



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

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

July 13, 1999

MEMORANDUM

SUBJECT: Trifloxystrobin. Results of HED Metabolism Assessment Review Committee Meeting held 6/15/99. DP Barcode 257835

TO: George Kramer, Executive Secretary
HED Metabolism Assessment Review Committee

FROM: Fred Ives, Chemist
Health Effects Division (7509C) *Fred Ives*
and
Bill Greear, Toxicologist
Registration Action Branch 3
Health Effects Division (7509C)

THRU: Richard Loranger, Chair *R. Loranger*
HED Metabolism Assessment Review Committee
Health Effects Division (7509C)

A. Summary of Deliberations

The Committee reviewed and discussed material in the HED briefing memorandum for the fungicide trifloxystrobin [(E,E)-methoxyimino-[2-[1-(3-trifluoromethyl-phenyl)-ethylideneaminoxymethyl]-phenyl]acetic acid methyl ester, (code CGA-279202) (Fred Ives, Maxie Nelson, William Greear, 6/9/99) and in an EFED memo for the same chemical on water (Ron Bloom, 6/9/99). Included in the HED memo was a summary of plant (apple, cucumber, peanut, wheat) and animal (rat, goat, hen) metabolism, rotational crop, analytical methodology and magnitude of the residue studies. Also included in the HED memo were two directed questions:

1. Does the Committee concur with the petitioner's recommendation that trifloxystrobin be the only residue regulated in plant and animal commodities?
2. What residue does the committee recommend for risk assessment purposes.

The Committee considered a number of factors in its deliberations: that both acute (2.5 mg/kg bw) and chronic (0.05 mg/kg bw) reference doses had been estimated, that EFED had some concern for the environmental persistence of the primary environmental degradant and acid metabolite CGA-321113, the lack of any substantial toxicology information for CGA-321113, that

6. The MARC concluded that any future petitions for uses on leafy vegetables, cereals or other crops not specified in 5 above would require additional metabolism studies.
7. The MARC recommended that clarification be sought from the registrant as to whether the configurational isomers of trifloxystrobin and its acid metabolite CGA-321113 are determined by the analytical procedure.
8. The residues of concern in drinking water are the parent and acid metabolite. The latter is more persistent and more mobile than the parent.

A. Attendance

1. MARC Members attending

Sanjivani Diwan	Richard Loranger (chair)
Leung Cheng	Chris Olinger
George Kramer	Alberto Protzel
Nancy Dodd	William Wassell

2. MARC Members absent

Kit Farwell, Nelson Thurman, John Doherty

3. Other responsible scientists participating

Mary Rust	Maxie Nelson
Fred Ives	Stephen Dapson
William Greear	Ghazi Dannan .
Ron Bloom	Stephen Carey

cc: HED Metabolism Committee file (G.Kramer), Cynthia Giles-Parker/Janet Whitehurst (PM 22), Francis (Dick) Griffith (BEAD-7503C), Mary Rust, PP#8F04955

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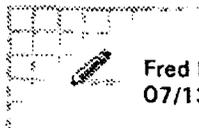
To: Fred Ives/DC/USEPA/US@EPA
cc:
Subject: Re: Trifloxystrobin MARC Decision memo 

Fred,

The MARC decision memo looks fine to me. I concur. Hope to be in tomorrow to sign it.

Bill

Fred Ives



Fred Ives
07/13/99 08:55 AM

To: William Greear/DC/USEPA/US@EPA
cc: Richard Loranger/DC/USEPA/US@EPA, Randolph Perfetti/DC/USEPA/US@EPA, Margaret Stasikowski/DC/USEPA/US@EPA, Maxie Nelson/DC/USEPA/US@EPA
Subject: Trifloxystrobin MARC Decision memo

Bill, I will leave a copy of the attached MARC decision memo (signed by me) and dated July 13th on your desk for your signature, after which I will deliver to Rick. If you are not coming in, please indicate via e:mail your concurrence or not so I can get it to Rick.

Rick, the document is essentially the same as the June 24th draft considered by MARC, except for (1) revising "conformational" isomers to "configurational" isomers per ChemSAC discussion (2) updating the decision for trifluoroacetic acid to reflect Alberto's note (3) moving the decision for cyano compounds from the text to the numbered decisions and adding a T:drive address, I hope in accordance with MARC SOP.



trflxyMARCdec3.

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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: June 9, 1999

SUBJECT: PP#8F04955. Reduced Risk New Chemical: Trifloxystrobin (ISO-proposed common name CGA-279202) in or on imported bananas, cucurbit vegetables, grapes, peanuts, peanut hay, pome fruit and apple pomace. Briefing memorandum for June 15, 1999 Meeting of the MARC. PC Code: 12942

FROM: Fred Ives, Chemist
HED (7509C)

and

Maxie Jo Nelson, Chemist
RAB2/HED (7509C)

and

William Greear, Toxicologist
Registration Action Branch 3/HED (7509C)

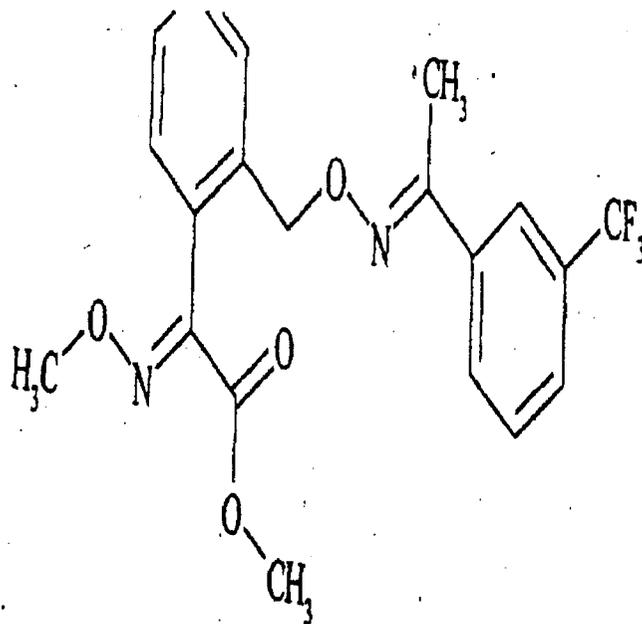
THRU: Richard Loranger, Branch Senior Scientist
RAB2/HED (7509C)

TO: George Kramer, MARC Executive Secretary
RAB1/HED (7509C)

This memo provides a briefing for the June 15, 1999 MARC consideration of trifloxystrobin. The chemistry portion is based on the contractor review and is intended to be in accordance with the 6/23/98 MARC SOP. Attached to this memo for reference you will find:

1. Table 1 - Trifloxystrobin metabolism in plants - a summary. This summary information was extracted as representative information from tables presented in the contractor review.
2. Tables 18a and 18b. These are summaries (TFMP and GP labels respectively) of the goat metabolism study taken from the contractor review.
3. Table 21a taken from the contractor review. It summarizes metabolites found in poultry with the TFMP label and is intended to be representative for the committee, although information on the GP label is also available.

4. Plant metabolism schematics - No metabolism schematics are included in the contractor review. Fig. 35 apple metabolism schematic is a good representative for plant metabolism. It is taken from MRID 444968-22. MRID schematics from original studies are also attached for cucumber (Fig. 18), wheat (Fig. 14) and peanuts (Fig. 204).
5. Animal metabolism schematics - Fig. 42, a goat metabolism study from MRID 444968-18 is a good representative for animal metabolism. Also attached are hen metabolism schematics (Fig. 45 and 32).
6. Fig. 34 Rat metabolism as part of the toxicology contribution.
7. Attachment II, Fig. 1 taken from the contractor review. It summarizes chemical names and structures of trifloxystrobin in plants and animals and identifies the matrix in which each was identified.



