C-Pyridyl]CGA-184927 in Field Grown Spring Wheat						
PHI	Plant Parts	TRR (ppm)[1]	Extracted Radioactivity (%TRR)		Non-extracted Radioactivity (%TRR)	Sum of Extracted and Non-extracted Radioactivity (%TRR)
			Cold Extract	Soxhlet Extract		
49 days (ear emergence)	Leaves	0.019	64.1	4.0	41.5	109.6
68 days (milky stage)	Husks Leaves	0.012 0.024	39.3 41.0	5.0 4.1	61.7 51.4	106.0 96.5
91 days (maturity)	Grain Husks Straw	0.014 0.024 0.067	20.3 21.3 21.6	3.9 7.5 7.1	76.9 71.0 73.7	101.1 99.8 102.4

[1] in equivalents of CGA-184927

Partitioning of the cold extract with dichloromethane (CH_2Cl_2) at pH 3 yields an organosoluble phase and a water soluble phase. Table 9 gives the distribution of the radioactivity in the organosoluble and water soluble phases.

Table 9. Distribution of Radioactivity in the Organosoluble and Water Soluble Phases after Partitioning of the Cold Extract at pH 3				
PHI	Plant Parts	Extractable Radioactivity in the Cold Extract (%TRR)	CH_2Cl_2 Phase (%TRR)	Water Phase (%TRR)
49 days	Leaves	64.1	7.9	56.2
68 days	Husks Leaves	39.3 41.0	4.8 4.6	34.5 36.5
91 days	Grain Husks Straw	20.3 21.3 21.6	3.8 4.3 5.3	16.5 17.0 16.3

Treatment of the water phases with the enzyme cellulase did not cleave any conjugates. Conjugates in the water phases were cleaved by hydrolysis with hydrochloric acid (1.0 N HCl).

Characterization/identification of residues

Metabolites in the CH_2Cl_2 phase and acid hydrolyzed water phase were analyzed by thin layer chromatography (TLC), high performance liquid chromatography (HPLC), and mass spectroscopy (MS). The residues in leaves (49-day PHI; ear emergence), husks and leaves (68-day PHI; milky stage), and mature grain, husks, and straw (91-day PHI) were analyzed for parent; no CGA-184927 (parent) was detected. Only the residues in 49-day PHI leaves, 68-day PHI leaves, and 91-day PHI straw were further identified, as reported in Table 10 below. The only metabolite which was identified was 2-hydroxy-3-fluoro-5-chloro-pyridine (IV_2). The proposed metabolic pathway in wheat is shown in Figure 1 (Attachment 2).

Table 10. Identification of Residues of [2-^{14}C-pyridyl] CGA-184927 in the CH_2Cl_2 Phase and Acid Hydrolyzed Water Phase in Spring Wheat

Plant Part-PHI	TRR (ppm)	CGA-184927 [1]		IV_2 [2]		IV_1 (unknown)		Unresolved	
		%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Leaves-49 days (ear emergence)	0.019	---	<0.001	17.2	0.0033	6.6	0.0012	11.2	0.0021
Leaves-68 days (milky stage)	0.024	---	<0.001	10.8	0.0026	4.2	0.0010	4.7	0.0011
Straw-91 days (maturity)	0.067	---	<0.001	5.6	0.0038	2.9	0.0019	2.9	0.0019

[1] No CGA-184927 (parent) was detected; the limit of detection was 0.001 ppm.

[2] IV_2 = 2-hydroxy-3-fluoro-5-chloro-pyridine

Storage stability

The field biological phase of the study was conducted between 4/16/87 and 8/13/87. The analytical phase was conducted between 5/14/87 and 5/31/90. Samples were stored frozen (-18°C).

Summary

The fate of [2-^{14}C-pyridyl] CGA-184927 [(R) (2-[4-(5-chloro-3-fluoro-2-pyridinyloxy)phenoxy]-propanoic acid, 2-propynyl ester)] was studied in field grown spring wheat in St. Aubin, Switzerland after post-emergence foliar spray application of [2-^{14}C- pyridyl]CGA-184927 at 2X. Leaves (49-day PHI; ear emergence), husks and leaves (68-day PHI; milky stage), and mature grain, husks, and straw (91-day PHI) were extracted. The non-extractable radioactivity in leaves was 41.5% TRR at ear emergence and 51.4% TRR at milky stage; the non-extractable radioactivity in grain, husks, and straw at maturity accounted for 76.9%, 71.0%, and 73.7% TRR, respectively. Metabolites were analyzed by thin layer chromatography (TLC), high performance liquid chromatography (HPLC), and mass spectroscopy (MS). The residues in leaves (49-day PHI), husks and leaves (68-day PHI), and mature grain, husks, and straw (91-day PHI) were analyzed for parent; no CGA-184927 (<0.001 ppm) was detected. Only the residues in 49-day PHI leaves, 68-day PHI leaves, and 91-day PHI straw were further identified. The only metabolite which was identified was 2-hydroxy-3-fluoro-5-chloro-pyridine (IV_2); it accounted for 17.2% TRR in leaves (ear emergence; 49-day PHI), 10.8% TRR in leaves (milky stage; 68-day PHI), and 5.6% TRR in straw (91-day PHI). Only one other metabolite was isolated; this unknown accounted for <10% TRR in leaves and straw.

The identification of 2-hydroxy-3-fluoro-5-chloro-pyridine supports the proposed metabolic pathway as described under MRID 44399203: [2-^{14}C-pyridyl] labeled CGA-184927 in wheat is metabolized by 1) hydrolysis of the parent ester molecule CGA-184927 to form the acid CGA-193469, and subsequent sugar conjugation of the acid; 2) hydroxylation of the 6-position of the pyridyl ring in CGA-193469 to form metabolite II_2 and subsequent sugar conjugation; 3) cleavage of the ether bridge between the pyridinyl and phenyl rings in CGA-193469, yielding CGA-214111 and its corresponding sugar conjugate; and 4) cleavage of CGA-193469 at the phenoxy-propanoic acid ether bridge to form CGA-193468.

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 [2-^{14}C- pyridyl] CGA-184927 study:

a. Due to large amounts of the radioactivity being nonextractable with acetonitrile:water (8:2) and by Soxhlet extraction with methanol, only 17.2% TRR, 10.8% TRR, and 5.6 %TRR were identified in leaves (ear emergence), leaves (milky stage), and straw (mature), 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.

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 (D263288, N. Dodd, 2/25/00) to be clodinafop-propargyl and its acid metabolite CGA-193469. HED may revisit the MARC after additional wheat metabolism data have been submitted.

OPPTS GLN 860.1300; NATURE OF THE RESIDUE IN ANIMALS

RUMINANTS

1991; MRID 44399205

A goat metabolism study was submitted (see citation below). The performing laboratory was Inveresk Research International, Tranent, Scotland.

MRID 44399205 Cameron, B.D. (1991) Absorption, Distribution and Excretion of [U-^{14}C]-Phenyl CGA-184927 After Multiple Oral Administration to a Lactating Goat, Laboratory Project No. 139307, Nexus Study Number 400-91, unpublished study sponsored by Novartis Crop Protection, Inc., 90 pp.

In-life phase

One lactating goat was dosed with 5.9 ppm [^{14}C-phenyl] CGA-184927 for ten consecutive days. (Based on each capsule containing 8.2 mg [^{14}C-phenyl] CGA-184927 and an average daily feed of 1.4 kg, the dose level was equivalent to ca 5.9 ppm in the daily feed. The feeding level of 5.9 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 [^{14}C-phenyl] CGA-184927 was ≥99.6%; the specific activity was 1.74 MBq/mg (47.05 μCi/mg). The goat was milked in

the morning prior to dosing and in the afternoon about 7 hours after dosing. The goat was sacrificed ca 24 hours after the last dose.

Total radioactive residues (TRR)

Total radioactive residues were determined in milk, muscle, fat, liver, and kidney by combustion (of solid samples) and liquid scintillation counting. Transfer of radioactivity into milk was low; radioactivity found in milk during the study accounted for 0.15% of the total administered dose. As shown in Tables 11 and 12 below, total radioactive residues (expressed as clodinafop-propargyl equivalents) were ≤0.018 ppm in milk, ≤0.001 ppm in muscle, ≤0.004 ppm in fat, 0.011 ppm in liver, and 0.077 ppm in kidney.

Table 11. Total Radioactive Residues of [^{14}C-Phenyl] CGA-184927 in Goat Milk From 10 Consecutive Daily Doses at 5.9 ppm (18X)		
Study Day	CGA-184927 Equivalents (ppm)	
	a.m.	p.m.
1	0.000 (predose)	0.004
2	0.013	0.014
3	0.016	0.015
4	0.018	0.014
5	0.016	0.015
6	0.017	0.017
7	0.015	0.014
8	0.016	0.015
9	0.015	0.016
10	0.015	0.015
11	0.014	--
Mean ± S.D.	0.016* ± 0.001	0.015* ± 0.001

* The a.m. mean is for days 2-11; the p.m mean is for days 2-10.

Table 12. Total Radioactive Residues of [^{14}C-Phenyl]CGA-184927 in Goat Tissues Following 10 Consecutive Daily Doses at 5.9 ppm (18X)	
Tissue	CGA-184927 Equivalents (ppm)
muscle	
hindquarter	0.001*
forequarter	0.000**
tenderloin	0.000*
fat	
omental	0.004
subcutaneous	0.002*
renal	0.003*
liver	0.011
kidney	0.077

*These data are derived from less than 30 dpm above background; the limit of reliable quantitation is 30 dpm above background.
**The data are derived from less than 10 dpm above background.

Urinary elimination was the major route of excretion, accounting for ca 81% of the total administered dose whereas fecal elimination accounted for ca 12% of the total dose as determined by liquid scintillation counting. Excretion of total radioactivity in urine and feces was rapid, with ca 64-97% of the daily dose excreted in urine and ca 7-25% of the daily dose excreted in feces.

Storage stability

The goat was sacrificed on 5/26/89. Milk samples were stored initially at 1-5 °C and then at -20 °C. Muscle, fat, liver, and kidney samples were stored at -20 °C.

Summary

One lactating goat was dosed with 5.9 ppm [^{14}C-phenyl] CGA-184927 for ten consecutive days. Total radioactive residues, expressed as clodinafop-propargyl equivalents, were ≤0.018 ppm in milk, ≤0.001 ppm in muscle, ≤0.004 ppm in fat, 0.011 ppm in liver, and 0.077 ppm in kidney.

1997; MRID 44399204

A second goat metabolism study was submitted, which was a continuation of MRID 44399205 (see citation below). The performing laboratory was Novartis Crop Protection AG, Basle, Switzerland.

MRID 44399204 Thanei, Dr. P. (1997) The Nature of the Metabolites in Milk, Eggs, Tissues, and Excreta of a Goat and Hens after Multiple Oral Administration of [U-14C] Phenyl CGA-184927, Laboratory Project Report 19/96, Nexus Study Number 459-97, unpublished study sponsored by Novartis Crop Protection, Inc., 114 pp.

In-life phase

Representative samples of tissues and milk were obtained from study MRID 44399205 (discussed above).

Total radioactive residues (TRR)

Total radioactivity was determined by combustion (of solid samples) and liquid scintillation counting as reported in Table 13 below.

Table 13. Total Radioactive Residues of [^{14}C-Phenyl]CGA-184927 in Goat Milk and Tissues		
Commodity	Sampling Time in 10-Day Study (hours)	CGA-184927 Equivalents (ppb)
milk	48-55 55-72	15 18
hindquarter muscle	240	1*
forequarter muscle	240	<1**
tenderloin	240	<1*
omental fat	240	4
subcutaneous fat	240	2*
renal fat	240	3*
liver	240	11
kidney	240	77

* data derived from less than 30 dpm above background
** data derived from less than 10 dpm above background

Extraction and hydrolyses of residues

Residues in urine were analyzed without extraction. Residues in goat feces were extracted once with methanol and twice with methanol/water (8/2, v/v).

Residues in milk and tissues were extracted, partitioned with solvents, and subjected to alkaline and acidic hydrolysis as described below:

Milk containing 17 ppb CGA-184927 equivalents was extracted with acetonitrile four times and then twice with acetonitrile/acetic acid (99/1, v/v). The combined extracts (94% TRR) were partitioned with hexane five times, leaving 2% TRR in the aqueous phase and 92% TRR in the hexane phase. The hexane phase [MA1-12 (92% TRR)] was separated into two parts: one part was purified by preparative TLC, which separated the residue into two components [MA1-121 (89% TRR) and MA1-122 (3% TRR)]; the other part was refluxed for two hours with 1N potassium hydroxide (1N KOH) in methanol, followed by acidification with formic acid to pH 2 and extraction three times with methylene chloride to obtain an organic phase [MA1-12(2)V1 (91% TRR)] and an aqueous phase (1% TRR). The organic phase was purified by preparative TLC to obtain two components [MA1-12(2)V11 (77% TRR) and MA1-12(2)V12 (14% TRR)]. MA1-12, MA1-121, MA1-12(2)V1, and MA1-12(2)V11 were used to identify residues.

Meat (pooled hindquarter muscle, forequarter muscle, and tenderloin) containing ca 1 ppb CGA-184927 equivalents (<LOQ) was extracted with acetonitrile. The extract was purified by preparative TLC into two fractions [MUA1-11 and MUA1-12]. MUA1-12 was used to identify residues.

Fat (pooled renal fat, omental fat, and subcutaneous fat) containing 3 ppb CGA-184927 equivalents (ca LOQ) was extracted with chloroform and filtered to obtain an organic phase (74% TRR) and residue (26% TRR). The organic phase (74% TRR) was partitioned with 0.1 N NaH_2PO_4 (pH 8) to obtain an organic phase (FEA1-11, 55% TRR) and an aqueous phase (FEA1-12, 19% TRR). The aqueous phase (FEA1-12, 19%TRR) was acidified with formic acid to >pH 2 and extracted twice with methylene chloride to obtain an organic phase FEA1-121 (18% TRR) and an aqueous phase (FEA1-122, 1% TRR). FEA-121 was used to identify residues.

Liver containing 11 ppb CGA-184927 equivalents was extracted three times with acetonitrile and then with acetone to obtain an acetonitrile extract (67% TRR), an acetone extract (1% TRR), and residue (32% TRR). The acetonitrile extract (67% TRR) was separated into two parts: one part was purified by preparative TLC to obtain two components [LA1-11 (8% TRR) and LA1-12 (59% TRR)]; the other part was purified on a different TLC system to obtain two components [LA1-1(2)1 (15% TRR) and LA1-1(2)2 (52% TRR)]. LA1-12 and LA1-1(2)2 were used to identify residues.