TRIFLOXYSTROBIN

RESIDUE CHEMISTRY SECTION

Use information/Identification of Chemical

Trifloxystrobin [(E,E)-methoxyimino-[2-[1-(3-trifluoromethyl-phenyl)-ethylideneaminoxymethyl]-phenyl]acetic acid methyl ester], [code CGA-279202] is one of a new class of β -methoxyacryl ester (MAE) fungicides which are synthetic analogs of strobilurin A, an antifungal metabolite of the fungus *Strobilurus tenacellus*. Via PP#8F04955 Novartis Crop Protection, Inc. proposes permanent tolerances for CGA-279202 (parent compound only) in conjunction with Section 3 uses of a 50% water dispersible granular formulation (CGA-279202 50WG) on imported bananas (0.1 ppm), cucurbit vegetables (0.25 ppm), grapes (1.5 ppm), peanuts (0.02 ppm), peanut hay (4.0 ppm), pome fruits (0.4 ppm) and apple pomace 1.5 ppm). While three conformational isomers of trifloxystrobin (CGA-331409, CGA-357261 and CGA-357262) may occur at low levels, they are not proposed to be included in the tolerance nor is whether they would be determined by the proposed analytical method addressed. It is likely that they would be determined if present.

Uses in summary:

	<u>Formulation</u>	No. <u>Appl.</u>	Interval <u>Days</u>	<u>lb. ai/appl</u>	lb ai/ <u>season</u>	PHI <u>Days</u>
bananas*	75 g/L EC	10	—	0.1	1	—
cucurbits	50% WDG	8	7-14	0.063-0.125	1	0
grapes	50% WDG	6	7-21	0.063-0.094	0.563	14
peanuts	50% WDG	8	10-14	0.063-0.094	1	14
pome fruits	50% WDG	5	7-14	0.063-0.094	0.3125	14

* Good Agricultural Practices (GAP = use information) for bananas is lacking. That indicated was the use in field trials.

Summary of Plant and Livestock Metabolism Studies

Plants

The nature of residue studies for trifloxystrobin in plants have been conducted on apples, cucumbers, peanuts and wheat. In separate experiments for each crop trifloxystrobin is labeled in the glyoxyphenyl (GP) or trifluoromethylphenyl (TFMP) rings. Initial extractions generally were with acetonitrile (ACN):water, except in the case of peanut nutmeats it was with hexane. A wide variety of separative techniques were utilized, including liquid/liquid partitioning, column chromatography and analyses by TLC (1-D, 2-D, normal phase, reversed phase), LSC or combustion/LSC, HPLC, MS (different types), NMR and confirmations via derivatization. Various fractions were subjected to acid, base or enzymatic hydrolysis prior to further analyses. Table 1, extracted from the contractor's review, briefly summarizes representative results for apples, cucumbers, peanuts and wheat.

Metabolism indicated for plants includes hydrolysis of the methyl ester to the CGA-321113 acid metabolite, hydroxylation on the TFMP ring, oxidation of the aminooxymethyl group on the bridge, conjugations with sugars and breakdown of the methoxyiminoacetic acid side chain and minor cis/trans isomerization.

Apples - 67-95% of TRR was characterized/identified in foliage, surface rinse, peel and flesh. From the GP label, radioactivity was 86.9, 11.2 and 1.9% in surface rinse, peel and flesh one hour after the fourth GAP application (similar with the TFMP label). At the 14 day proposed GAP PHI with both labels trifloxystrobin was the major residue (ca. 81-83%) in whole apple with three cis-trans isomers of trifloxystrobin (CGA-331409, 357261, and 357262) at $\leq 5.2\%$ each or $<11\%$ total of the TRR. Approximately 1% was the acid metabolite CGA-321113 or its two isomers CGA-373466 or -373465. Lesser metabolites were also reported. Results were similar with both labels.

Cucumbers - Residues were characterized from the GP and TFMP labels in foliage and in both small and large greenhouse grown cucumbers which were sampled after 3 applications at approximate GAP, both at the 0 day PHI (1 hr.) and after one day and 7 days. Although the TRR in absolute terms was higher (3-8 times) after 7 days in the small cucumbers (2.3 ppm GP label) compared to large cucumbers (0.3 ppm GP label) and somewhat less with the TFMP label, similar metabolite profile results were obtained at all PHIs, with both labels and with either cucumber size. Metabolite profile results were similar for fruit and foliage and markedly similar to those obtained with apples. As an example, after 7 days residues as %TRR in fruit of small cukes was 87% trifloxystrobin, and its cis/trans isomers 2% CGA-331409, 0.9% -357261, and <0.1% -357262. Trifloxystrobin's acid metabolite CGA-321113 was 2.3%. Low residues of other metabolites were also reported.

Peanuts - Starting at bloom stage peanut plants were treated 4 times (the latter at nut maturity) at ~0.5 lb. ai/A or ~2X the GAP seasonal rate with either the GP or TFMP labels. Nutmeat, hay and immature vine samples were taken. Immature vines were sampled on the day of 1st application and 14 days after the 2nd application. Mature plants were sampled 14 days (i.e. at GAP) after final application and separated into nutmeats, hulls and hay.

The residue profile in nutmeat was markedly different than in apple and cucumbers and to a lesser extent even in hay and immature vines. This resulted in subsection of peanuts samples to more elaborate separative and analytical approaches than required for apples and cucumbers. In nutmeat with the GP label only about 45% of the TRR was identified. Only 2% of the TRR was trifloxystrobin, ~24% was shown to be in the form of triglycerides, 3.4% "metabolite B", 8.8% "metabolite A" (glucoside conjugate of metabolite B hydrolyzed to the acid at the methyl ester) and 6% phthalic acid. Unidentified TRR was characterized with via different solvent partitions and after hydrolysis with acid, base and enzymes, but were unidentified. A somewhat similar result was found with the TFMP label, especially the low relative portion of trifloxystrobin and relatively similar triglyceride levels.

In the case of hay and immature vines the residue profiles were similar, and closer to that found in apple and cucumber. Trifloxystrobin was on the order of 30% TRR, plus about 6% of TRR in the form of cis/trans isomers of trifloxystrobin and about 10-15% as the acid metabolite CGA-321113, its isomers, or conjugates.

Wheat - Although uses are not proposed for wheat, metabolism studies were conducted on spring wheat with both the GP and TFMP labels. Included were penetration investigations. Plants were treated at late boot (41 days) and early ear emergence (58 days) at ~0.22 lb ai/A (~0.44 lb ai/season). Wheat shoots were collected 1 hr. after the 1st and 2nd applications, at 50% maturity (24 hrs after 2nd application) and at maturity (52 days after 2nd application).

Contrasted to the apple, cucumber and peanut, only low levels (<15% of TRR) were identified in the metabolism studies. In stalk for the GP label only about 4% was trifloxystrobin, about 2% its conformational isomers. Similar results with somewhat lower trifloxystrobin was found for grain,

hulls and straw. Different from studies with apple, cucumber and peanuts were significant levels (5-10%TRR) of metabolites NOA-413161 (methyl group of ethylideneaminoxymethyl bridge of trifloxystrobin metabolite CGA-321113 oxidized to the acid) and its conformational isomer NOA-413163 and in hulls and straw 4 and 5.4% respectively of metabolite NOA-414412 (CGA-321113 hydroxylated on the CF ring). Also noteworthy was the 10-15%TRR in stalk and grain as sugar conjugates. Results for the TFMP label were similar.

In the penetration part of the investigation one hour after a single application trifloxystrobin accounted for 89% of surface rinse, decreasing to 76.5% after 14 days. Of the penetrated radioactivity trifloxystrobin accounted for 73.5% after 1 hour and only 9.1% after 14 days. Most of the remaining radioactivity in the surface rinse or penetrated consisted of trifloxystrobin conformational isomers or its acid metabolite CGA-321113.

Livestock

Metabolism studies were conducted in lactating goats and poultry. Indicated metabolism for livestock includes hydrolysis of the methyl ester to form the CGA-321113 acid metabolite, demethylations, ring and chain hydroxylations and conjugation.

Goats

Two lactating goats were administered either GP- or TFMP-labeled trifloxystrobin for 4 consecutive days via gelatin capsule at approximately 100 ppm in the diet (ca. 23X maximum theoretical dietary burden). Milk was collected twice daily and the animals were sacrificed 6 hours after the last dose for collection of liver, kidney, bile, fat (perirenal and omental) and muscle (leg and tenderloin). Using procedures similar to those for plant metabolism studies, samples were analyzed for TRR and for identification/characterization. Results are summarized in Tables 18a (TFMP label) and 18b (GP label) taken from the contractor's review.

Except for 54.7% and 60.3% in liver with the TFMP and GP labels respectively, $\geq 68.9\%$ of TRR was identified in all matrices. Trifloxystrobin was a significant or major portion of the residue in all matrices except liver and kidney (1.5-2.1% TRR) and somewhat for muscle where it was $\leq 23\%$ TRR. Where trifloxystrobin was not a significant or major portion of the TRR in the matrices, its acid metabolite CGA-321113 was.

In milk 48.5-60% of the TRR was trifloxystrobin and other metabolites each approximately 4% or less, except for 10.3% metabolite L7a (aminoethylsulfonic acid conjugate of the acid metabolite (TFMP label)). In muscle trifloxystrobin was 16.8 - 22.8% of TRR and its acid metabolite CGA-321113 43.9-49.3% of TRR. Other identified metabolites were $\leq 2.4\%$ of TRR each. In fat trifloxystrobin accounted for 68-71.8% of TRR and its acid metabolite CGA-321113 8.8-9.3%. Other identified metabolites were each $\leq 0.5\%$ TRR.

In liver slight quantitative differences are observed between the GP and TFMP labels, although as indicated, in both cases unchanged trifloxystrobin accounted for only a small portion of the TRR. The acid metabolite CGA-321113 was 10.1-31.6% of TRR, metabolite L7a 4.2-20.3% TRR, metabolite L7b (glycine conjugate of CGA-321113) ca. 9% TRR. Evidence suggests that CGA-357276 at 7% TRR with the TFMP label resulted from CGA-321113 due to a microwave extraction step. CGA-166988 was reported at 8% of TRR with the GP label. Other identified metabolites were less than 2.2% TRR.

In kidney a somewhat similar profile to that in liver was observed, although the acid metabolite CGA-321113 was higher at 47.2-64.4% TRR and other identified metabolites $\leq 4.4\%$ of TRR, except for MET L7a at 11% of TRR.

Poultry

Two separate groups of five hens were administered via gelatin capsule either GP- or TFMP-labeled trifloxystrobin for 4 consecutive days at approximately 100 ppm dietary equivalent, estimated to be ~20,000X the maximum theoretical dietary burden. Eggs were collected twice daily and hens sacrificed 6 hours after that last dose for collection of liver, kidney, thigh and breast muscle, peritoneal fat and skin with attached fat. Approximately 74-87% of administered dose was eliminated via excreta. After 78 hours most of the radioactivity in eggs was in the yolk (2-3.6 ppm trifloxystrobin equivalent) compared to 0.07-0.3 ppm in the white. As determined by scintillation counting in individual tissues trifloxystrobin equivalent residues were similar between the two labels TFMP/GP, e.g. liver 3.9-8.6/4.6-8.1 ppm, muscle 0.13-0.35/0.13-0.20 ppm, skin (with fat) 0.8-1.8/0.7-0.8 ppm and peritoneal fat 1.9-2.8/0.8-1.3 ppm.

Separative and analytical procedures employed were somewhat similar to those used for ruminants and results for pooled tissues are summarized in tables 21a (TFMP label) taken from the contractor review. Trifloxystrobin was found in all matrices, except egg white, albeit at low levels (0.3-1.1% TRR) in liver. Compared to the ruminant studies, somewhat less of the radioactivity was identified in poultry matrices, especially in egg yolk (4.3-17.3 in egg yolk; 27-61% in muscle; 34-50% in liver and higher at in 57-74% TRR in egg white; and 60-85% in fat + skin). Except in egg white, the acid metabolite CGA-321113 accounted for less of the TRR than in the ruminant studies with fewer individual metabolites contributing a major portion of identified residue.

In contrast to other poultry matrices, in egg white acid metabolite CGA-321113 was a significant portion of the TRR (10.3-19.5%). While CGA-357276 was reported at 28.9% of egg white TRR (TFMP label), it was thought to have resulted from sample work up degradation of MET 1U or a conjugate thereof. Therefore, MET 1U (demethylated acid metabolite CGA-321113) is likely a major component of egg white TRR as confirmed at 21.7% with the GP label (not of other poultry matrices). The next highest was MET L13b (trifloxystrobin hydroxylated in the TFMP ring) at 3.6-8.5% TRR. As noted, in egg yolk $\leq 17.3\%$ of TRR was identified. Up to 7% of that was trifloxystrobin with remaining metabolites common to other matrices, but each $< 4\%$ of TRR. About 26-35% of TRR was designated as unidentified metabolite EGR10.

Although only 27% of TRR was identified in muscle with the GP label, with the TFMP label ca. 24% of TRR was trifloxystrobin. Significant residues with this label were also reported for MET 12U (8.8% TRR), MET 2F (demethylated trifloxystrobin) (8.1% TRR) and MET L14 (7.3% TRR), with other metabolites at <6% TRR each. In fat + skin 26-53% of TRR was reported as trifloxystrobin. Other major identified metabolites were MET 2F (12-14% TRR) and MET L13b (trifloxystrobin hydroxylated in the TFMP ring) (2.6-10.7% TRR). Other identified metabolites were \leq 4.1% TRR, except for ME 3U (trifloxystrobin hydroxylated on ethylideneamino bridge and nitrated on the acetic acid methyl ester group) at 3.5-5.9% TRR.

In liver only 0.3-1.1 % of TRR was trifloxystrobin. The major identified metabolites were MET 13b (6.4-11.2% TRR) and Met L14 (10.5% TRR, TFMP label). Except for CGA-357276 (5.6% TRR, GP label), other identified metabolites were each less than 5% TRR.