Kidney containing 77 ppb CGA-184927 equivalents was extracted three times with acetonitrile and then with acetone to obtain an acetonitrile extract (NA1-1, 64% TRR), an acetone extract (1% TRR), and residue (35% TRR). The acetonitrile extract was purified by preparative TLC to obtain two components [NA1-11 (4% TRR) and NA1-12 (60% TRR)]. NA1-1 and NA1-12 were used to identify residues.

The extractable and nonextractable radioactivities (as a percent of total radioactive residues, %TRR) are reported in Table 14 below.

Table 14. Extractable/Nonextractable Residues of [^{14}C-Phenyl]CGA-184927 from Milk and Tissues of a Goat (in %TRR and ppb CGA-184927 Equivalents)						
Matrix	Residue (ppb)	Extractable		Nonextractable		Total (%)
		%TRR	ppb	%TRR	ppb	
Milk	17	94	16	6	1	100
Meat[1]	~1 (<LOQ)	---[3]	---[3]	---[3]	---[3]	---
Fat[2]	3 (~LOQ)	74[4]	2[4]	26[4]	1[4]	100
Liver	11	67[5]	7	32	4	100
Kidney	77	64[5]	49	35	27	100

[1] pool of forequarter muscle, hindquarter muscle, and tenderloin

[2] pool of renal fat, omental fat, and subcutaneous fat

[3] Due to a residue level below the LOQ, no reliable values can be calculated.

[4] Due to a residue level at the LOQ, no reliable values can be calculated; values can only be regarded as an estimation.

[5] An additional 1% is extractable with acetone.

Characterization and identification of residues

Residues in goat urine were identified by two-dimensional TLC and cochromatography with reference standards. Most of the total radioactive residue in goat urine was CGA-193469: 96.3% from 0-24 hours; 96.7% from 96-120 hours; and 97.0% from 192-216 hours. CGA-184927 was not detected in urine.

Residues in the extracts from goat feces were identified by two-dimensional TLC and cochromatography with reference standards. Most of the total radioactive residue in goat feces was CGA-193469: 82.3% from 0-24 hours; 81.2% from 96-120 hours; and 75.2% from 192-216 hours. CGA-184927 was not detected in feces.

Residues in milk, meat, fat, liver, and kidney were determined by thin layer chromatography with multiple solvent systems and cochromatography with reference standards.

Extractable residues (from Table 14 above) were characterized/identified in Table 15 below. The proposed metabolic pathway in goats is portrayed in Figure 2 (Attachment 3).

Table 15. Characterization/Identification of Extractable Residues
(in % TRR and ppb CGA-184927 Equivalents)

Matrix	Total (ppb)	CGA-193469		CGA-193468		Hybrid Acylglycerides		Total Identified/ Characterized		Unknown		Nonextractable		Total (%TRR)
		% TRR	ppb	% TRR	ppb	% TRR	ppb	% TRR	ppb	% TRR	ppb	% TRR	ppb	
Milk	17	---	nd[10]	---	nd[10]	94[3]	16[3]	94%	16	---	nd[10]	6	1	100
Muscle[1]	~1 (<LOQ)	---[4]	<1[4]	---	nd[10]	---	nd[10]	---[4]	<1[4]	---	nd[10]	---[4]	---[4]	---
Fat[2]	3 (~LOQ)	19[5]	<1[5]	---	nd[10]	55[5,6]	2[5,6]	74[5]	<3[5]	---	nd[10]	26[5]	1[5]	100
Liver	11	45	5	---	traces	---	traces	45	5	22	2[8]	32	4	99[7]
Kidney	77	54	42	3	2	2	2	59[7]	46	5	3[9]	35	2	99[7]

[1] pool of forequarter muscle, hindquarter muscle, and tenderloin
[2] pool of renal fat, omental fat, and subcutaneous fat
[3] saponification releases 3 different xenobiotic acids in about equal amounts, one being CGA-193469
[4] Due to a residue level below LOQ, no reliable values can be calculated in % of total radioactive residues.
[5] Due to a residue level at LOQ, no reliable values can be calculated; values can only be regarded as an estimation.
[6] incorporation of CGA-193469 as xenobiotic acid
[7] An additional 1% is extractable with acetone.
[8] Two unknowns, each 1 ppb, were found.
[9] Two unknowns, one 2 ppb and one 1 ppb, were found.
[10] nd = not detected

Storage stability

Storage stability was determined in urine and feces using goat urine and hen excreta samples collected on 5/21/89 and 5/25/89, respectively, and stored frozen (-18°C). The goat urine and hen excreta were analyzed on 6/6/89 and 6/8/89, respectively; the goat urine and hen excreta were reanalyzed on 8/14/89 and 8/16-17/89, respectively. The excreta was extracted once with methanol and twice with methanol/water (8/2, v/v), and analyzed quantitatively by two-dimensional TLC. The goat urine was analyzed directly by two-dimensional TLC. The percent of the TRR in the various fractions in the TLC-radiochromatograms and the pattern of degradation products in the TLC-radiochromatograms did not change significantly in urine and feces. This study indicates that residues in urine and feces are stable under frozen conditions (-18°C) for 69 and 70 days, respectively.

The goat was sacrificed on 5/26/89. The excreta, milk, and tissue samples were stored frozen until shipment. The samples were shipped on 8/16/89 by air freight on dry ice to Novartis Crop Protection AG, Basle, Switzerland. The samples were received frozen on 8/17/89 and stored frozen (-18°C) until analysis. The experimental phase of the study terminated on 7/19/91.

The time from sampling to analysis should be clarified for milk and tissues. If the time between sampling and 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.

Summary

One lactating goat was dosed with [^{14}C-phenyl] CGA-184927 for ten consecutive days at a level of 5.9 ppm (18X). Samples containing the following residue levels (expressed as CGA-184927 equivalents) were extracted: 17 ppb in milk, ~1 ppb in meat, 3 ppb in fat, 11 ppb in liver, and 77 ppb in kidney. Extractable residues were 94% TRR in milk, 74% in fat, 67% in liver, and 64% in kidney. Due to a residue level below the LOQ (~1 ppb) in meat, no reliable values for percent extracted can be calculated. CGA-184927 was metabolized in the goat via hydrolysis to CGA-193469, which was further metabolized to form hybrid acylglycerides or CGA-193468. Most of the total radioactive residue in goat urine (96.3% - 97.0%) and feces (75.2% - 82.3%) was CGA-193469. Parent CGA-184927 was not detected in urine or feces. In milk, the radioactivity (17 ppb CGA-184927 equivalents) was 94% hybrid acylglycerides, which released CGA-193469 and two unidentified compounds upon saponification. In muscle containing 1 ppb CGA-184927 equivalents, only CGA-193469 was detected (<1 ppb). In fat containing 3 ppb CGA-184927 equivalents, CGA-193469 was found free (<1 ppb) and incorporated into hybrid acylglycerides (2 ppb). In liver containing 11 ppb CGA-184927 equivalents, CGA-193469 (5 ppb) and traces of CGA-193468 and hybrid acylglycerides were found. In kidney containing 77 ppb CGA-184927

equivalents, CGA-193469 (42 ppb), CGA-193468 (2 ppb) and hybrid acylglycerides (2 ppb) were found.

Conclusion

The nature of the residue in ruminants is not adequately understood for the purposes of a permanent tolerance for the following reason: The time from sampling to analysis should be clarified for milk and tissues. If the time between sampling and 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 residues in milk and tissues are hybrid acylglycerides (containing CGA-193469 as one component) and/or CGA-193469. The residues of concern in ruminants were determined by HED's Metabolism Assessment Review Committee on 2/15/00 (D263288, N. Dodd, 2/25/00) to be clodinafop-propargyl and its acid metabolite CGA-193469.

POULTRY

1991; MRID 44399206

A poultry metabolism study was submitted (see citation below). The performing laboratory was Inveresk Research International, Tranent, Scotland.

MRID 44399206 Cameron, B.D. (1991) Distribution and Excretion of [U-^{14}C]-Phenyl CGA-184927 After Multiple Oral Administration to Laying Hens, Laboratory Project No. 139291, Nexus Study Number 399-91, unpublished study sponsored by Novartis Crop Protection, Inc., 90 pp.

In-life phase

Four laying hens were dosed with 4.6 ppm [^{14}C-phenyl] CGA-184927 for 14 consecutive days. (The feeding level of 4.6 ppm is 92X the maximum theoretical residue level in the diet of poultry, as calculated in this review under OPPTS GLN 860.1480.) The specific activity of the [^{14}C-phenyl]CGA-184927 was 1.74 MBq/mg (47.05μCi/mg). The radiochemical purity was $\geq$99.6%. Eggs were collected continuously during the study. The hens were sacrificed ca 24 hours after the last dose.

Total radioactive residues (TRR)

Total radioactive residues were determined in meat, fat, liver, kidney, and eggs by combustion (of solid samples) and liquid scintillation counting. Total radioactive residues found in poultry tissues and eggs are tabulated in Tables 16 and 17 below.

Table 16. TRR in Meat, Fat, Liver, and Kidney of Four Laying Hens Dosed for 14 Consecutive Days with [^{14}C-Phenyl]CGA-184927 at a Dosing Level of 4.6 ppm (92X)

Commodity	ppm				Average ppm ± Standard Deviation
	Hen #182LAD9	Hen #183LAD9	Hen #185LAD9	Hen #186LAD9	
lean meat	0.001*	0.002	0.001*	0.001	0.001 ± 0.001
skin (including fat)	0.013	0.014	0.008	0.009	0.011 ± 0.003
peritoneal fat	0.023	0.065	0.007	N/A	0.032 ± 0.030
liver	0.126	0.124	0.110	0.192	0.138 ± 0.037
kidney	2.626	2.922	3.208	3.901	3.164 ± 0.546

* derived from data <30 dpm above background

N/A = not available because of loss of most of the sample due to a handling error

Table 17. TRR in Eggs (Whites and Yolks) of Four Laying Hens Dosed for 14 Consecutive Days at 4.6 ppm (92X)										
Time of Study (hours)	ppm CGA-184927 Equivalents								Average (ppm) ± *Standard Deviation*	
	Hen #182LAD9		Hen #183LAD9		Hen #185LAD9		Hen #186LAD9			
	White	Yolk	White	Yolk	White	Yolk	White	Yolk	White	Yolk
0-24	*0.001*	*0.000*[1]	*0.002*	*0.000*[1]	*0.001*	*0.000*[1]	*0.000*[1]	*0.000*[1]	*0.001±0.001*	*0.000 ±0.000*
24-48	--[3]	--[3]	--[3]	--[3]	--[3]	--[3]	0.001	0.001[2]	–[4]	–[4]
48-72	0.001	0.009	0.001	0.015	0.001	0.008	--[3]	--[3]	0.001 ±0.000	0.011 ±0.004
72-96	0.000	0.022	0.001	0.033	0.001	0.020	0.001	0.029	0.001 ±0.001	0.026 ±0.006
96-120	0.002	0.027	0.001	0.047	0.001	0.028	0.002	0.057	0.002 ±0.001	0.040 ±0.015
120-144	0.000	0.041	0.001	0.062	0.001	0.036	--[3]	--[3]	0.001 ±0.001	0.046 ±0.014
144-168	0.001	0.047	0.001	0.065	0.001	0.039	0.002	0.084	0.001 ±0.001	0.059 ±0.020
168-192	0.001	0.048	0.000	0.067	0.002	0.040	0.001	0.101	0.001 ±0.001	0.064 ±0.027
192-216	0.000	0.047	--[3]	--[3]	--[3]	--[3]	--[3]	--[3]	–[4]	–[4]
216-240	0.001	0.033	0.001	0.066	0.001	0.038	0.003	0.094	0.002 ±0.001	0.058 ±0.028
240-264	0.000	0.052	--[3]	--[3]	0.001	0.041	0.002	0.101	0.001 ±0.001	0.065 ±0.032
264-288	0.001	0.056	0.001	0.070	0.001	0.042	0.001	0.101	0.001	0.067 ±0.025
288-312	0.001	0.057	0.001	0.072	0.002	0.047	0.003	0.107	0.002 ±0.001	0.071 ±0.026
312-336	0.000[2]	0.060	0.002	0.072	--[3]	--[3]	--[3]	--[3]	0.001	0.066

[1] derived from data <10 dpm above background

[2] derived from data <30 dpm above background

[3] No egg was laid at this time point.

[4] There is insufficient data to average since only one hen laid an egg.

TRR in eggs (white and yolk combined), based on 70% white and 30% yolk by weight, are tabulated in Table 18 below:

Table 18. TRR in Eggs (White and Yolk Combined) of Four Laying Hens Dosed for 14 Consecutive Days with [^{14}C-Phenyl] CGA-184927 at 4.6 ppm (92X)

Time of Study (hours)	CGA-184927 Equivalents (ppm)				Average[2] (ppm)
	Hen #182LAD9	Hen #183LAD9	Hen #185LAD9	Hen #186LAD9	
0-24	0.0007	0.0014	0.0007	0.0000	0.0007
24-48	----[1]	----[1]	----[1]	0.0014	0.0014 (n=1)
48-72	0.0034	0.0052	0.0031	----[1]	0.0039 (n=3)
72-96	0.0066	0.0106	0.0067	0.0094	0.0083
96-120	0.0095	0.0148	0.0091	0.0185	0.0130
120-144	0.0123	0.0193	0.0115	----[1]	0.0144 (n=3)
144-168	0.0148	0.0202	0.0124	0.0266	0.0185
168-192	0.0151	0.0201	0.0134	0.0310	0.0199
192-216	0.0141	----[1]	----[1]	----[1]	0.0141 (n=1)
216-240	0.0106	0.0205	0.0121	0.0303	0.0184
240-264	0.0156	----[1]	0.0130	0.0317	0.0201 (n=3)
264-288	0.0175	0.0217	0.0133	0.0310	0.0209
288-312	0.0178	0.0223	0.0155	0.0342	0.0224
312-336	0.0180	0.0230	----[1]	----[1]	0.0205 (n=2)

[1] No egg was laid at this time point.
[2] n=4 unless otherwise stated

Of the total radioactivity administered during the study, 85.10% was recovered in excreta.

Storage Stability

The hens were sacrificed on 6/1/89. Egg samples were stored initially at 1-5 °C and then at -20 °C. Tissue samples were stored at -20 °C.