Rotational Crop Studies

Rotational crop studies were conducted with both the GP- and TFMP labels in silt loam soil with applications at 2 lb ai/A (2X rate proposed for cucurbits and peanuts) to bare soil plots. Planted were turnips, spinach and wheat, components of each analyzed for TRR and for identification/characterization of residues at 30 and 120 days after application. Trifloxystrobin-equivalent residues were higher for the TFMP label than with the GP label. For the TFMP label trifloxystrobin equivalent after 30 /120 days were: turnip leaves 0.06/0.04 ppm, turnip roots 0.02 ppm, spinach 0.25/0.26 ppm, 25% mature wheat forage 0.28/0.19 ppm, mature wheat forage 0.14/0.1 ppm, wheat straw 0.17/0.2 ppm and wheat grain 0.07/0.06 ppm. Generally with the GP label only a relatively small portion of the TRR in aqueous and organic soluble fractions was identified/characterized (6 - 46% TRR of each) with trifloxystrobin being <2% of TRR in each case, although one of its three conformational isomers also at about the same levels. The acid metabolite CGA-321113 was higher in some matrices (e.g. up to 8.5% of the DCM fraction of turnip leaves and 17.6% for turnip root (0.003 ppm).

With the TFMP label the identified/characterized % TRR was much higher, especially in aqueous fractions where 37- >100% TRR was characterized/identified.. Again, only low levels of trifloxystrobin, its conformational isomers, the acid metabolite and its isomers and phthalic acid were reported, all generally <0.01 ppm. Trifluoroacetic acid was by far the major residue identified with the TFMP label, ranging generally 20 - 94% of a given matrix TRR with the levels even for this generally being less than 0.2 ppm.

Residue Analytical Methods

Analytical method AG-659A is proposed for enforcement of tolerances for trifloxystrobin on plant and animal commodities. It also determines residues of the acid metabolite of trifloxystrobin CGA-321113, although that is not proposed for inclusion in the residue for enforcement. It is based on extraction of samples (homogenized solid samples) with ACN:water (80:20 v:v, filtration,

liquid:liquid partitioning with a three solvent system (sodium chloride saturated water, toluene and hexane), clean up on a C18 solid extraction column, partitioned into methyl-tert-butyl ether:hexane, concentrated to dry, taken up in 0.1% polyethylene glycol in acetone for GC analysis with a nitrogen phosphorus detection detector using a DBWAX capillary column. The reported limit of quantitation is 0.02 ppm in all matrices except peanut hay at 0.05 ppm LOQ and in milk at 0.01 ppm LOQ.

The petitioner conducted method validation of both trifloxystrobin and CGA-321113 on fortified plant and animal commodities for the most part at the reported LOQ's and at higher levels with average recoveries for CGA-321113 ranging from 70-120% and for trifloxystrobin at 74-107%. An independent laboratory validation was conducted on method AG-659, which AG-659A supercedes. AG-659 (or REM 177.03 which is the same except with EC detection) was used in the field trials, rotational crop, storage stability and field trial studies. An independent validation was also conducted on AG-659A, but only for soil residues. As previously noted, while three conformational isomers of trifloxystrobin (CGA-331409, CGA-357261 and CGA-357262) may occur at low levels, they are not proposed to be included in the tolerance nor is whether they would be determined by the proposed analytical method addressed. It is likely that they would be determined if present. These same comments apply to CGA-3321113 and its conformational isomers CGA-3734466 and CGA-373465.

Multi-residue Methods

Study 44496829 (1997) reports on multiresidue testing for recovery of trifloxystrobin and CGA-321113. Trifloxystrobin was tested in accordance with PAM I Appendix II, through Protocols C (GLC systems), D (complete method without cleanup) and E (standards and fortified samples through cleanup columns with different solvent systems) and its acid metabolite CGA-32113 through Protocols B (methylation) and C.

Trifloxystrobin gave adequate responses through protocol C; it was completely recovered from fortified apple samples when analyzed through the Section 302 multiresidue method (Protocol D); standard solutions thereof were completely recovered through Protocol E Section 303 C2 (MeCL Florisil cleanup) and recovery was complete from fortified apple samples through Protocol E Section 303 E4/C2 complete method. It was not recovered through Section 303 C1 Florisil columns (ethyl ether/petroleum ether) or Section 303 E4/C1.

CGA-321113 - Methylation through protocol B was effective. Unmethylated CGA-321113 gave adequate responses only on one GC system, but the methylated derivative (trifloxystrobin) on several. CGA-321113 was completely recovered through Section 402 C1a gel permeation cleanup (Protocol B - GPC) and residues from CGA-321113 fortified apples was completely recovered through Section 402 E2/C1 multiresidue method (extraction with methylene chloride).

Crop Field Trials and Livestock Feeding Studies

Crop Field Trials

Supervised trials have been conducted on apple, pear, peanuts, cucumber, cantaloupe, summer squash, grapes, processed products and bananas.

Bananas - The proposed tolerance is 0.1 ppm. At 0 or 7 days after that last of 10-11 applications of a 75 g/L EC formulation at 0.1 lb ai/A (presumed 1X GAP) maximum residues were 0.06 ppm in bagged bananas and 0.03 ppm in unbagged bananas on day 0, but 0.05 ppm on day two. 2X data were also available. CGA-321113 was ≤ 0.02 ppm. Data are considered adequate if GAP is confirmed to be the same as that at which the trials were conducted.

Cucurbits - The proposed tolerance is 0.25 ppm. At the proposed 1X per application and seasonal rate and proposed 0 day PHI residues of trifloxystrobin were 0.02-0.22 ppm in cucumber, 0.03-0.024 ppm in cantaloupe and <0.02 -0.23 ppm in summer squash. In all cases CGA-321113 was <0.02 ppm. In other experiments at 1X seasonal rate, but 2X the per application rate maximum residues for trifloxystrobin were 0.03-0.28 ppm in cucumber, 0.03-0.58 ppm in cantaloupe and 0.04-0.33 ppm in summer squash. CGA-321113 was 0.02 ppm except two summer squash samples at 0.02 -0.03 ppm. Decline data were also available. Geographic representation is judged to be inadequate, but an additional trial was to be conducted in Region 5, which will be submitted as an amendment. Adequacy of the proposed tolerance will be reconsidered at that time. HED likely will not support a fractional tolerance as proposed.

Grapes - The proposed tolerance is 1.5 ppm. At the 14 day proposed PHI and at 1.3X the proposed per application and per season rate trifloxystrobin residues were <0.02 -1.1 ppm. CGA-321113 was <0.02 -0.068 ppm. Data are considered adequate. HED may suggest 2 ppm. While residues do not concentrate in juice, conflicting studies preclude a conclusion on the need for MRLs for raisins. In one study trifloxystrobin concentrated 2-2.5X and in another with measurable residues in grapes residues did not concentrate. A 3 or 4 ppm limit for raisins may be needed.

Peanuts - The proposed tolerance is 0.02 ppm in peanut and 4.0 ppm in peanut hay. Trifloxystrobin or CGA-321113 residues were <0.02 ppm from 2/3 to 4X proposed maximum GAP rates (0.5-3X seasonal rates). Trifloxystrobin residues in peanut hay from maximum proposed GAP were 0.15-3.7 ppm and CGA-321113 0.089-0.67 ppm, at 14-17 days (14 days GAP PHI). Data are considered adequate. HED may suggest 5 ppm for peanut hay. Residues are not expected to result in meal or refined oil.

Pome fruits - The proposed tolerance is 0.4 ppm in pome fruit. At the approximate proposed per application rates and 1.1X seasonal rate and the proposed 14 day PHI trifloxystrobin residues were 0.09-0.37 ppm in apple and 0.05-0.23 ppm in pears. CGA-321113 was <0.02 - <0.03 ppm in apple and <0.02 -0.04 ppm in pears. Data are considered adequate. HED may suggest 0.5 ppm for pome fruit. A 1.5 ppm tolerance is proposed for apple pomace. That is judged too low. A 4 or 5 ppm tolerance may be recommended for apple pomace based on the highest average field trial residue of 0.3 ppm and the average concentration factor (from 6 processing studies) of 13.3X.

Livestock Feeding Studies

The petitioner does not propose tolerances for animal commodities, but HED will require such since the maximum feeding levels were only 4.6X compared to the agency policy to base the decision to exclude the need for tolerances on a 10X feeding rate.

Poultry

A poultry feeding study was not submitted. Since peanut meal is the only poultry feeding item and residues are not expected to exceed the 0.02 ppm limit of determination, the expected dietary burden has been estimated at 0.005 ppm. Poultry metabolism studies were conducted at ca. 100 ppm (20,000X). Maximum trifloxystrobin-equivalent residues were 8.6 ppm (liver). On this basis no residues of trifloxystrobin are expected in poultry meat or eggs, thus no feeding study is required for the proposed uses.

Cattle

Feeding studies were conducted at 2, 6 and 20 ppm (0.5, 1.4 and 4.6 times the 4.4 ppm dietary burdens estimated for dairy cattle respectively (5.2 ppm for beef cattle). Trifloxystrobin residues were less than the LOQ for milk, muscle, kidney and liver, but in omental and perirenal fat maximum residues were 0.05 and 0.06 ppm respectively. Acid metabolite was below the LOQ's except for kidney (0.02 ppm) and liver (up to 0.09 ppm). If the metabolism committee concludes that trifloxystrobin is the only residue in need of regulation, the contractor recommends LOQ tolerances for milk, muscle, kidney and liver and 0.06 ppm for fat. 0.1 ppm may be preferable for fat.

International Considerations

No Codex, Canadian or Mexican limits are established for trifloxystrobin.

TOXICOLOGY SECTION

On May 11, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of trifloxystrobin and selected doses and endpoints for acute and chronic dietary, as well as occupational and residential exposure risk assessments, and addressed the sensitivity of infants and children from exposure to trifloxystrobin as required by the Food Quality Protection Act (FQPA) of 1996. The HIARC's conclusions are presented below.

Acute Reference Dose (Acute RfD) Females (13 +years)

Study Selected: Developmental Toxicity - Rabbit §83-3b

MRID No.: 44496709

Executive Summary: In a developmental study (MRID# 44496709), 5 groups of 19 THOMAE RUSSIAN, Chbb:HM Rabbits from Dr. K. Thomae GmbH (Chemisch-Pharmazeutische Fabrik, 7950 Biberach, Germany) received CGA 279202 Technical (Trifloxystrobin, Purity: 96.4%; Batch No.: P.405009) in a 0.5% w/w aqueous solution of sodium carboxymethylcellulose at either 0, 10, 50, 250 or 500 mg/kg/day by oral gavage from gestation days 7 through 19, inclusive. Maternal observations and measurements included daily mortality, cage-side observations, body weights and food consumption determined on days 4, 7, 12, 16, 20, 24 and 29 post coitum. The maternal animals were sacrificed on gestation day 29 and subject to a gross necropsy, the uterine contents were examined and the fetuses were examined for external, visceral or skeletal anomalies by standard techniques.

Maternal systemic toxicity was seen as reduced body weights in the 250 and 500 mg/kg/day dose groups during dosing and reduced body weight gains in the 50 mg/kg/day dose group and above during the dosing period (gestation days 7-19, statistically significant at the 2 higher doses, $p < 0.01$), for the dosing period plus post dosing period (gestation days 7-29) and for the entire gestation period (gestation days 0-29), also for the net body weight gain (gestation days 7-29) and corrected body weight gain (gestation days 0-29) and there was a rebound in body weight gain in the 250 and 500 mg/kg/day dose groups for the post dosing period (gestation days 19-29). There was reduced food consumption in the 50 mg/kg/day dose groups and above during the dosing period, for the dosing plus post dosing period and for the entire gestation period with a rebound in food consumption noted during the post dosing period. There was reduced food efficiency noted during the same time periods for the 50 mg/kg/day dose groups and above. **The Maternal Toxicity NOAEL was 10 mg/kg/day and the Maternal Toxicity LOAEL was 50 mg/kg/day based on reduced body weights, body weight gains, food consumption and food efficiency.**

Developmental toxicity was observed as a very marginal increase in fetal and litter incidence of fused sternbrae #3 and 4 at the 500 mg/kg/day dose group, no other observations were noted. **The Developmental Toxicity NOAEL was 250 mg/kg/day and the Developmental Toxicity LOAEL was 500 mg/kg/day based on a marginal increased incidence of skeletal anomalies.**

This study is classified as Acceptable-Guideline and satisfies the requirement (OPPTS 870.3700, OPP §83-3b) for a developmental toxicity study in rabbits.

Dose and Endpoint for Risk Assessment: Developmental NOAEL based on increase in fetal incidence of fused sternebrae #3 and 4 at 500 mg/kg/day (LOAEL).

Comments about Study/Endpoint: The developmental effects are presumed to occur after a single exposure (dose). Since this is an *in utero* effect, it is applicable only to the population subgroup Females 13+.

Uncertainty Factor (UF): 100 (includes 10x for intra-species extrapolation and 10x for inter-species variation).

$$\text{Acute RfD} = \frac{250 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}} = 2.5 \text{ mg/kg/day}$$

Chronic RfD

Study Selected: Chronic Toxicity - Dog §83-1b

MRID No.: 44496704

Executive Summary: In a chronic toxicity study (MRID # 44496704), 4 beagle dogs/sex/group were treated orally with 0, 2, 5, 50 or 200 mg/kg/day of CGA-279202 Technical (purity: 96.4%) in gelatin capsules for 12 months. No mortality resulted from the treatment. Animals in the 200 mg/kg/day group suffered from an increased frequency and severity of diarrhea and vomiting. Dark discoloration of the hair, skin of the paws, thorax and abdomen was noted in animals in the 50 and 200 mg/kg/day treatment groups. Food consumption was significantly reduced ($p < 0.05$) in the high dose female group for weeks 2 and 3. However, treatment did not affect the mean body weight values. Although some hematological parameters for the treated animals were statistically different from those of the control animals, none of the parameters demonstrated a significant treatment effect. Mean serum albumin levels were reduced for the males in the 50 ($p < 0.05$) and 200 mg/kg groups ($p < 0.01$) for the three sampling times (weeks 13, 26, and 52). The albumin level for the females was not affected. Total bilirubin was reduced at weeks 13 and 26 for the 200 mg/kg males ($p < 0.05$) and all three sampling times for the 200 mg/kg females (13 and 52 weeks, $p < 0.05$, 26 weeks, $p < 0.01$). Triglycerides were increased for the 200 mg/kg males at 13 and 52 weeks ($p < 0.01$) and for the 200 mg/kg females at 13 ($p < 0.05$) and 26 weeks ($p < 0.01$). Mean serum alkaline phosphatase activities were increased for the 200 mg/kg males at all sampling times ($p < 0.01$) and for the 50 mg/kg males at 26 ($p < 0.05$) and 52 weeks ($p < 0.01$). Serum alkaline phosphatase activities for the 200 mg/kg females were increased at week 52 ($p < 0.05$). There were no treatment-related effects upon the urinalysis parameters.