Summary

Four laying hens were dosed with [^{14}C-phenyl] CGA-184927 for 14 consecutive days at a dosing level of 4.6 ppm (92X). Total radioactive residues, expressed as CGA-184927 equivalents, were 2.626-3.901 ppm (av 3.164 ppm) in kidney, 0.110-0.192 ppm (av 0.138 ppm) in liver, 0.007-0.065 ppm (av 0.032 ppm) in peritoneal fat, 0.008-0.014 ppm (av 0.011 ppm) in skin (including fat), and 0.001- 0.002 ppm (av 0.001 ppm) in lean meat. Residues in eggs (white and yolk combined) ranged from 0.0000 ppm to 0.0342 ppm. The highest average daily residue level in eggs was 0.0224 ppm (n=4) on day 13. The average residue level in eggs over the 14-day study was 0.0147 ppm (n= 45). [The ppm for eggs represents a weighted sum of the residues in egg whites and yolks; when the weight of the shell is excluded, eggs are 70% white and 30% yolk by weight.]

1997: MRID 44399204

A second poultry metabolism study was submitted, which was a continuation of MRID 44399206 (see citation below). The performing laboratory was Novartis Crop Protection AG, Basle, Switzerland.

MRID 44399204 Thanei, Dr. P. (1997) The Nature of the Metabolites in Milk, Eggs, Tissues, and Excreta of a Goat and Hens after Multiple Oral Administration of [U-14C] Phenyl CGA-184927, Project Report 19/96, Nexus Study Number 459-97, unpublished study sponsored by Novartis Crop Protection, Inc., 114 pp.

In-life phase

Representative samples of tissues and eggs were obtained from study MRID 44399206 (discussed above).

Total radioactive residues (TRR)

Total radioactivity was determined by combustion (of solid samples) and liquid scintillation counting as reported in Table 19 below.

Table 19. Total Radioactive Residues in Poultry Eggs and Tissues		
Commodity	Sampling Time (hours)	CGA-184927 Equivalents (ppb)
egg white	288-312	2
egg yolk	288-312	71
lean meat	336	1
skin and attached fat	336	11
peritoneal fat*	336	65
liver	336	138
kidney	336	3164

* Due to high variation of residues from individual animals (7-65 ppb), the pool (32 ppb) was not used; only the peritoneal fat from hen 183LAD9, representing 65 ppb, was used.

Extraction and hydrolyses of residues

Residues in hen excreta were extracted once with methanol and twice with methanol/water (8/2, v/v). The extract was extracted again with methanol.

Residues in eggs and tissues were extracted, partitioned with solvents, and subjected to alkaline and acidic hydrolysis as described below:

Egg white containing 2 ppb (ca LOQ) CGA-184927 equivalents was extracted with acetonitrile to obtain an acetonitrile extract (95% TRR) and residue (5% TRR). The acetonitrile extract (EWA1-1, 95% TRR) was purified by preparative TLC to obtain two components [EWA1-11 (20% TRR) and EWA1-12 (75% TRR)]. EWA1-1 and EWA1-12 were used to identify residues.

Egg yolk containing 71 ppb CGA-184927 equivalents was extracted with acetone to obtain an acetone extract (91% TRR) and residue (9% TRR). The acetone extract (91% TRR) was partitioned three times with hexane to obtain an aqueous phase (8% TRR) and a hexane phase (EGA1-12, 83% TRR). The hexane phase (83% TRR) was treated with 1N potassium hydroxide (1N KOH) in methanol, acidified with formic acid to pH 2, and extracted three times with methylene chloride to obtain an organic phase (82% TRR) and an aqueous phase (1% TRR). The organic phase (EGA1-12V1, 82% TRR) was purified by preparative TLC to obtain two components [EGA1-12V11 (73% TRR) and EGA1-12V12 (8% TRR). EGA1-12, EGA1-12V1, and EGA1-12V11 were used to identify residues.

Meat containing 1 ppb (ca LOQ) CGA-184927 equivalents was extracted three times with methanol/water (1/1, v/v) and then with acetone to obtain a methanol/water extract (30% TRR), an acetone extract (23% TRR), and residue (47% TRR). The methanol/water extract (30% TRR) was partitioned three times with chloroform and twice with hexane to obtain an aqueous phase (18% TRR), a chloroform phase (11% TRR), and a hexane phase (1% TRR). The aqueous phase was evaporated to dryness, ultrasonicated with methanol, and filtered to obtain a filtrate (MUB1-111, 18% TRR) and a precipitate (MUB1-112, 0% TRR). The acetone extract (23% TRR) was treated with 1N potassium hydroxide (1N KOH) in methanol, acidified with formic acid to pH 2-3, and extracted three times with methylene chloride to form a methylene chloride phase (15% TRR) and an aqueous phase (8% TRR). The aqueous phase was purified by preparative TLC to obtain two components [MUB1-3V11 (13% TRR) and MUB1-3V12 (2% TRR)]. MUB1-3V11 was used to identify residues.

Fat (peritoneal) containing 65 ppb CGA-184927 equivalents was extracted with chloroform to obtain a chloroform extract (PFEA1-1; 95% TRR) and residue (5% TRR). The chloroform extract (95% TRR) was treated with 1N potassium hydroxide (1N KOH) in methanol, acidified with formic acid to pH 2-3, filtered, and extracted three times with methylene chloride to obtain an organic phase (PFEA1-1V2; 36% TRR), an aqueous phase (8% TRR), and a precipitate (51% TRR). The precipitate was dissolved in methylene chloride and purified by preparative TLC to obtain two components [PFEA1-1V11 (37% TRR) and PFEA1-1V12 (14% TRR)]. PFEA1-1, PFEA1-1V2, and PFEA1-1V11 were used to identify residues.

Skin and attached fat containing 11 ppb CGA-184927 equivalents was extracted with chloroform and three times with methanol to obtain a chloroform extract (29% TRR), a methanol extract (SFEA1-2, 38% TRR), and residue (33% TRR). The chloroform extract (29% TRR) was partitioned with 0.1 N NaH_2PO_4 (pH 8) to obtain an organic phase (26% TRR) and an aqueous phase (3% TRR). The organic phase (26% TRR) was refluxed with 1N KOH in methanol, acidified with formic acid to pH 2-3, filtered to remove the precipitate, and extracted three times with methylene chloride to form an aqueous phase (5% TRR). The precipitate was dissolved in methanol/methylene chloride (1/1, v/v); the dissolved precipitate and organic phase were combined to form a precipitate + organic phase (21% TRR). The precipitate + organic phase (21% TRR) was purified by preparatory TLC to form two components [SFEA1-11V12 (3% TRR) and SFEA1-11V11 (18% TRR). SFEA1-2 and SFEA1-11V11 were used to identify residues.

Liver containing 138 ppb CGA-184927 equivalents was extracted three times with acetonitrile, once with chloroform, and three times with methanol/water (1/1, v/v) to obtain combined acetonitrile and methanol/water extracts (LB1-1, 49% TRR), a chloroform extract (1% TRR), and nonextractable residue (50% TRR). LB1-1 was used to identify residues.

Kidney (first sample) containing 3164 ppb CGA-184927 equivalents was extracted three times with acetonitrile, once with acetone, once with hexane, twice with methanol/water (4/1, v/v), once with water, and twice with methanol/water (1/1, v/v) to obtain combined extracts (NB1-1,

65% TRR) and residue (35% TRR). (Note: The radioactivity extracted was contained in the acetone; the other extraction solvents contained no radioactivity.) The combined extracts (65% TRR) were partitioned three times with chloroform to obtain an aqueous phase (NB1-11, 63% TRR) and an organic phase (2% TRR). NB1-1 was subjected to acid hydrolysis (6N HCl, 120°C, 24 hr). NB1-1 (before and after acid hydrolysis) was used to identify residues. A fraction of NB1-11 was reacted with BCl_3 and another fraction was hydrolyzed with acid (HCl) before being used to identify residues.

Kidney (second sample) containing 3164 ppb CGA-184927 equivalents was extracted three times with methanol/water (4/1, v/v), twice with methanol/water (1/1, v/v), once with water, followed by Soxhlet extraction with methanol, treatment with 2N HCl and extraction with water to obtain combined methanol/water and water extracts (NB2-1, 47% TRR), a Soxhlet methanol extract (NB2-2, 13% TRR), a 2N HCl/water extract (NB2-3, 28% TRR), and residue (12% TRR). The combined methanol/water and water extracts (NB2-1, 47% TRR) were evaporated to dryness and extracted with methanol and then with methanol/water (1/1, v/v) to obtain a methanol extract (NB2-12, 18% TRR), a methanol/water extract (NB2-11, 28% TRR), and residue (1% TRR). The methanol extract (NB2-12, 18% TRR) was refluxed in methanol to obtain the component NB2-12R. The methanol/water extract (NB2-11, 28% TRR) was treated with 0.2 N NaOH and acidified with HCl to obtain the component NB2-11V. NB2-3 was evaporated to dryness and extracted with methanol to obtain a methanol extract (NB2-31, 24% TRR) and residue (4% TRR). NB2-2, NB2-11, NB2-12, NB2-12R, and NB2-31, NB2-11V were used to identify residues.

The extractable and nonextractable radioactivities (as a percent of total radioactive residues, %TRR) are reported in Table 20 below.

Table 20. Extractable/Nonextractable Residues of CGA-184927 from Eggs and Tissues of Hens (in % TRR and ppb CGA-184927 Equivalents)						
Matrix	Residue (ppb)	Extractable		Nonextractable		Total (%)
		%TRR	ppb	%TRR	ppb	
egg white	2 (~ LOQ)	95	2	5	<1	100
egg yolk	71	91	65	9	6	100
lean meat	1 (~LOQ)	30+23[1,2]	<1[2]	47[2]	<1[2]	100
peritoneal fat	65	95	62	5	3	100
skin and attached fat	11	38+29[3]	4/3	33	4	100
liver	138	50[4]	69	50	69	100
kidney	3164	65	2057	35	1107	100

[1] methanol/water (1/1, v/v) and acetone extracts, respectively

[2] Due to individual residues at or below the LOQ, no reliable values can be calculated; values can only be regarded as an estimation.

[3] chloroform and methanol extracts, respectively

[4] Includes 1% extractable with chloroform

Characterization and identification of ^{14}C-residues

Residues in hen excreta were isolated/characterized by two-dimensional thin layer chromatography (TLC) and cochromatography with reference standards using multiple solvent systems. The major metabolite was Metabolite 1E, accounting for 51.3-54.5% of the TRR (i.e., 53.7% from 0-24 hours; 54.5% from 144-168 hours, and 51.3% from 288-312 hours). Ten minor metabolites were resolved, of which three were identified and quantitated as % TRR over the same time periods: CGA-214111 (2.6-4.6%), CGA-193469 (6.1-8.6%), and CGA-184927 (1.3%). The remaining metabolites were each ≤4% of the TRR. Metabolite 1E was identified as 2-[4-(6-hydroxy-5-chloro-3-fluoro-2-pyridinyloxy)-phenoxy]-propanoic acid by TLC, cochromatography with reference standards, LC, HPLC, nuclear magnetic resonance (NMR) spectroscopy, and mass spectroscopy.

Residues in egg white, egg yolk, meat, peritoneal fat, skin and attached fat, liver, and kidney were identified by TLC with multiple solvent systems and cochromatography with one or more reference standards. Residues in kidney were also subjected to high voltage electrophoresis.

Extractable residues (from Table 20 above) were characterized/identified as detailed in Table 21 below. The proposed metabolic pathway in hens is portrayed in Figure 3 (Attachment 4).

Table 21. Characterization/Identification of Extractable Residues in Hens (in % TRR and ppb CGA-184927 Equivalents)																		
Matrix	Total (ppb)	CGA-214111		MET 1E		CGA-193469		Hybrid Acyl-glycerides		Total Identified/ Characterized		Origin		An Unknown		Non-extractable		Total
		% TRR	ppb	% TRR	ppb	% TRR	ppb	% TRR	ppb	% TRR	ppb	% TRR	ppb	% TRR	ppb	% TRR	ppb	% TRR
egg white	2 (~LOQ)	---	nd[1]	---	nd[1]	95	2	---	nd[1]	95	2	---	---	---	---	5	<1	100
egg yolk	71	---	nd[1]	---	nd[1]	---	nd[1]	91[2]	65[2]	91	65	---	---	---	---	9	6	100
lean meat	1 (~LOQ)	---	nd[1]	---	nd[1]	30[3]	<1[3]	23[3]	<1[3]	53	<1+ <1	---	---	---	---	47[3]	<1[3]	100
perito-neal fat	65	---	nd[1]	---	nd[1]	---	nd[1]	88[2]	57[2]	88	57	---	---	7	5	5	3	100
skin and attached fat	11	---	nd[1]	38	4	---	nd[1]	29[2]	3[2]	67	7	---	---	---	---	33	4	100
liver	138	---	traces	3	4	---	nd[1]	---	nd[1]	3	4	46[4]	64	---	---	50	69	99[5]
kidney[6]	3164	---	traces	2	62	---	nd[1]	---	nd[1]	2	62	63[7]	1995	---	---	35	1107	100
kidney[8]	3164	19	601.2	0	0	---	nd[1]	---	nd[1]	19	601.2	46	1455.4	---	---	35	1107.4	100
kidney[9]	3164	50	1582	---	nd[1]	---	nd[1]	---	nd[1]	50	1582	---	---	---	---	12	380	62

[1] nd = not detected

[2] releases CGA-193469 on saponification

[3] Due to individual residues at or below the LOQ, no reliable values can be calculated; values can only be regarded as an estimation.
[4] includes an artifact, most probably originating from the fraction remaining at the origin
[5] An additional 1% was recovered in chloroform.
[6] results from the first kidney sample before acid hydrolysis
[7] includes 49% TRR at the origin and 14% TRR as an artifact which most probably originated from the material at the origin
[8] results from the first kidney sample after acid hydrolysis (6N HCl, 120°C, 24 hr), which caused the disappearance of Metabolite 1E, a slight decrease (3%) in material at the origin, and a corresponding increase in CGA-214111
[9] results from the second kidney sample which was extracted with methanol/water, water, Soxhlet extracted with methanol, hydrolyzed with 2N HCl, and hydrolyzed with 0.2 N NaOH; About 50% of the TRR (1582 ppb) in kidney was identified as CGA-214111 and/or a precursor which can be released from the non-extractables, polar metabolite fractions remaining at the origin, and Metabolite 1E upon harsh extraction and acidic and alkaline treatment.