At the necropsy, the mean absolute liver and testes weights were increased for the 50 ($p < 0.05$) and 200 mg/kg males ($p < 0.01$). The mean relative liver weight was increased for

the 200 mg/kg male group ($p < 0.01$). The mean relative testes weights were increased for the 50 ($p < 0.05$) and 200 mg/kg groups ($p < 0.01$). The mean relative liver weight was increased for the 200 mg/kg females ($p < 0.01$). An increased number of animals exhibited hepatocellular hypertrophy in the 50 mg/kg females (3/4) and the 200 mg/kg males (3/4) and females (4/4), compared to the control group (1/4 males, 0/4 females). Likewise, bone marrow hypocellularity was noted for a greater number of animals in the 200 mg/kg group (males: 3 vs. 1 for the controls, females: 4 vs. 2 for the controls). No potential adverse effect indicated.

The LOAEL is 50 mg/kg/day, based on The NOAEL is 5 mg/kg/day.

This chronic toxicity study in the dog is Acceptable-Guideline, and satisfies the requirement for a chronic oral study (83-1b) in dogs.

Dose and Endpoint for Establishing RfD: NOAEL = 5 mg/kg/day based on increased incidence of clinical signs, increased mean liver weight, and hepatocellular hypertrophy. The LOAEL is 50 mg/kg/day.

Uncertainty Factor(s): 100 (includes 10x for intra-species extrapolation and 10x for inter-species variation).

$$\text{Chronic RfD} = \frac{5 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}} = 0.05 \text{ mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factor(s): This study was selected because it is a chronic study and the NOAEL (systemic) of 5 mg/kg/day is lower than the NOAEL of 9.8 mg/kg/day derived in the chronic rat study. Also, the toxic effects observed (liver effects and/or body weight decreases) are also seen in the chronic rat and the multigeneration study in rats.

Classification of Carcinogenic Potential

- The classification of trifloxystrobin was made by an ad hoc subcommittee of the Cancer Assessment Review Committee on May 27, 1999, that trifloxystrobin would be classified as a "Not Likely Human Carcinogen".

HAZARD CHARACTERIZATION

The database is incomplete in that an acute neurotoxicity study in the rat is a data gap. Trifloxystrobin is Toxicity III-IV for acute toxicity. However, trifloxystrobin is a strong dermal sensitizer. Trifloxystrobin is positive for mutagenicity in Chinese Hamster V79

cells, albeit at cytotoxic dose levels. However, trifloxystrobin is negative in the remaining 7 mutagenicity studies. Developmental NOAELs and LOAELs for both rats and rabbits occurred at either the same dose levels or were above the NOAELs and LOAELs for maternal toxicity. The NOAEL for offspring effects in the 2-generation rats reproduction study occurred at a dose level equivalent to the NOAEL for parental findings. Based on these data, there was no increased susceptibility demonstrated under FQPA for infants and children. Trifloxystrobin was not carcinogenic in mice following dietary administration to Tif: MAGf (SPF) mice for 18 months. Trifloxystrobin was negative for carcinogenicity in rats in a 2-year study at dose levels up to 1500 ppm (62.2 mg/kg/day). There is a high degree of confidence in the studies upon which the acute and chronic RfDs are based. The study from which an acute RfD (females 13+) was derived was a developmental toxicity study in rabbits. It is considered to be appropriate for an acute risk assessment by the HIARC because the skeletal anomalies seen at the LOAEL are presumed to occur after a single dose. An appropriate endpoint could not be determined for the risk assessment for the general population acute RfD. The study selected for the chronic RfD was a chronic toxicity study in dogs. This study exposed a common strain of laboratory dog (beagle) to a wide range of doses of trifloxystrobin. The dose selected upon which to base the RfD was 5 mg/kg/day (NOAEL).

Rat Excreta Metabolites

In a rat metabolism study (MRID # 44496822), urine, feces, and bile that were recovered from a previous CGA-279202 pharmacokinetics study (MRID 44496821) were pooled by group and sex, subjected to methods involving solvent extractions, chemical purification (LC and HPLC), quantification (HPLC), and metabolites characterization (MS and NMR), and the information was used to elucidate and propose a metabolic pathway. Based on the identified structures of more than 30 metabolites, schemes of metabolic pathways were proposed (copies attached) with the following major reaction types: 1) Hydrolysis of the methyl ester to the corresponding acid (e.g., CGA 321113). 2) O-Demethylation of the methoxyimino group to the hydroxyimino derivative(s) (e.g., NOA 405637). 3) Oxidation of the methyl side chain to the primary alcohol (e.g., MET 2U) with further partial oxidation to the corresponding carboxylic acid (e.g., MET 13U). The metabolism of the methyl side chain to a primary alcohol was more pronounced in female than in male rats resulting in various sex specific major urinary metabolites. There were other minor reaction types including chain shortening by oxidative decarboxylation of the glyoxyl moiety to a benzoic acid amide (MET 13U), hydrolysis of the hydroxyimino group to a ketone (MET 5U) followed by oxidative decarboxylation to a benzoic acid derivative (MET 4U), oxidation of the hydroxyimino group to a nitro group (MET 3U), and hydroxylations of the phenyl rings. In addition, nearly 10% of the administered dose was accounted for by cleavage between the glyoxyl-phenyl and the trifluoromethyl-phenyl moieties with further metabolism by one or more of the above described reactions to yield several one phenyl ring metabolites including *ortho*-phthalic acid and *meta*-trifluoromethyl benzoic acid, among others.

SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary Females 13+	NOAEL = 250 UF = 100	Increased fetal skeletal anomalies	Developmental Toxicity-Rabbit
	Acute RfD = 2.5 mg/kg		
Chronic Dietary	NOAEL = 5 UF = 100	Increased incidence of clinical signs, increased mean liver weight, and hepatocellular hypertrophy	Chronic Toxicity - Dog
		Chronic RfD = 0.05 mg/kg/day	
Short-Term (Dermal)	Dermal NOAEL = 100	Increases in liver and kidney weights	28-Day Dermal Toxicity Study in Rats
Intermediate-Term (Dermal)	Dermal NOAEL = 100	Increases in liver and kidney weights	28-Day Dermal Toxicity Study in Rats
Long-Term (Dermal) ^a	NOAEL = 5	Increased incidence of clinical signs, increased mean liver weight, and hepatocellular hypertrophy	Chronic Toxicity - Dog
Inhalation Short	NOAEL = 250	Increased fetal skeletal anomalies	Developmental Toxicity-Rabbit
- • Inter/Long	NOAEL = 5	-- Increased incidence of clinical signs, increased mean liver weight, and hepatocellular hypertrophy	- Chronic Toxicity - Dog

a= Since an oral NOAEL was selected, a dermal absorption rate of 33 % should be used for route-to-route extrapolation

RESIDUES IN WATER SECTION

See separate submission.