Storage stability

Storage stability was determined in urine and feces using goat urine and hen excreta samples collected on 5/21/89 and 5/25/89, respectively, and stored frozen (-18°C). The goat urine and hen excreta were analyzed on 6/6/89 and 6/8/89, respectively; the goat urine and hen excreta were reanalyzed on 8/14/89 and 8/16-17/89, respectively. The excreta was extracted once with methanol and twice with methanol/water (8/2, v/v), and analyzed quantitatively by two-dimensional TLC. The goat urine was analyzed directly by two-dimensional TLC. The percent of the TRR in the various fractions in the TLC-radiochromatograms and the pattern of degradation products in the TLC-radiochromatograms did not change significantly in urine and feces. This study indicates that residues in urine and feces are stable under frozen conditions (-18°C) for 69 and 70 days, respectively.

The hens were sacrificed on 6/1/89. The excreta, egg, and tissue samples were stored frozen (-20°C) until shipment. The samples were shipped on 8/16/89 by air freight in dry ice to Novartis Crop Protection AG, Basle, Switzerland, received frozen on 8/17/89, and stored frozen (-18°C) until analysis. The experimental phase of the study terminated on 7/19/91.

The time from sampling to analysis should be clarified for eggs and tissues. If the time between sampling and 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.

Summary

Four laying hens were dosed with [^{14}C-phenyl] CGA-184927 for 14 consecutive days at a level of 4.6 ppm (92X). Samples containing the following residue levels (expressed as CGA-184927 equivalents) were extracted: 2 ppb in egg white, 71 ppb in egg yolk, 1 ppb in lean meat, 11 ppb in skin and attached fat, 65 ppb in peritoneal fat, 138 ppb in liver, and 3164 ppb in kidney. Extractable residues were 95% TRR in egg white, 91% in egg yolk, 53% in lean meat, 95% in peritoneal fat, 67% in skin and attached fat, 50% in liver, and 65% in kidney. CGA-184927 was metabolized in hens via hydrolysis to CGA-193469. CGA-193469 was incorporated into hybrid acylglycerides or further metabolized to 2-[4-(6-hydroxy-5-chloro-3-fluoro-2-pyridinyloxy)-phenoxy]-propanoic acid (Metabolite 1E) or 2-(4-hydroxy-phenoxy)-propanoic acid (CGA-214111). In hen excreta, the major metabolite was Metabolite 1E, accounting for 51.3-54.5% of the TRR. Ten minor metabolites were resolved, of which three were identified: CGA 214111 (2.6-4.6%), CGA-193469 (6.1-8.6%), and CGA-184927 (1.3%). The remaining metabolites in excreta were each ≤4% of the TRR. In egg white, 95% of the TRR (2 ppb) was CGA-193469. In egg yolk, 91% of the TRR (65 ppb) was hybrid acylglycerides which released CGA-193469 upon saponification. In lean meat containing 1 ppb CGA-184927 equivalents, CGA-193469 (<1 ppb) and hybrid acylglycerides (<1 ppb) were found. In peritoneal fat, 88% of the TRR (57 ppb) was hybrid acylglycerides yielding CGA-193469 upon saponification. In skin and attached fat containing 11 ppb CGA-184927 equivalents, the identified residues were Metabolite 1E (38% TRR; 4 ppb) and hybrid acylglycerides (29%TRR; 3 ppb), which released CGA-193469 upon saponification. In liver containing 138 ppb CGA-184927 equivalents, the extractable residues were mainly very polar unidentified products remaining at the origin in the TLC radiochromatogram (46%TRR; 64 ppb). Metabolite 1E (3%TRR; 4 ppb) and traces of CGA-214111 were detected in liver. In kidneys containing 3164 ppb CGA-184927 equivalents, about ⅔ of the residue was extractable (2057 ppb); TLC indicated traces of CGA-214111, Metabolite 1E (2%TRR; 62 ppb), and a highly polar fraction remaining at the origin of the TLC radiochromatogram (63%TRR; 1995 ppb). Significant amounts of CGA-214111 (50%TRR; ca 1582 ppb) were released from the non-extractables, the unidentified polar fraction remaining at the origin, and Metabolite 1E upon harsh extraction and drastic acidic or alkaline hydrolysis of a second kidney sample.

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 from sampling to 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 purpose of a tolerance with an expiration date. The major residues in eggs, lean meat, and fat were CGA-193469 and/or hybrid acylglycerides which released CGA-193469 on hydrolysis. Metabolite 1E (38% TRR) and hybrid acylglycerides (29% TRR) were found in skin and attached fat. Small amounts of Metabolite 1E and traces of CGA-214111 were found in liver and kidney. In liver, 50% of the radioactivity remained unextracted. In kidney, 35% of the TRR was unextracted before acid and base hydrolysis. Upon acid and base hydrolysis, 50% of the TRR was identified as products which yield CGA-214111, leaving 50% unidentified including 12% unextracted. Due to the low residues expected in poultry tissues at the 1X feeding level of 0.05 ppm (as calculated in this review under OPPTS GLN 860.1480), additional metabolism data (beyond that required in the above paragraph for a permanent tolerance) are not needed for this use on wheat. The residues of concern in poultry were determined by HED's Metabolism Assessment Review Committee on 2/15/00 (D263288, N. Dodd, 2/25/00) to be clodinafop-propargyl and its acid metabolite CGA-193469.

OPPTS GLN 860.1340: RESIDUE ANALYTICAL METHODS

PLANTS

Method REM 138.01 (1990; MRID 44399211)

Method REM 138.01, which determines CGA-184927 in plants, was used (with modifications for some substrates) to analyze all of the residue/processing samples in the US and Canada and 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-184927 is 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 is 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-184927 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 the 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 clodinafop-propargyl 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 44568401)

The petitioner submitted an independent laboratory method validation for Method REM 138.01 for determination of CGA-184927 in wheat (see citation below). The performing laboratory was Novartis Crop Protection, Inc., Greensboro, NC.

MRID 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-184927. 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-184927 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 for CGA-184927 were obtained in the first trial for wheat grain and forage and in the second trial for wheat straw. Problems encountered were as follows: 1) A procedural modification was made before the study began. To avoid elution of impurities from the silica Sep-Pak that have a retention time identical to CGA-184927, the Sep-Pak was preconditioned with 5 mL of ether followed by 5 mL of hexane; 2) In the CGA-184927 analysis, an in-line solvent debaser caused

baseline oscillations and was removed; 3) In the analysis of wheat grain for CGA-184927, injections must be timed so that a late eluting peak (with a retention time of 58 minutes) does not interfere with analyses; 4) In the analyses of CGA-184927 in wheat straw, interfering peaks in chromatograms were believed to be caused by allowing the C-18 cartridge to dry under vacuum in the elution step. Critical steps were as follows: 1) In the C-18 elution step, the cartridge must not be allowed to 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 22 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 the CGA-184927 standard. The independent laboratory indicated 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 22. *Independent Laboratory Method Validation Results*				
Commodity[1]	Chemical Added	PPM Added	PPM Found	% Recovery
wheat grain	CGA-184927	0.00	<0.02	--
		0.00	<0.02	--
		0.02	0.03	122
		0.02	0.03	101
		0.04	0.04	79
		0.04	0.04	88
		0.10	0.11	106
wheat forage	CGA-184927	0.00	<0.05	--
		0.00	<0.05	--
		0.05	0.08	99
		0.05	0.07	76
		0.10	0.11	76
		0.10	0.11	71
		0.20	0.19	76
wheat straw	CGA-184927	0.00	<0.05	--
		0.00	<0.05	--
		0.05	0.04	84
		0.05	0.04	70
		0.10	0.08	83
		0.10	0.10	95
		0.20	0.16	81

[1] Results are reported from the successful trials only: Trial # 1 for wheat grain and forage and Trial #2 for wheat straw.

Method REM 138.02 (1990; MRID 44399214)

Method REM 138.02, which determines CGA-193469 in the grain of cereals (wheat and barley), was used to determine residues in grain in three residue studies in Canada (see citation below). The performing laboratory was Novartis Crop Protection AG, Basle, Switzerland.

MRID 44399214 Altenburger, Dr. E. (1990) Determination of Residues of Metabolite CGA-193469 By Liquid Chromatography (HPLC) [Wheat], Analytical Method REM 138.02, Nexus Study Number 358-90, unpublished study sponsored by Novartis Crop Protection, Inc., 17 pp.

Homogenized grain samples are extracted with an acetone-buffer pH 3 mixture. (The buffer pH 3 mixture is citrate-hydrochloric acid.) Conjugated residues are hydrolyzed by heating the extract in 0.1N hydrochloric acid. After adding 1 N sodium hydroxide (NaOH) to the hydrolysis test tube to obtain an alkaline pH, fatty coextracts are removed by partitioning into ethyl acetate and hexane. After adding 1N HCl to obtain an acidic pH, CGA-193469 is extracted into hexane-diethyl ether. After evaporation of solvent, the residue is dissolved in 0.1N HCl and the extraction step into hexane-diethyl ether is repeated. The residue is cleaned up further by solid phase extraction on a silica cartridge. CGA-193469 is determined by HPLC with UV-detection under reversed phase conditions. The limit of quantitation (as indicated in Table 45) is 0.05 ppm for wheat grain.

Extraction Efficiency

Recoveries were reported in MRID 44399214 for wheat grain as follows:

Table 23. Recoveries of CGA-193469 in Wheat Grain

Crop Matrix	Fortification Level (ppm)	Recoveries (%)
wheat grain	0.1	77, 120, 105, 75 (average 94)
	1.0	85, 97, 119, 99 (average 100)

Recoveries are included in the section "OPPTS GLN 860.1500: Magnitude of the Residue in Plants." Recovery data at the limit of quantitation of 0.05 ppm were not provided. Recoveries from a fortification level of 0.05 ppm would be needed if this method were used to support residue data which are acceptable; however, HED is not recommending that the petitioner attempt to upgrade the Canadian residue studies.

Radiovalidation

No radiovalidation data were provided. Radiovalidation would be needed for this method if it were used to collect residue data which are acceptable. This method was only used to collect residue data in the Canadian field trials. HED is not recommending that the petitioner attempt to upgrade the Canadian residue studies.

Interference Study/Confirmatory Method

No interference study or confirmatory method were provided. The interference study and confirmatory method are not needed for this method since it is not a proposed enforcement method.

Method REM 138.05 (1991; MRID 44399212)

Method REM 138.05, which determines CGA-193469 in straw and grain of cereals (wheat), was used for analysis of residues of CGA-193469 in wheat straw in three of the residue studies in Canada (see citation below). The performing laboratory was Novartis Crop Protection AG, Basle, Switzerland.

MRID 44399212 Altenburger, Dr. E. (1991) Determination of Residues of Metabolite CGA-193469 By Liquid Chromatography (HPLC) [Wheat], Analytical Method REM 138.05, Nexus Study Number 403-91, unpublished study sponsored by Novartis Crop Protection, Inc., 19 pp.

Homogenized grain samples are extracted with an acetone-buffer pH 3 mixture. (The buffer pH 3 mixture is citrate-hydrochloric acid.) Conjugated residues are hydrolyzed by heating the extract in 0.1N hydrochloric acid. After adding 1 N sodium hydroxide (NaOH) to the hydrolysis test tube to obtain an alkaline pH, fatty coextracts are removed by partitioning into ethyl acetate and hexane. After adding 1N HCl to obtain an acidic pH, CGA-193469 is extracted into hexane-diethyl ether. CGA-193469 is cleaned up by solid phase extraction on a silica gel column and then by solid phase extraction on a C-18 column. After evaporation of solvent, the residue is dissolved in 0.1N HCl and the extraction step into hexane-diethyl ether is repeated. CGA-193469 is determined by HPLC with UV-detection under reversed phase conditions. The limit of quantitation (as indicated in Table 45) is 0.05 ppm for wheat straw.

Extraction Efficiency

Recoveries were reported in MRID 44399212 for wheat straw, grain, and whole plant as follows:

Table 24. Recoveries of CGA-193469 in Wheat Straw, Grain, and Whole Plant		
Crop Matrix	Fortification Level (ppm)	Recoveries (%)
wheat straw	0.1	88, 107 (average 98)
	1.0	85, 83 (average 84)
wheat grain	0.1	76
	1.0	76
whole wheat plant	0.1	108
	1.0	68

Recoveries are included in the section "OPPTS GLN 860.1500: Magnitude of the Residue in Plants." Recovery data at the limit of quantitation of 0.05 ppm were not provided. Recoveries from a fortification level of 0.05 ppm would be needed if this method were used to support residue data which are acceptable; however, HED is not recommending that the petitioner attempt to upgrade the Canadian residue studies.

Radiovalidation

No radiovalidation data were provided. Radiovalidation would be needed for this method if it were used to collect residue data which are acceptable. This method was only used to collect residue data in the Canadian field trials. HED is not recommending that the petitioner attempt to upgrade the Canadian residue studies.

Interference Study/Confirmatory Method

No interference study or confirmatory method were provided. The interference study and confirmatory method are not needed for this method since it is not a proposed enforcement method.

Method REM 138.06 (1991; MRID 44399213)

Method REM 138.06 was used for analysis of residues of CGA-193469 in wheat straw and grain in some storage stability samples and in most of the residue studies in Canada (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-193469 is 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. The organic solution is evaporated, taken up in ion pair reagent solution, and cleaned up by extraction with hexane. The metabolite is then 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-193469 is 0.05 ppm for wheat forage, grain, and straw.

Extraction efficiency

Recoveries were determined in the independent 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 clodinafop-propargyl 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 metabolites of CGA-184927 in wheat (see citation below). The performing laboratory was Novartis Crop Protection, Inc., Greensboro, NC.

MRID 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-193469 at levels of 0.05, 0.10, and 0.20 ppm. The limit of quantitation (LOQ) of the method for CGA-193469 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-193469 were obtained in the first trial for wheat grain and forage and in the third trial for wheat straw. In the analysis of CGA-193469, column 2 became contaminated rapidly; it is recommended that a guard column be used in the HPLC system before column 2.

Results of the independent laboratory validation are presented in Table 25 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-193469 standard. The independent laboratory indicated that a set of seven samples can be worked up in one eight-hour day. Automated HPLC chromatographic analysis can be performed overnight.

Table 25. Independent Laboratory Method Validation Results				
Commodity[1]	Chemical Added	PPM Added	PPM Found	% Recovery
wheat forage	CGA-193469	0.00	<0.05	--
		0.00	<0.05	--
		0.05	0.05	108
		0.05	0.06	120
		0.10	0.12	115
		0.10	0.13	128
		0.20	0.18	91
wheat straw	CGA-193469	0.00	<0.05	--
		0.00	<0.05	--
		0.05	0.03	68
		0.05	0.04	74
		0.10	0.08	77
		0.10	0.09	89
		0.20	0.17	83
wheat grain	CGA-193469	0.00	<0.05	--
		0.00	<0.05	--
		0.05	0.05	93
		0.05	0.05	100
		0.10	0.08	83
		0.10	0.09	90
		0.20	0.15	74

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

Method REM 138.10 (1993; MRID 44755302)

Method REM 138.10 was used for analysis of residues of CGA-193469 in wheat grain, forage, and straw in all of the residue/processing studies in the US and in some of the storage stability studies (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-193469 is 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. After the organic phase is dried, CGA-193469 is redissolved in a buffer solution (pH 7) and cleaned up by partitioning with hexane. The analyte is cleaned up on a C-18 solid phase extraction cartridge. (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 is 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-193469 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 26. Recoveries of CGA-193469 in Wheat Straw, Grain, and Whole Plant

Crop Matrix	Fortification Level (ppm)	Recoveries (%) (average, n=8)
wheat grain	0.02	90, 85, 82, 81, 84, 82, 87, 77 (average 84)
	0.2	92, 86, 93, 88, 87, 91, 84, 89 (average 89)
wheat straw	0.05	70, 58, 67, 58, 76, 62, 42, 58 (average 61)
	0.5	80, 80, 80, 74, 80, 80, 83, 97 (average 82)
green plant material	0.05	81, 80, 84, 86, 88, 76, 84, 90 (average 84)
	0.5	85, 89, 85, 86, 84, 83, 86, 88 (average 86)

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 clodinafop-propargyl 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-193469 would be LC/MS. Selected residue samples (in MRID 44755303) were analyzed for CGA-193469 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-184927 in some wheat storage stability samples. 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-184927 in wheat in all of the residue/processing samples in the US and Canada and some of the storage stability samples. CGA-184927 is determined separately by high performance liquid chromatography (HPLC) with UV-detection. The limits of quantitation of the method for CGA-184927 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-184927 on wheat grain, forage, and straw.

Analytical method REM 138.02 was used to determine residues of CGA-193469 in grain in three residue studies in Canada. CGA-193469 is determined by HPLC with UV-detection under reversed phase conditions. The limit of quantitation (as indicated in Table 45) is 0.05 ppm for wheat grain. Recovery data at the limit of quantitation of 0.05 ppm were not provided. Recoveries from a fortification level of 0.05 ppm would be needed if this method were used to support residue data which are acceptable; however, HED is not recommending that the petitioner attempt to upgrade the Canadian residue studies.

Analytical method REM 138.05 was used for analysis of residues of CGA-193469 in wheat straw in three of the residue studies in Canada. CGA-193469 is determined by HPLC with UV-detection under reversed phase conditions. The limit of quantitation (as indicated in Table 45) is 0.05 ppm for wheat straw. Recovery data at the limit of quantitation of 0.05 ppm were not provided. Recoveries from a fortification level of 0.05 ppm would be needed if this method were used to support residue data which are acceptable; however, HED is not recommending that the petitioner attempt to upgrade the Canadian residue studies.

Analytical method REM 138.06 was used to determine CGA-193469 in wheat in some storage stability samples and in most of the residue studies in Canada. CGA-193469 is determined by high performance liquid chromatography (HPLC) with UV-detection. The limit of quantitation of the method for CGA-193469 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-193469 on wheat grain, forage, and straw.

Analytical method REM 138.10 was used to determine CGA-193469 in wheat in all the residue/processing studies in the US and in some storage stability samples. CGA-193469 is determined by HPLC with UV-detection. The limits of quantitation for CGA-193469 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-193469 on wheat grain, forage, and straw.

Analytical method REM 138.12, a minor improvement of REM 183.01, was used to determine CGA-184927 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. (Radiovalidation data and recovery data at the limit of quantitation would be needed for Methods REM 138.02 and 138.05 if they were used to collect residue data which are acceptable. Methods REM 138.02 and 138.05 were used only to collect the Canadian residue data. HED is not recommending that the petitioner attempt to upgrade the Canadian residue studies); 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 clodinafop-propargyl 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 Methods 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-184927 and CGA-193469 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-184927 and CGA-193469 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-184927 was tested per Protocols C, D, and E. CGA-193469 was tested per Protocols B and C.

CGA-184927

Protocol C: CGA-184927 yielded adequate detector responses to Section 302 DG5, DG13, and DG18 gas-liquid chromatography (GLC) systems.

Protocol D: CGA-184927 was completely recovered through Florisil cleanup (Section 302 C1), and partially recovered through the complete method with Florisil cleanup (Section 302 E4/C1). No interferences were observed with Florisil cleanup. Significant interferences were observed in the method without Florisil cleanup.

Protocol E: CGA-184927 was completely recovered through Florisil cleanup (Section 303 C1/C2) , but only partially recovered through the complete method (Sections 303 E3/C1 and E3/C2). No significant interference was observed.

CGA-193469

Protocol B: CGA-193469 was partially recovered through gel permeation chromatography (GPC) (Section 402 C1a). The methyl ester of CGA-193469 was completely recovered through Florisil cleanup (Section 402 C1c); however, the methyl ester of CGA-193469 was only partially recovered through the complete method (Section 402 E4/C1). No interferences were observed.

Protocol C: CGA-193469 did not yield adequate detector responses to any of the Section 302 DG5, DG13, and DG18 gas-liquid chromatography (GLC) systems; however, the methyl ester of CGA-193469 yielded adequate responses to the GLC systems.

Conclusion

Multiresidue method testing data for CGA-184927 and CGA-193469 in wheat grain have been submitted. CGA-184927 and CGA-193469 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-184927 was tested per Protocols C, D, and E. CGA-193469 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 has been 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-184927 and CGA-193469 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-184927 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-193469 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-184927 and 152 days for CGA-193469; the maximum time between extraction and analysis was 7 days for CGA-184927 and 10 days for CGA-1923469. The storage time between processing and analysis of the processed commodities was ≤25 days for CGA-184927. The storage time between processing and analysis for CGA-193469 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 CGA-184927 and CGA-193469 in specific wheat commodities are reported in Table 27 below.

Table 27. Storage Intervals for Wheat Commodities

Matrix	CGA-184927		CGA-193469	
	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-184927, and ≤51 days for CGA-193469 except for germ (125 days).

Canadian Samples (1997; MRID 44399215; 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 4-13 days before analysis. The other studies do not give extraction dates. Storage containers were not described. The storage time between sampling and analysis for grain and straw ranged from 55 to 580 days for CGA-184927 and 98 to 458 days for CGA-193469. The storage time between sampling and analysis for forage for CGA-184927 and CGA-193469 ranged from 412-434 days.

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

1994; MRID 44399207

A storage stability study for CGA-193469 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, 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-193469 was extracted from samples on days 0, 30, 92, 184, and 380. Analytical methods for CGA-193469 were REM 138.06 (for days 0-30 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-193469 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-193469 were submitted. Storage stability fortification recovery data for CGA-193469 in wheat straw are reported in Table 28 below.

Table 28. Storage Stability Fortification Recovery Data for CGA-193469 in Wheat Straw							
Commodity	Analyte	Residue Level Added (ppm)	Storage Period[1] (days)	Residues Found in Stored Sample, Uncorrected[2] (ppm)	Fresh Fortification Recovery[3] (%)	Apparent Recovery[4] in Stored Sample (%)	Corrected Recovery[5] in Stored Sample (%)
wheat straw	CGA-193469	1.1	0	1.13, 1.11, 1.10, 0.74, 0.82 (av 0.98)	88, 86 (av 87)	100	100
			30	1.16, 1.05, 1.22, 0.97, 0.92 (av 1.06)	79, 96 (av 88)	108	107
			92	0.98, 1.08, 1.15, 1.01, 1.06 (av 1.06)	84, 70 (av 77)	108	122
			184	1.08, 1.11, 1.10, 1.15, 1.10 (av 1.11)	91, 115 (av 103)	113	96
			380	1.29, 1.10, 1.17, 1.09, 1.39 (av 1.21)	101	123	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-193469 were stable in wheat straw stored at -18°C for 380 days.

1995; MRID 44399208

A storage stability study for CGA-184927 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, milled in a cross beater mill with dry ice, placed in polyethylene plastic bags, and stored frozen (-18°C) for two years. Samples were extracted on days 0, 14, 30, 85, 178, 372, 728 for CGA-184927 and on day 749 for CGA-193469. Analytical methods were REM 138.01 (for days 0-178) and REM 138.12 (for the rest of the study) for CGA-184927, and REM 138.10 for CGA-193469. (REM 138.12 is a minor improvement of 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-184927 at approximately 0.1 ppm. Fresh fortification recovery samples were fortified with CGA-184927 at 0.2 ppm. Representative chromatograms of standards, controls, freshly fortified samples, and stored samples for CGA-184927 were submitted. Storage stability fortification recovery data for CGA-184927 in wheat grain are

reported in Table 29 below. As shown in Table 30 below, no residues of the metabolite CGA-193469 (<0.04 ppm) were found after 749 days frozen storage of CGA-184927 fortified samples.

Table 29. Storage Stability Fortification Recovery Data for CGA-184927 in Wheat Grain							
Commodity	Analyte	Residue Level Added (ppm)	Storage Period[1] (days)	Residues Found in Stored Sample, Uncorrected[2] (ppm)	Fresh Fortification Recovery[3] (%)	Apparent Recovery[4] in Stored Sample (%)	Corrected Recovery[5] in Stored Sample (%)
wheat grain	CGA-184927	0.15	0	0.12, 0.12, 0.12, 0.13, 0.13 (av 0.12)	92, 91 (av 92)	100	100
			14	0.13, 0.13, 0.13, 0.13, 0.12 (av 0.13)	91, 93 (av 92)	108	108
			30	0.12, 0.11, 0.12, 0.11, 0.12 (av 0.12)	89, 90 (av 90)	100	102
			85	0.12, 0.10, 0.11, 0.11, 0.11 (av 0.11)	92, 90 (av 91)	92	93
			178	0.10, 0.10, 0.10, 0.09, 0.09 (av 0.10)	87, 86 (av 86)	83	89
			372	0.10, 0.10, 0.09, 0.09, 0.08 (av 0.09)	87, 92 (av 90)	75	77
			728	0.07, 0.07, 0.07, 0.07, 0.07 (av 0.07)	85, 105 (av 95)	58	56

[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 0.2 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).

Table 30. Residues of the Metabolite CGA-193469 in Wheat Grain after 749 Days Frozen Storage of CGA-184927 Fortified Samples.			
Commodity	Analyte	Residues Found, Uncorrected[1] (ppm)	Fresh Fortification Recovery[2] (%)
wheat grain	CGA-193469	<0.04, <0.04, <0.04, <0.04, <0.04	85, 77

[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-184927 declined 7%, 11%, 23% and 4% in wheat grain stored at -18°C for 85, 178, 372, and 728 days, respectively.

1995; MRID 44399209

A storage stability study for CGA-184927 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 placed into double layered polyethylene plastic bags for storage at -18°C for two years. The CGA-184927 residue level added to the storage stability samples was 0.4 ppm. Stored samples were analyzed for CGA-184927 after 0, 15, 29, 85, 182, 380, and 731 days of storage. Stored samples were analyzed for CGA-193469 after 759 days of storage. Analytical methods REM 138.01 and REM 138.12 were used to determine residues of CGA-184927 in stored straw. Analytical method REM 138.10 was used to determine residues of CGA-193469. At each analysis interval, five samples of stored fortified material, one untreated control, and two fresh fortification samples were analyzed. 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-184927 were submitted. Storage stability fortification recovery data for CGA-184927 in wheat straw are

reported in Table 31 below. As shown in Table 32 below, residues of the metabolite CGA-193469 were found after 759 days frozen storage of CGA-184927 fortified samples.

Table 31. Storage Stability Fortification Recovery Data for CGA-184927 in Wheat Straw							
Commodity	Analyte	Residue Level Added (ppm)	Storage Period[1] (days)	Residues Found in Stored Sample, Uncorrected[2] (ppm)	Fresh Fortification Recovery[3] (%)	Apparent Recovery[4] in Stored Sample (%)	Corrected Recovery[5] in Stored Sample (%)
wheat straw	CGA-184927	0.4	0	0.31, 0.33, 0.32, 0.33, 0.34 (av 0.33)	85, 85 (av 85)	100	100
			15	0.31, 0.31, 0.30, 0.29, 0.30 (av 0.30)	88, 87 (av 88)	91	88
			29	0.29, 0.29, 0.29, 0.30, 0.31 (av 0.30)	89, 85 (av 87)	91	89
			85	0.23, 0.24, 0.25, 0.27, 0.23 (av 0.24)	89, 84 (av 86)	73	72
			182	0.22, 0.21, 0.22, 0.22, 0.21 (av 0.22)	87, 88 (av 88)	67	64
			380	0.21, 0.18, 0.23, 0.22, 0.20 (av 0.21)	97, 76 (av 86)	64	63
			731	0.16, 0.15, 0.14, 0.15, 0.17 (av 0.15)	86, 82 (av 84)	45	46

[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 32. Residues of the Metabolite CGA-193469 in Wheat Straw after 759 Days Frozen Storage of CGA-184927 Fortified Samples

Commodity	Analyte	Residues Found, Uncorrected [1] (ppm)	Fresh Fortification Recovery [2] (%)
wheat straw	CGA-193469	0.15, 0.18, 0.17, 0.16, 0.18	84, 82

[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-184927 declined 28%, 36%, 37%, and 54% in wheat straw stored at -18°C for 85, 182, 380, and 731 days, respectively.

1993; MRID 443992-10

A storage stability study for CGA-193469 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 CGA-193469 at 1 ppm and stored at -20°C for two years. Stored samples were analyzed for CGA-193469 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 CGA-193469 into dichloromethane, and analysis of CGA-193469 by HPLC with UV detection. Storage stability fortification recovery data for CGA-193469 in wheat grain are reported in Table 33 below.

Table 33. Storage Stability Fortification Recovery Data for CGA-193469 in Wheat Grain						
Commodity	Analyte	Residue Level Added (ppm)	Storage Period (days)[1]	Residues Found, Uncorrected (ppm)	Fresh Fortification Recovery[2] (%)	Corrected Recovery[3] in Stored Sample (%)
wheat grain	CGA-193469	1.0 ppm	0	not reported	81, 83	104, 99
			14		90, 86	98, 105
			28		89, 89	100, 100
			91		76, 82	84, 105
			184		67, 66	105, 108
			365		94, 94	97, 100
			727		82, 91	92, 95

[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-193469 in wheat grain stored at -20°C is stable for 727 days.