QUESTIONS TO THE COMMITTEE

1. Does the committee concur with the petitioner's recommendation that trifloxystrobin be the only residue regulated in plant and animal commodities?
2. What residue does the committee recommend for risk assessment purposes?

c:\...\wpdocs\hed99\trflxybrf3.wpd

C:\...HED98\trifl.tbl.wpd **TRIFLOXYSTROBIN METABOLISM IN PLANTS - A SUMMARY**
TABLE 1

Moiety	Whole Apples IX Seasonal GAP rate 14 days (~GAP)		Small Cucues GP Label 7 days (similar to 0 day - GAP) and similar to large cucues		Peanuts GP label 2X GAP Rate (TFMP similar)			Spring Wheat GP Label (TFMP similar)				
	TRR ppm	TRR ppm	TRR ppm	TRR ppm	TRR ppm	TRR ppm	TRR ppm	TRR ppm	TRR ppm	TRR ppm	TRR ppm	TRR ppm
	GP label	TFMP label	Foilage	Fruit	Nutmeat	Hay	Immature vines	stalk	grain	hull	straw	TRR
Trifloxystrobin	83	80.7	81.8	87		29.3	33.2	3.9	1.3	0.8	2.2	5.5 ppm
Trifloxystrobin + isomers + acid					1.98							
331409 (cf. isomer of trifloxystrobin)	2.2	3.4	1.4	2	--	2.6	3.5	0.5				0.7
357261 (cf. isomer of trifloxystrobin)	3.3	5.2	1.2	0.9	--	2.2	3.2	0.9	1.2	1.4	1	
357262 (cf. isomer of trifloxystrobin)	1.4	2.2	<0.1	<0.1	--	1.3	2.7	0.4				0.4
321113 (acid)			1.3	2.3	--	3.2	1.8	0.2		0.6	1.8	
373466 (acid isomer)	0.4	0.6			--	1.7	0.2					
373465 (acid isomer)					--	--	0.07					
321113 or OH-321113 conj.					--	5.4	11.6					
phthalic acid					6	2.7	1.6					
triglycerides					23.7							

Moiety	Whole Apples IX Seasonal GAP rate 14 days (=GAP)		Small Cucumbers GP Label 7 days (similar to 0 day = GAP) and similar to large cukes		Peanuts GP label 2X GAP Rate (TFMP similar)			Spring Wheat GP Label (TFMP similar)				
	TRR 1.3 ppm	TRR 0.67 ppm	TRR 24.9 ppm	TRR 2.3 ppm	TRR 0.27 ppm	TRR 26.3 ppm	TRR 7.7 ppm	TRR 4.7 ppm	TRR 0.10 ppm	TRR 0.78 ppm	TRR 5.5 ppm	
	GP label	TFMP label	Foliage	Fruit	Nutmeat	Hay	Immature vines	stalk	grain	hull	straw	
metabolite A (gluc. conj. of B)					8.8	7.9	6.8					
Metabolite B (left side of trifloxystrobin w acid @ break)					3.4	1.2	1.3					
Metab. WFH-IX- 86 (oxime)						2.5	1.5					
320299	<0.1											
NOA-414412 (acid metab. w. -OH on CF, ring)			0.7	0.4								
NOA-413161 (oxidized GP, on right chain of 31113 oxidized to the acid)								0.9				
NOA-413163 (conf. isomer of 413161)								6.2	10.1	5.1	6	
Total I.D.'d	90.4	92.1	<86.6	<93	44.9	60.1	69	14.9	12.6	13.6	20.1	
characterized												

Moiety	Whole Apples IX Seasonal GAP rate 14 days (-GAP)		Small Cukes GP Label 7 days (similar to 0 day - GAP) and similar to large cukes		Peanuts GP label 2X GAP Rate (TFMP similar)			Spring Wheat GP Label (TFMP similar)			
	TRR 1.3 ppm	TRR 0.67 ppm	TRR 24.9 ppm	TRR 2.3 ppm	TRR 0.27 ppm	TRR 26.3 ppm	TRR 7.7 ppm	TRR 4.7 ppm	TRR 0.10 ppm	TRR 0.78 ppm	TRR 5.5 ppm
II _{8a}	GP label	TFMP label	Foilage	Fruit	Nutmeal	Hay	Immature vines	stalk	grain	hull	straw
II _{10a}	1.5	0.3	1.1	0.9							
II _{11a}		0.4	0.7(III)	0.2							
II _{22a-c}	0.3	0.1									
origin	1.5										
propanol/H ₂ O extr	0.1	0.6						6.8			
ACN/H ₂ O					25.6						
1% NaCl					11.4	4.1					
enzyme hydrol.					11.8	1.4					
sugar conj.								15.4	10.1		1
MeOH/EtOH									13.9		2.5
Tota ID'd/ /characterized	93.9	93.9	<88.4	<94.1	95.1	69.2	69	37.1	53.6	13.6	29.2

Table 18a. Summary of radioactive residues characterized/identified in milk and tissues of a lactating goat orally dosed with [TFMP-¹⁴C]trifloxystrobin at 100 ppm (-23x) for 4 days.

Fraction	Milk (TRR = 0.085 ppm)		Muscle (TRR = 0.058 ppm)		Fat (TRR = 0.191 ppm)		Liver (TRR = 4.815 ppm)		Kidney (TRR = 1.830 ppm)	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
Identified *										
Trifloxystrobin	48.5	0.041	16.8	0.010	71.8	0.137	2.1	0.102	1.6	0.029
CGA-321113	2.9	0.002	49.3	0.029	8.8	0.017	10.1	0.486	47.2	0.864
CGA-357276 ^b	--	--	--	--	--	--	7.0	0.337	--	--
MET 1U	0.7	<0.001	0.8	<0.001	0.4	0.001	--	--	1.7	0.030
MET 2U	1.5	0.001	1.5	0.001	0.3	0.001	--	--	2.7	0.049
MET 6U	3.3	0.003	--	--	--	--	3.3	0.158	--	--
MET 11U	--	--	--	--	--	--	--	--	0.3	0.005
MET 12U	2.5	0.002	1.4	0.001	0.5	0.001	--	--	--	--
MET L7a	10.3	0.009	1.0	<0.001	--	--	20.3	0.980	11.0	0.202
MET L7b	--	--	1.1	<0.001	--	--	8.5	0.407	4.4	0.081
MET 1G	--	--	--	--	--	--	3.4	0.163	--	--

	Milk (TRR = 0.085 ppm)		Muscle (TRR = 0.058 ppm)		Fat (TRR = 0.191 ppm)		Liver (TRR = 4.815 ppm)		Kidney (TRR = 1.830 ppm)	
Total identified	69.7	0.059	71.9	0.042	81.8	0.156	54.7	2.634	68.9	1.261
Characterized										
MET MU2	9.4	0.008	1.4	0.001	--	--	--	--	--	--
MET MU3	--	--	0.5	<0.001	--	--	--	--	--	--
MET MU4	1.6	0.001	0.5	<0.001	--	--	--	--	--	--
MET U8	--	--	--	--	--	2.9	0.138	2.3	0.043	--
MET LR5	--	--	--	--	--	4.2	0.201	--	--	--
MET N11	--	--	--	--	--	--	--	0.5	0.009	--
Apolar unknown	--	--	--	--	--	0.5	0.026	--	--	--
Polar unknown	--	--	--	--	--	--	--	6.4	0.117	--
Total identified/characterized	80.7	0.069	74.3	0.043	81.8	0.156	62.3	3.000	78.1	1.429
Nonextractable	4.5	0.004	9.7	0.006	6.6	0.013	5.0	0.241	6.2	0.113

* See Figure 1 (Attachment II for chemical names and structures of identified metabolites.

† This metabolite was only found in liver following microwave-assisted extraction of nonextractable residues; the petitioner concluded (based on a control experiment) that this compound resulted from the thermal decarboxylation of CGA-321113 during the microwave extraction procedure.