Conclusion

Storage stability data were submitted for CGA-184927 in wheat grain and straw. CGA-184927 declined 7%, 11%, 23% and 44% in wheat grain stored at -18°C for 85, 178, 372, and 728 days, respectively. CGA-184927 declined 28%, 36%, 37%, and 54% in wheat straw stored at -18°C for 85, 182, 380, and 731 days, respectively. The storage times for CGA-184927 in grain and straw in the storage stability studies are adequate to cover maximum storage times for CGA-184927 in grain and straw residue samples (62 days for grain and 70 days for straw in the US residue data and 580 days for grain and straw in the Canadian residue data). (Note: Since degradation was shown for CGA-184927 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-193469 in wheat grain and straw. CGA-193469 is stable in wheat straw stored at -18°C for at least 380 days. Pending receipt of the additional information requested below for MRID 44399210, HED tentatively concludes that CGA-193469 is stable in wheat grain stored at -20°C for at least 727 days. The storage times for CGA-193469 in grain and straw in the storage stability studies are adequate to cover maximum storage times for CGA-193469 in grain and straw residue samples (i.e., 95 days for grain and 141 days for straw in US residue data and 458 days for grain in the Canadian residue data) except for some straw residue samples in Canada (which were stored up to 458 days).

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-184927 and the 218-day storage interval for CGA-193469 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-184927 and CGA-193469 in the Canadian residue samples; however, HED is not recommending that the petitioner attempt to upgrade the Canadian residue studies to an acceptable level.

c. If Canadian studies could be used (i.e., upgraded to acceptable), storage stability data for CGA-193469 on straw for 458 days would be needed 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.

d. No storage stability data were submitted for wheat processed commodities. The storage time between processing and analysis was ≤25 days for CGA-184927; storage stability data are not needed for CGA-184927 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-193469 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-193469 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-193469 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-184927 and CGA-193469 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 240 EC formulation (DISCOVER™) was applied with ground equipment. (DISCOVER™ contains 2 lbs CGA-184927 ai/gal.) The test material was applied to spring wheat at the 1X rate of 28.33 g CGA-184927 ai/A (0.06 lb ai/A). 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) 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-184927 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-193469 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-184927. (The modifications, made to minimize interfering peaks and obtain acceptable recoveries, are listed in Table 3 of MRID 44755303.) CGA-184927 was extracted from wheat substrates with acetonitrile and cleaned up by solvent partition and solid phase extraction. CGA-184927 is 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-184927 were 59-100% (average 87%, n=10) for forage, 82- 110% (average 96%, n=7) for hay, and 71-105% (average 88%, n= 8) for straw at fortifications of 0.05 ppm. Recoveries of CGA-184927 were 74-103% (average 86%, n=9) for grain at fortifications of 0.02 ppm. Recoveries for CGA-184927 are tabulated in Table 34 below.

Table 34. Procedural Recoveries for CGA-184927 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	91
	hay	0.05	101
	straw	0.05	105
		0.50	77
	grain	0.02	91
		0.20	102
OW-HR-211-98/MN	forage	0.05	97
		0.10	94
	hay	0.20	92
	straw	0.05	90
		1.00	83
	grain	0.02	83
		0.10	85
OW-HR-212-98/ND	forage	0.05	85, 96
		0.10	58, 101
		0.50	66
	hay	0.05	84, 87, 108
		0.20	70
		0.50	77
	straw	0.05	77, 85, 94
		0.20	76
		0.50	82
		1.00	71
	grain	0.02	74, 81, 103
		0.05	97
		0.50	77

Table 34. Procedural Recoveries for CGA-184927 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	84, 94
		0.20	85, 100
	hay	0.05	100
		0.50	88
	straw	0.05	76
		0.10	83
	grain	0.02	78
OW-HR-214-98/MT	forage	0.05	59, 68
		0.20	66
	hay	0.05	110
		0.50	82
	straw	0.05	71
		0.20	73
	grain	0.02	79
OW-HR-215-98/SD	forage	0.05	94, 100
		0.10	93
		0.50	75
	hay	0.05	82
	straw	0.05	105
	grain	0.02	88
		0.10	82

Analytical Method REM 138.10, with modifications, was used to determine the metabolite CGA-193469. (The modifications, made to minimize interfering peaks and obtain acceptable recoveries, are listed in Table 3 of MRID 44755303.) CGA-193469 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-193469 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-193469 were 56-100% (average 78%, n= 6) for forage, 74-127% (average 101%, n=3) for hay, 65-111% (average 88%, n= 8) for straw, and 68-127% (average 104%; n=7) for grain at fortifications of 0.05 ppm. Recoveries for CGA-193469 are tabulated in Table 35 below.

Table 35. Procedural Recoveries for CGA-193469 in Wheat Grain, Forage, Hay, and Straw Using Method REM 138.10			
Study #	Commodity	PPM Added	% Recovery
OW-HR-210-98/ND	forage	1.00	85, 90
	hay	0.05	127
	straw	0.05	66
		0.50	65
	grain	0.05	68
		0.20	79
OW-HR-211-98/MN	forage	0.05	100
		0.10	80, 85
	hay	0.20	81
	straw	0.05	50* , 66, 111
		1.00	61, 62, 71*
	grain	0.05	89
		0.10	95
OW-HR-212-98/ND	forage	0.05	56, 94
		0.10	68,106
		0.50	66
	hay	0.05	74
		0.20	68
		0.50	87
	straw	0.05	105, 111
		0.20	79
		0.50	67
		1.00	78
	grain	0.05	101
		0.50	82, 93, 95
OW-HR-213-98/MT	forage	0.20	76, 94

Table 35. Procedural Recoveries for CGA-193469 in Wheat Grain, Forage, Hay, and Straw Using Method REM 138.10			
Study #	Commodity	PPM Added	% Recovery
	hay	0.50	82
	straw	0.05	69
		0.10	66
	grain	0.05	127
OW-HR-214-98/MT	forage	0.05	68, 70
		0.20	76
	hay	0.05	101
		0.50	72
	straw	0.05	55*, 57*, 107
		0.20	61
	grain	0.05	97
OW-HR-215-98/SD	forage	0.05	79
		0.10	74
		0.50	75
	hay	1.00	74
	straw	0.05	65
	grain	0.05	126
		0.10	116

*Analyzed for CGA-193469 by HPLC with mass spectrometric detection (LC/MS) after extraction and cleanup as described above

Residues of CGA-184927 and CGA-193469 were determined in spring wheat from all field trials including the aerial-simulation study and the residue decline study. Residues of CGA-184927 and CGA-193469 are reported in Tables 36-40 below. Controls for CGA-184927 were <0.02 ppm for wheat grain and <0.05 ppm for forage, hay, and straw. Controls for CGA-193469 were <0.05 ppm for wheat grain, forage, hay, and straw, except for one grain control (0.06 ppm in OW-HR-212-98/ND). Representative chromatograms of standards, controls (forage, hay, grain, and straw), fortified samples (forage, hay, grain, and straw), and treated samples (forage, hay, grain, and straw) were submitted for CGA-184927 and CGA-193469. Residues reported in Tables 36-40 are corrected for recoveries. Residues which are uncorrected for recoveries are reported in the raw data (MRID 44755303) and are footnoted in Tables 36-40 when >LOQ. Values reported in the tables as <LOQ were also <LOQ before correction for recoveries.

Fortification recoveries of a few CGA-193469 controls were corrected for residues found in controls before fortification.

Table 36. Residues of CGA-184927 and its Metabolite CGA-193469 in Wheat Forage at 1X			
Study #/State	PHI (days)	CGA-184927 (ppm)	CGA-193469 (ppm)
OW-HR-210-98/ND	0	0.95, 0.51 [1]	8.69, 7.37 [2]
OW-HR-211-98/MN		0.69, 0.55 [3]	6.08, 8.43 [4]
OW-HR-212-98/ND		0.10, 0.09 [5]	2.61, 2.27 [6]
OW-HR-213-98/MT		<0.05, <0.05	1.30, 1.46 [7]
OW-HR-214-98/MT		<0.05, <0.05	7.56, 9.52 [8]
OW-HR-215-98/SD		<0.05, <0.05	1.65, 1.55 [9]
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 [10], <0.05 [10]
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] uncorrected 0.86, 0.46 ppm CGA-184927 with 90.82% recovery
[2] uncorrected 7.86, 6.67 ppm CGA-193469 with 90.45% recovery
[3] uncorrected 0.67, 0.54 ppm CGA-184927 with 97.43% recovery
[4] uncorrected 5.60, 7.77 ppm CGA-193469 with 92.17% recovery
[5] uncorrected 0.082, 0.074 ppm CGA-184927 with 84.76% recovery
[6] uncorrected 2.451, 2.137 ppm CGA-193469 with 94.07% recovery
[7] uncorrected 1.226, 1.374 ppm CGA-193469 with 94.31% recovery
[8] uncorrected 5.108, 6.434 ppm CGA-193469 with 67.57% recovery
[9] uncorrected 1.256, 1.182 ppm CGA-193469 with 76.28% recovery
[10] obtained by LC/MS analysis

Table 37. Residues of CGA-184927 and its Metabolite CGA-193469 in Wheat Hay at 1X			
Study #/State	PHI (days)	CGA-184927 (ppm)	CGA-193469 (ppm)
OW-HR-212-98/ND	0	0.41, 0.53 [1]	5.14, 5.66 [2]
OW-HR-212-98/ND	7	<0.05, <0.05	0.06, 0.12 [3]
OW-HR-212-98/ND	14	<0.05, <0.05	0.28, 0.19 [4]
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 0.344, 0.441 ppm with 83.86% recovery
[2] uncorrected 3.795, 4.185 ppm with 73.89% recovery
[3] uncorrected 0.038, 0.079 ppm with 67.60% recovery
[4] uncorrected 0.210, 0.141 ppm with 75.51% recovery

Table 38. Residues of CGA-184927 and its Metabolite CGA-193469 in Wheat Straw at 1X			
Study #/State	PHI (days)	CGA-184927 (ppm)	CGA-193469 (ppm)
OW-HR-212-98/ND)	46	<0.05, <0.05	<0.05, <0.05
OW-HR-212-98/ND)	53	<0.05, <0.05	<0.05, 0.05
OW-HR-214-98/MT	57	<0.05, <0.05	0.12 [1], 0.11 [2]
OW-HR-211-98/MN	58	<0.05, <0.05	0.09 [3, 5], 0.07 [4, 6]
OW-HR-212-98/ND	60	<0.05, <0.05	<0.05, <0.05
OW-HR-213-98/MT	60	<0.05, <0.05	<0.05, <0.05
OW-HR-215-98/SD	60	<0.05, <0.05	<0.05, <0.05
OW-HR-210-98/ND	61	<0.05, <0.05	<0.05, <0.05
OW-HR-212-98/ND)	67	<0.05, <0.05	<0.05, <0.05

[1] uncorrected 0.102 ppm with 84.32% recovery; 0.17 ppm by LC/MS (uncorrected 0.097 ppm with 56.0% recovery)

[2] uncorrected 0.096 ppm with 84.32% recovery; **0.21 ppm by LC/MS** (uncorrected 0.115 ppm with 56.0% recovery)

[3] 0.08 ppm on reanalysis (uncorrected 0.067 ppm with 86.05% recovery); 0.07 ppm by LC/MS (uncorrected 0.043 ppm with 60.52% recovery)

[4] 0.09 ppm on reanalysis (uncorrected 0.075 ppm with 86.05% recovery); 0.08 ppm by LC/MS (uncorrected 0.047 ppm with 60.52% recovery)

[5] uncorrected 0.059 CGA-193469 with 64.34% recovery

[6] uncorrected 0.044 ppm CGA-193469 with 64.34% recovery

Table 39. Residues of CGA-184927 and its Metabolite CGA-193469 in Wheat Grain at 1X			
Study #/State	PHI (days)	CGA-184927 (ppm)	CGA-193469 (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	61	<0.02, <0.02	<0.05, <0.05
OW-HR-212-98/ND	67	<0.02, <0.02	<0.05, <0.05

Table 40. Residues of CGA-184927 and its Metabolite CGA-193469 in Wheat Grain and Straw at 5X (Study OW-HR-210-98/ND)			
commodity	PHI (days)	CGA-184927 (ppm)	CGA-193469 (ppm)
wheat grain	61	<0.02	<0.05
wheat straw	61	<0.05	<0.05

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, Basle, Switzerland.

MRID 44399215 Williams, Robert K. (1997) Summary of Residue Trials for CGA-184927 on Spring Wheat in Canada, Laboratory Project No. ABR-97082, Study Number 488-97, 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 spring wheat were conducted in Canada in 1989 (3), 1990 (3), 1991 (6), and 1992 (3). In the summary report MRID 44399215, 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) was applied at a

rate of 80 g CGA-184927 ai/ha (0.07 lb ai/A; 1.2X) 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-184927 and REM 138.06 for CGA-193469 except in MRID's 44399328, 44399329, and 44399330. In MRID's 44399328, 44399329, and 44399330, the methods were REM 138.01 for determination of CGA-184927 in grain and straw, REM 138.02 for determination of CGA-193469 in grain, and REM 138.05 for determination of CGA-193469 in straw. The limits of quantitation (see Table 45) were 0.02 ppm for CGA-184927 in grain and forage, 0.05 ppm for CGA-184927 in straw, 0.01 or 0.05 ppm for CGA-193469 in grain, and 0.05 ppm for CGA-193469 in forage and straw. Procedural recoveries are reported in Tables 41-44 below. Residues in grain and straw are reported in Table 45 below. Residue results were not corrected for controls or recoveries.

Table 41. Procedural Recoveries for CGA-184927 in Wheat Grain, Straw, and Forage Using Method REM 138.01			
MRID #	Commodity	PPM Added	% Recovery
44399217	wheat grain	0.04 0.2 0.4	98 86 91
	wheat straw	0.1 0.5 1.0	88 91 93
44399220 44399221 44399225	wheat grain	0.04 0.4	95 89
	wheat straw	0.1 1.0	111 95
44399222	wheat forage	0.04 0.2 0.4	69 77 80
44399223	wheat forage	0.04 0.2 0.4	87 83 82
44399224	wheat forage	0.04 0.2 0.4	83 100 84
44399226 44399227 44399231	wheat grain	0.04 0.4	103 93
	wheat straw	0.1 1.0	94 93
44399228 44399229 44399230	wheat grain	0.04 0.4	74 91
	wheat straw	0.1 1.0	80[1] 82[1]

[1] Recoveries of CGA-184927 in straw were corrected for the controls.

Table 42. Procedural Recoveries for CGA-193469 in Wheat Grain, Straw, and Forage Using Method REM 138.06			
MRID #	Commodity	PPM Added	% Recovery
44399217 44399218 44399219	wheat grain	0.04 0.2 0.4	89 91 92
	wheat straw	0.1 0.5 1.0	70 81 91
44399220 44399221 44399225	wheat grain	0.1 1.0	71[1] 89[1]
	wheat straw	0.1 1.0	89 94
44399222	wheat forage	0.1 0.5 1.0	85 88 84
44399223	wheat forage	0.1 0.5 1.0	94 91 92
44399224	wheat forage	0.1 0.5 1.0	80 69 73
44399226 44399227 44399231	wheat grain	0.1 1.0	73 73
	wheat straw	0.1 1.0	104 64

[1] Recoveries of CGA-193469 in grain were corrected for control.

Table 43. Procedural Recoveries for CGA-193469 Using REM 138.02 in Wheat Grain			
MRID #	Commodity	PPM Added	% Recovery
44399228 44399229 44399230	wheat grain	0.1 1.0	75 99

Table 44. Procedural Recoveries for CGA-193469 Using REM 138.05 in Wheat Straw			
MRID #	Commodity	PPM Added	% Recovery[1]
44399228 44399229 44399230	wheat straw	0.1 1.0	107 83

[1] Recoveries of CGA-193469 in straw were corrected for the controls.

Table 45. Residues of the Active Ingredient CGA-184927 and its Metabolite CGA-193469 in Wheat Grain, Straw, and Forage after One Application at a Rate of 80 g ai/ha (0.07 lb ai/A)						
MRID #	Formulation/ Harvest Date	Location	Commodity	PHI (days)	CGA-184927 (ppm)	CGA-193469 (ppm)
44399217[1, 2, 5]	240 EC Oct/92	Estlin, Saskatchewan (Zone 7)	grain straw	105 105	<0.02 (n=4) <0.05 (n=4)	<0.01 (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)	<0.01 (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)	<0.01 (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)	0.08,0.08, 0.05 <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, 0.06, 0.07 <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 <0.05 <0.05 <0.05	<0.05 (n=4) **0.28** **0.33** **0.45** **0.33**
44399226[1, 3, 6]	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[3]	100 EC Aug/89	Teulow, Manitoba (Zone 5)	grain straw	69 69	<0.02 (n=3) <0.05 (n=3)	<0.05 (n=3) <0.05 (n=3)
44399229[3]	100 EC Aug/89	Indian Head, Saskatchewan (Zone 7)	grain straw	55 55	<0.02 (n=3) <0.05 (n=3)	<0.05 (n=3) <0.05 (n=3)
44399230[3]	100 EC Aug/89	Davin, Saskatchewan (Zone 7)	grain straw	86 86	<0.02 (n=3) <0.05 (n=3)	<0.05 (n=3) <0.05 (n=3)
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-184927 and <0.01 ppm CGA-193469 in grain, and <0.05 ppm CGA-184927 and <0.05 ppm CGA-193469 in straw.

[3] Controls were <0.02 ppm CGA-184927 and <0.05 ppm CGA-193469 in grain, and <0.05 ppm CGA-184927 and <0.05 ppm CGA-193469 in straw.

[4] Controls were <0.02 ppm CGA-184927 and <0.05 ppm CGA-193469 in forage.

[5] Although the title indicates that the field trial was conducted in Crossfield, Alberta, the data indicate that the location was Estlin, Saskatchewan.

[6] Although the title indicates that the field trial was conducted in Strathmore, Saskatchewan, the data indicate that the location was Strathmore, Alberta.

Summary

In the US, six field trials on spring wheat to determine residues of CGA-184927 and CGA-193469 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 240 EC formulation (DISCOVER™) was applied with ground equipment at the rate of 28.33 g CGA-184927 ai/A (0.06 lb ai/A; 1X). A 5X rate was also applied in one study (OW-HR-210-98/ND) 61 days before harvest. 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-184927 by HPLC with ultraviolet detection. The limit of quantitation for CGA-184927 (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-184927 were 59-100% (average 87%, n=10) for forage, 82-110% (average 96%, n=7) for hay, and 71-105% (average 88%, n= 8) for straw at fortifications of 0.05 ppm. Recoveries of CGA-184927 were 74-103% (average 86%, n=9) for grain at fortifications of 0.02 ppm. Analytical method REM 138.10, with modifications, was used to determine the metabolite CGA-193469 by HPLC with UV detection. The limit of quantitation for CGA-193469 (based on the lowest acceptable recovery level) was 0.05 ppm for forage, hay, straw, and grain. Recoveries of CGA-193469 were 56-100% (average 78%, n= 6) for forage, 74-127% (average 101%, n=3) for hay, 65-111% (average 88%, n= 8) for straw, and 68-127% (average 104%; n=7) for grain at fortifications of 0.05 ppm. Selected samples were analyzed for CGA-193469 by HPLC with mass spectrometric detection (LC/MS). Residues in the US studies at 1X were <0.05 ppm CGA-184927 + <0.05 ppm CGA-193469 in wheat forage at a 7-day PHI (one study) and a 29-32 day PHI (6 studies); <0.05 ppm CGA-184927 + <0.05 ppm CGA-193469 in wheat hay at a 30-day PHI; <0.05 ppm CGA-184927 + ≤0.21 ppm CGA-193469 in wheat straw at an approximately 60-day PHI; and <0.02 ppm CGA-184927 + <0.05 ppm CGA-193469 in grain at a 60-day PHI. Residues at 5X and a 61-day PHI were <0.02 ppm CGA-184927 and <0.05 ppm CGA-193469 in wheat grain; and <0.05 ppm CGA-184927 + <0.05 ppm CGA-193469 in wheat straw.

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) was applied at a rate of 80 g CGA-184927 ai/ha (0.07 lb ai/A; 1.2X) 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-184927 and REM 138.06 for CGA-193469

except in MRID's 44399328, 44399329, and 44399330. In MRID's 44399328, 44399329, and 44399330, the methods were REM 138.01 for determination of CGA-184927 in grain and straw, REM 138.02 for determination of CGA-193469 in grain, and REM 138.05 for determination of CGA-193469 in straw. The limits of quantitation for CGA-184927 using REM 138.01 were 0.02 ppm in wheat grain and forage and 0.05 ppm in straw. The limits of quantitation for CGA-193469 using REM 138.06 were 0.01 or 0.05 ppm in wheat grain and 0.05 ppm in forage and straw. The limits of quantitation for CGA-193469 in wheat grain using REM 138.02 and in wheat straw using REM 138.06 were 0.05 ppm. Recoveries for CGA-184927 using REM 138.01 were 74-103% (average 92%, n=4) in wheat grain and 69-87% (average 80%, n=3) in wheat forage at a fortification level of 0.04 ppm, and 80-111% (average 93%, n=4) in wheat straw at a fortification level of 0.1 ppm. Recoveries for CGA-193469 at a fortification level of 0.1 ppm using REM 138.06 were 71-73% (average 72%, n=2) in wheat grain, 80-94% (average 86%, n=3) in wheat forage, and 70-104% (average 88%, n=3) in wheat straw. Recoveries for CGA-193469 at a fortification level of 0.1 ppm were 75% (n=1) for wheat grain using REM 138.02 and 107% (n=1) for wheat straw using REM 138.05. Residues in Canada were <0.02 ppm CGA-184927 + <0.05 ppm CGA-193469 in wheat grain at PHI's ranging from 55-105 days, <0.05 ppm CGA-184927 + ≤0.45 ppm CGA-193469 in straw at PHI's ranging from 55-105 days, and <0.02 ppm CGA-184927 + <0.05 ppm CGA-193469 in forage at a 7-day PHI.

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-193469 were less than the limit of quantitation (LOQ) in grain, forage, and hay in the US and in grain and forage in Canada at these PHI's; for straw, residues of the parent were <LOQ but maximum residues of 0.21 ppm CGA-193469 were found in the US (MT; 57-day PHI) and maximum residues of 0.45 ppm CGA-193469 were found in Canada (Manitoba/1991 trials; 60-day PHI). (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-193469 was 0.05 ppm for grain, forage, hay, and straw. 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-193469 were 0.01 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. 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. 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.) 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 for the combined residues of clodinafop-propargyl (propanoic acid, (R)2-[4-[(5-chloro-3-fluoro-2-pyridinyl)oxy]phenoxy]-, 2-propynyl ester) and its metabolite (R)(2-[4-(5-chloro-3-fluoro-2-pyridinyloxy) phenoxy]-propanoic acid) at levels of 0.10 ppm for wheat grain, forage, and hay, and 0.50 ppm for wheat straw. These levels were obtained by adding the limits of quantitation and/or levels of residues for CGA-184927 and CGA-193469. (Note that an "(R)" is needed in the chemical name of the parent to designate the "R" isomer.)

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 twelve studies and only forage was analyzed 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 submitted/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 240 EC formulation (DISCOVER™) was applied to spring wheat at the rates of 1X [28.33 g CGA-184927 ai/A (0.06 lb ai/A)] and 5X. 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-184927 and ≤51 days (except for 125 days for germ) for CGA-193469.

Analytical Method REM 138.01, with modifications for some substrates, was used to determine residues of CGA-184927. CGA-184927 was extracted from wheat grain and processed grain fractions with acetonitrile and cleaned up by solvent partition and solid phase extraction. CGA-184927 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 are reported in Table 46 below:

Table 46. Procedural Recoveries of CGA-184927 from Grain and its Processed Commodities		
Matrix	Fortification Level (ppm)	% Recovery
grain	0.02	97
aspirated grain	0.10	63
germ	0.02	89
bran	0.20	76
middlings	0.02	99
shorts	0.50	95
low grade flour	0.02	88
patent flour	1.00	84

Analytical Method REM 138.10, with modifications, was used to determine the metabolite CGA-193469. CGA-193469 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 are reported in Table 47 below:

Table 47. Procedural Recoveries of CGA-193469 from Grain and its Processed Commodities		
Matrix	Fortification Level (ppm)	% Recovery
grain	0.05	121
aspirated grain	1.00	126
germ	0.05	70
	0.05	82[1]
	0.20	94[1]
bran	0.20	61
	0.20	129
middlings	0.05	124
shorts	0.50	86
low grade flour	0.05	74
patent flour	1.00	91

[1] analyzed for CGA-193469 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 48 below. Controls for CGA-184927 were <0.02 ppm for grain and the processed commodities. Controls for CGA-193649 were <0.05 ppm for grain and processed commodities except for bran (0.07 ppm, with a repeat analysis at 0.05 ppm). 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-193469. Residues in treated samples were not corrected for controls. Residues reported in Table 48 are corrected for recoveries. Residues which are uncorrected for recoveries are reported in the raw data (MRID 44755303). Values reported in the table as <LOQ were also <LOQ before correction for recoveries. Fortification recoveries of a few CGA-193469 controls were corrected for residues found in controls before fortification.

Table 48. Residues of CGA-184927 and its Metabolite CGA-193469 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-184927 (ppm)		CGA-193469 (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	0.08 <0.05[2]
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 28.33 g CGA-184927 ai/A (0.06 lb ai/A).
[2] Value obtained by LC/MS analysis of a second subsample

Summary

Wheat grain treated with a 240 EC formulation of CGA-184927 (Discover™) at 1X and 5X was processed. Residues of CGA-184927 and its metabolite CGA-193469 were <0.02 ppm in wheat grain and <0.05 ppm in the processed commodities (aspirated grain fractions, germ, bran, middlings, shorts, low grade flour, and patent flour). Wheat germ from the 5X study containing a residue of 0.08 ppm CGA-193469 was reanalyzed by LC/MS at <0.05 ppm CGA-193469.

Conclusion

Pending submission of storage stability data on CGA-193469 in processed commodities (see storage stability section of this review), HED concludes that no concentration of CGA-184927 or CGA-193469 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 44399205 and 44399204), a lactating goat was dosed with [U-^{14}C]phenyl CGA-184927 for ten consecutive days at a dose level of 5.9 ppm. Maximum total radioactive residues found at the 5.9 ppm dose level were 0.017 ppm in milk, 0.001 ppm in muscle, 0.003 ppm in fat, 0.011 ppm in liver, and 0.077 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 49 and 50 below.

Table 49. 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 straw	10	88	0.50	0.06
wheat hay	25	88	0.10	0.03
wheat milled byproducts	40	88	0.10	0.05
Total	100			0.24

Table 50. Maximum Theoretical Residues in the Diet of Dairy Cattle

Feedstuff	% of Diet	% Dry Matter	Proposed Tolerance (ppm)	Dietary Burden (ppm)
wheat forage	60	25	0.10	0.24
wheat straw	10	88	0.50	0.06
wheat hay	30	88	0.10	0.03
Total	100			0.33

Residues found in milk, muscle, fat, kidney, and liver in the goat metabolism study at the 5.9 ppm dose level and extrapolated to a 1X (0.33 ppm) dose level are tabulated in Table 51 below.

Table 51. Total Radioactive Residues (TRR) in a Goat from a 5.9 ppm Dosing Level and Extrapolated to 1X (0.33 ppm)

Goat Substrates	TRR from 5.9 ppm Dosing Level (ppm)	TRR Extrapolated to 1X (ppm)
milk	0.017[3]	0.00095
muscle[1]	0.001	0.00006
fat[2]	0.003	0.00017
kidney	0.077	0.00431
liver	0.011	0.00061

[1] pool of forequarter muscle, hindquarter muscle, and tenderloin
[2] pool of renal fat, omental fat, and subcutaneous fat
[3] maximum residues in milk

Summary

Based on the goat metabolism study and the maximum theoretical dietary burden, maximum radioactive residues (expressed as CGA-184927 equivalents) in goat tissues and milk resulting from the proposed use on wheat would be 0.00095 ppm in milk, 0.00006 ppm in muscle, 0.00017 ppm in fat, 0.00431 ppm in kidney, and 0.00061 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 44399206 and 44399204), four laying hens were dosed with [^{14}C-phenyl]CGA-184927 for 14 consecutive days at a dose level of 4.6 ppm. Maximum total radioactive residues found in muscle, fat, liver, and eggs at the 4.6 ppm dose level were 0.002 ppm in muscle, 0.065 ppm in fat, 0.192 ppm in liver, and 0.0342 ppm in eggs.

Poultry feedstuffs from wheat are grain and milled byproducts. No detectable residues (<0.02 ppm CGA-184927 and <0.05 ppm CGA-193469) 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 52 below.

Table 52. 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 4.6 ppm dose level and extrapolated to a 1X (0.10 ppm) dose level are tabulated in Table 53 below:

Table 53. Total Radioactive Residues in Hens from a 4.6 ppm Dosing Level and Extrapolated to 1X (0.10 ppm)

Commodity	Maximum TRR from 4.6 ppm Dose Level (ppm)	TRR Extrapolated to 1X (ppm)
muscle	0.002	0.00004
fat	0.065	0.0014
liver	0.192	0.0042
eggs	0.0342	0.00074

Summary

Based on the poultry metabolism study and the maximum theoretical dietary burden, maximum radioactive residues (expressed as CGA-184927 equivalents) in poultry tissues and eggs resulting from the proposed use on wheat would be 0.00004 ppm in muscle, 0.0014 ppm in fat, 0.0042 ppm in liver, and 0.00074 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 (1992; MRID 44399190)

A confined rotational crop study for clodinafop-propargyl was submitted (see citation below). The performing laboratory was Novartis Crop Protection AG, Basle, Switzerland.

MRID 44399190 Stingelin, Dr. J. (1992) Outdoor Confined Accumulation Study on Rotational Crops after Application of [2-^{14}C-Pyridyl] CGA-184927, Project 87JS11, Laboratory Project Report 16/92, Nexus Study Number 498-92, unpublished study sponsored by Novartis Crop Protection, Inc., 37 pp.

In-life phase

[2-^{14}C-pyridyl] CGA-184927 formulated as an emulsifiable concentrate (100 EC) was applied once post-emergently to field spring wheat (in a 6 m^2 plot) in a heavy loam soil in St. Aubin, Switzerland in 1987. The radiochemical purity of the test substance was >98%. The specific activity was 1.65 MBq/mg (44.5 μCi/mg). The application rate was 125 g clodinafop-propargyl ai/ha (0.11 lb ai/A; approximately 2X). Mature wheat plants were removed 91 days after treatment. Four rotational crops (lettuce, winter wheat, sugar beets, and corn) were planted. (Lettuce was transplanted; the other rotational crops were sown.) The times between application of the herbicide and planting of the rotational crops were 98 days for lettuce, 159 days for winter wheat, 379 days for sugar beets, and 379 days for corn.

Total radioactive residues (TRR)

Total radioactive residues were determined by combustion and liquid scintillation counting. The total radioactive residues of [2-^{14}C-pyridyl] clodinafop-propargyl in rotational crops after application to spring wheat are reported in Table 54 below.

Table 54. Total Radioactive Residues in Rotational Crops after Application of [2-^{14}C-pyridyl] CGA-184927 to Spring Wheat

Crop/Plant Part	Days between Application of the Herbicide 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-184927 Equivalents (ppm)
Lettuce, ½ mature, heads	98	42	*	0.001
Lettuce, mature, heads	98	68	2	<0.001
Winter wheat, fall cutting whole tops	159	41	0	<0.001
Winter wheat, ¼ mature whole tops	159	219	1	<0.001
Winter wheat, ½ mature whole tops	159	240	1	<0.001
Winter wheat, mature	159		21	
stalks		269		0.001
husks		269		<0.001
grains		269		<0.001
Sugar Beets, ¼ mature	379		3	
tops		49		0.001
roots		49		0.001
Sugar Beets, ½ mature	379		1	
tops		81		<0.001
roots		81		<0.001
Sugar Beets, mature	379		1	
tops		151		<0.001
roots		151		<0.001
Corn, ¼ mature, whole tops	379	49	4	<0.001

Crop/Plant Part	Days between Application of the Herbicide 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-184927 Equivalents (ppm)
Corn, ½ mature whole tops	379	81	1	<0.001
Corn, mature	379		43	
stalks		151		0.001
cobs		151		<0.001
grains		151		<0.001

* The date of analysis of ½ mature lettuce was given as 8/3/87, whereas the sampling date was given as 10/1/87. This needs correction.

Extraction and Hydrolysis of Residues

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

Characterization/Identification of Residues

Because of the low radioactivity (≤0.001 ppm) in the rotational crops, no attempt was made to characterize/identify the residues.

Storage Stability

At harvest, 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 54 above.

Summary

Following one application of [2-^{14}C-pyridyl]clodinafop-propargyl to spring wheat at the rate of 125 g CGA-184927 ai/ha (0.11 lb ai/A; approximately 2X), 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 [2-^{14}C-pyridyl]CGA-184927 and planting of the rotational crops: 98 days for lettuce, 159 days for winter wheat, 379 days for sugar beets, and 379 days for corn).

Conclusion

The submitted confined rotational crop data are adequate for a permanent tolerance provided that a) rotational crop restrictions are placed on the label of 98 days (or 3 months) for lettuce and other leafy vegetables, 159 days (or 5 months) for small grains (except wheat), and one year (or 12 months) for all other crops; and b) the dates of harvest and/or analysis of ½ mature lettuce are corrected.

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 0.06 lb CGA-184927 ai/A.

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 5). Canada has recently reviewed a petition on wheat. At this time, Canada has a default MRL of 0.1 mg/kg for clodinafop-propargyl on wheat. A Mexican limit exists for clodinafop-propargyl on wheat at 0.050 ppm. There are no Codex tolerances for clodinafop-propargyl 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 Clodinafop-propargyl and its Metabolites
Attachment 2: Proposed Plant Metabolism Pathway of [^{14}C-Phenyl]CGA-178486 (enantiomer) and [2-^{14}C-Pyridyl]CGA-184927
Attachment 3: Proposed Goat Metabolism Pathway of Clodinafop-propargyl (CGA-184927)
Attachment 4: Proposed Hen Metabolism Pathway of Clodinafop-propargyl
Attachment 5: International Residue Limit Status sheet

cc: RF, SF, N. Dodd (810C), PM# 23, PP#7F04924, 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

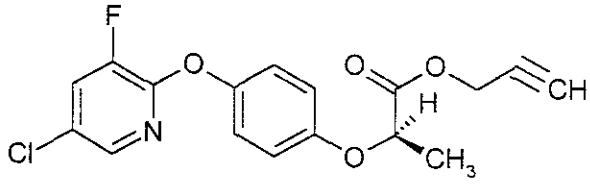
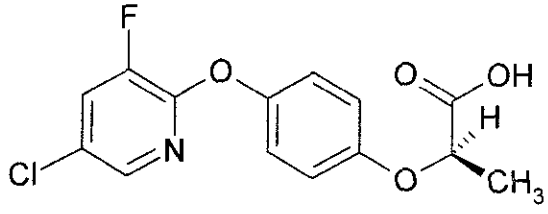
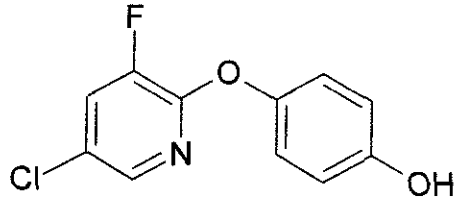
Table 55. Names and Structures of Clodinafop-propargyl and its Metabolites	
clodinafop-propargyl CGA-184927 (R) (2-[4-[(5-chloro-3-fluoro-2-pyridinyl)oxy]phenoxy]-propanoic acid, 2-propynyl ester) and CGA-178486 (R,S) (2-[4-[(5-chloro-3-fluoro-2-pyridinyl)oxy]phenoxy]-propanoic acid, 2-propynyl ester)	
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	

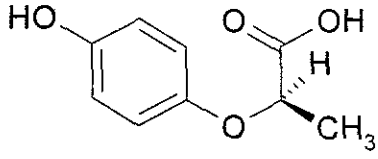
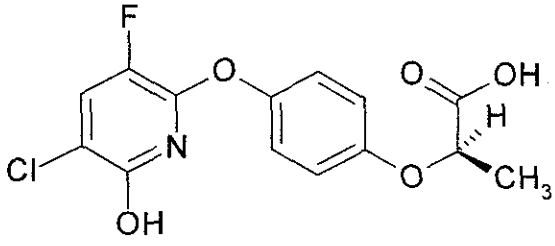
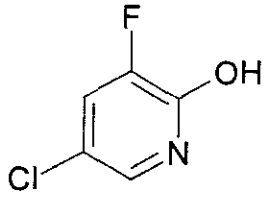
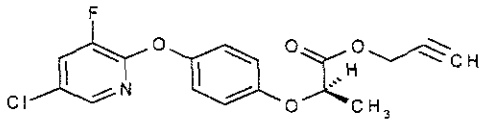
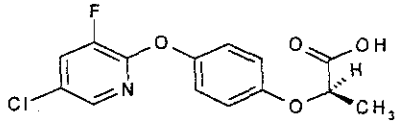
Table 55. Names and Structures of Clodinafop-propargyl and its Metabolites	
CGA-214111 (R) (2-(4-hydroxy-phenoxy)-propanoic acid) and CGA-146445 Metabolite II_3/ Metabolite II_1 (R,S) (2-(4-hydroxy-phenoxy)-propanoic acid)	
Metabolite II_2 (R,S) (2-[4-(6-hydroxy-5-chloro-3-fluoro-2-pyridinyloxy)phenoxy]-propanoic 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	

Figure 1. Proposed Wheat Metabolism Pathway of [^{14}C-Phenyl]CGA-178486/CGA-184927 and [2-^{14}C-Pyridyl]CGA-184927

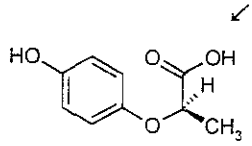


I
(R) CGA-184927/ (R,S) CGA-178486



→ Sugar Conjugate

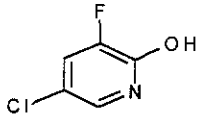
II_4/ (R) CGA-193469/ (R,S) CGA-144462



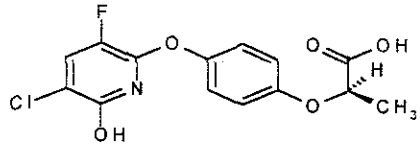
II_3/(R)CGA-214111/
(R,S) CGA-146445

↓

Sugar Conjugate



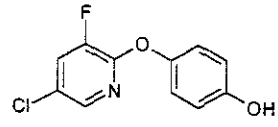
IV_2



II_2

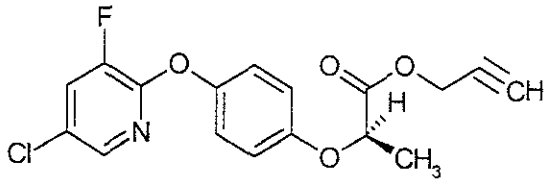
↓

Sugar Conjugate

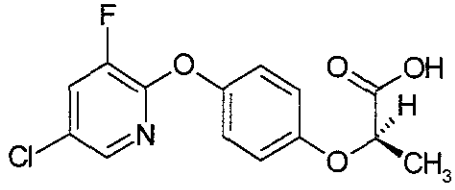


II_5
CGA-193468

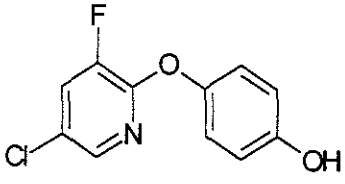
Figure 2. Proposed Goat Metabolism Pathway of Clodinafop-propargyl (CGA-184927)



CGA-184927



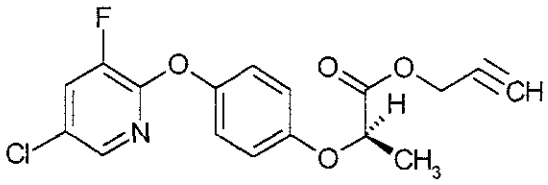
CGA-193469
(urine, feces, tissues)



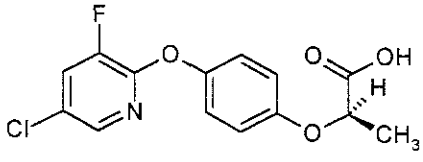
CGA-193468
(liver, kidney)

hybrid acylglycerides
(milk, adipose tissues, liver, kidney)

Figure 3. Proposed Hen Metabolism Pathway of Clodinafop-propargyl

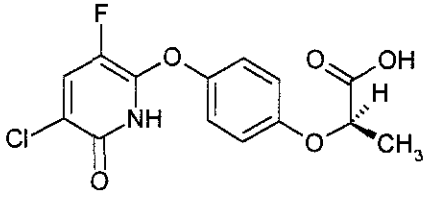


CGA-184927
(excreta)

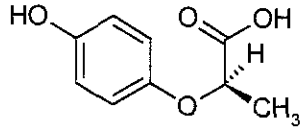


⇄ hybrid acylglycerides

CGA-193469
(excreta, egg white, muscle)



Metabolite 1E
(excreta, liver, kidney,
skin and attached fat)



CGA-214111
(excreta, kidney, liver)

ATTACHMENT 5

INTERNATIONAL RESIDUE LIMIT STATUS

Chemical Name: 2-[4-[(5-chloro-3-fluoro-2-pyridinyl)oxy]phenoxy]-propanoic acid, 2-propynyl ester	Common Name: clodinafop-propargyl	☒ Proposed tolerance ☐ Reevaluated tolerance ☐ Other	Date: 3/3/00

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: 7F04924 DP Barcode: D246730 Other Identifier:
Residue definition (step 8/CXL):	Reviewer/Branch: Nancy Dodd, RAB3
	Residue definition:clodinafop-propargyl and its acid metabolite (R)(2-[4-(5-chloro-3-fluoro-2-pyridinyloxy)phenoxy]-propanoic acid)

Crop (s)	MRL (mg/kg)	Crop(s)	Tolerance (ppm)
		wheat grain	0.10
		wheat forage	0.10
		wheat hay	0.10
		wheat straw	0.50

Limits for Canada	Limits for Mexico
☐ No Limits ☐ No Limits for the crops requested	☐ No Limits ☐ No Limits for the crops requested
Residue definition: clodinafop-propargyl	Residue definition: clodinafop-propargyl

Crop(s)	MRL (mg/kg)	Crop(s)	MRL (mg/kg)
wheat	0.1	wheat	0.050
Notes/Special Instructions:			

Rev. 1998

13544

002804

Chemical:	**Invalid PC Code**
PC Code:	**125203**
HED File Code	**11000 Chemistry Reviews**
Memo Date:	**04/07/2000**
File ID:	**DPD246730**
Accession Number:	**412-01-0056**

HED Records Reference Center
12/08/2000