Table 18b. Summary of radioactive residues characterized/identified in milk and tissues of a lactating goat orally dosed with [GP-¹⁴C]trifloxystrobin at 100 ppm (-23x) for 4 days.

Fraction	Milk (TRR = 0.089 ppm)		Muscle (TRR = 0.077 ppm)		Fat (TRR = 0.356 ppm)		Liver (TRR = 3.913 ppm)		Kidney (TRR = 2.331 ppm)	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
Identified *										
Trifloxystrobin	60.0	0.053	22.8	0.018	68.0	0.242	1.8	0.071	1.5	0.037
CGA-321113	3.9	0.003	43.9	0.034	9.3	0.033	31.6	1.237	64.4	1.502
CGA-166988	--	--	--	--	--	--	8.1	0.318	--	--
MET 1U	--	--	2.4	0.002	--	--	--	--	3.4	0.078
MET 2U	1.3	0.001	1.6	0.001	--	--	1.3	0.052	1.4	0.033
MET 6U	3.8	0.003	--	--	--	--	2.2	0.086	--	--
MET 2F	1.4	0.001	--	--	--	--	0.6	0.025	--	--
MET 3F	2.1	0.002	--	--	--	--	--	--	--	--
MET L7a	2.7	0.002	0.2	<0.001	--	--	4.2	0.165	1.2	0.028
MET L7b	0.9	0.001	1.7	0.001	--	--	9.0	0.352	4.3	0.100
MET 1G	--	--	--	--	--	--	1.5	0.059	2.6	0.061

	Milk (TRR = 0.089 ppm)		Muscle (TRR = 0.077 ppm)		Fat (TRR = 0.356 ppm)		Liver (TRR = 3.913 ppm)		Kidney (TRR = 2.331 ppm)	
Total identified	76.1	0.068	72.6	0.056	77.3	0.275	60.3	2.360	78.8	1.837
Characterized										
MET U8	0.9	0.001	--	--	--	--	2.8	0.109	3.0	0.070
Total identified/characterized	80.0	0.071	72.6	0.056	77.3	0.275	63.1	2.469	81.8	1.907
Nonextractable	2.8	0.002	11.1	0.009	1.7	0.006	0.5	0.020	5.2	0.121

* See Figure 1 (Attachment II for chemical names and structures of identified metabolites.

Table 21a. Summary of radioactive residues characterized/identified in eggs and tissues of laying hens orally dosed with [TFMP-¹⁴C]trifloxystrobin at ~100 ppm (~20,000x) for 4 days.

Fraction	Egg white (TRR = 0.125 ppm)		Egg yolk (TRR = 1.016 ppm)		Muscle (TRR = 0.210 ppm)		Fat + skin (TRR = 1.482 ppm)		Liver (TRR = 6.316 ppm)	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
Identified										
Trifloxystrobin	--	--	7.0	0.072	23.7	0.050	53.0	0.785	1.1	0.067
CGA-321113	19.5	0.024	--	--	--	--	1.2	0.017	4.6	0.290
CGA-337276	28.9 ^a	0.036	0.9	0.009	--	--	1.8	0.027	0.6	0.041
MET 1U	4.1	0.005	--	--	--	--	--	--	--	--
MET 2U	2.8	0.003	0.4	0.004	0.3	0.001	3.7	0.055	2.8	0.175
MET 3U	--	--	--	--	--	--	3.5	0.052	2.4	0.150
MET 5U	--	--	--	--	1.6	0.003	--	--	--	--
MET 6U	5.0	0.006	--	--	--	--	--	--	2.4	0.150
MET 12U	--	--	--	--	8.8	0.018	0.6	0.009	--	--
MET 2F	--	--	3.7	0.038	8.1	0.017	11.6	0.171	4.9	0.308
MET 1G	--	--	--	--	--	--	0.5	0.008	3.0	0.187
MET EW1 ^b	5.5	0.007	2.1	0.022	5.5	0.012	0.6	0.009	3.7	0.231
MET EW11	--	--	--	--	--	--	--	--	1.4	0.086
MET L13b	8.5	0.011	3.0	0.031	5.6	0.012	10.7	0.159	11.2	0.707
MET L14	--	--	--	--	7.3	0.015	1.0	0.016	10.5	0.665
MET L24	--	--	--	--	--	--	--	--	1.2	0.079
Total identified	74.4	0.093	17.3	0.175	60.9	0.128	84.6	1.254	49.6	3.136
Characterized										
EGR8	--	--	8.7	0.088	--	--	--	--	--	--
EGR9	--	--	14.5	0.147	--	--	--	--	--	--
EGR10	--	--	35.2	0.357	--	--	--	--	--	--
MET L4	--	--	--	--	0.9	0.002	--	--	5.4	0.341
MET EW1a	--	--	--	--	--	--	--	--	1.8	0.114
Apolar unknown(s)	--	--	--	--	8.2	0.017	1.0	0.016	0.9	0.059

(continued; footnotes follow)

Table 21a (TFMP label, continued).

Fraction	Egg white (TRR = 0.125 ppm)		Egg yolk (TRR = 1.016 ppm)		Muscle (TRR = 0.210 ppm)		Fat + skin (TRR = 1.482 ppm)		Liver (TRR = 6.316 ppm)	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
Polar unknown(s)	--	--	--	--	--	--	--	--	5.2	0.329
Total identified/characterized	74.4	0.093	75.7	0.769	70.0	0.147	85.6	1.269	62.9	3.973
Nonextractable	1.3	0.002	0.8	0.008	14.3	0.030	3.2	0.047	0.0	0.000

a. The petitioner believes that the presence of this metabolite in egg white is a result of degradation of MET 1U or a conjugate of MET 1U during sample workup.

b. When MET EW1 was isolated from liver it was determined to consist of two compounds, EW1a and EW1b; in liver, EW1b was present at about twice the level of EW1a. EW1b was identified (see Figure 1 (Attachment II)) but EW1a could not be identified.

TRIFLOXYS TROBIN Review

Page _____ is not included in this copy.

Pages 31 through 40 are not included in this copy.

The material not included contains the following type of information:

- _____ Identity of product inert ingredients.
- _____ Identity of product impurities.
- _____ Description of the product manufacturing process.
- _____ Description of quality control procedures.
- _____ Identity of the source of product ingredients.
- _____ Sales or other commercial/financial information.
- _____ A draft product label.
- _____ The product confidential statement of formula.
- _____ Information about a pending registration action.
- FIFRA registration data.
- _____ The document is a duplicate of page(s) _____.
- _____ The document is not responsive to the request.
- _____ Proprietary information pertaining to the chemical composition of an inert ingredient provided by the source of the ingredient.
- _____ Attorney-Client Privilege
- _____ Voluntarily submitted confidential business information

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

ATTACHMENT II

Figure 1. Trifloxystrobin and its metabolites in apple (MRIDs 44496819 and 44496822), cucumber (MRIDs 44496826 and 44496827), peanut (MRIDs 44496817 and 44496845), spring wheat (MRIDs 44496824, 44496828, and 44496848), goat (MRIDs 44496818 and 44496823), poultry (MRIDs 44496820 and 44496825), and rotational crop (MRID 44496844) commodities.

Common Name Chemical Name	Structure	Substrate
<p>Trifloxystrobin</p> <p>(E,E)-Methoxyimino-[2-[1-(3-trifluoromethyl-phenyl)-ethylideneaminoxymethyl]-phenyl]acetic acid methyl ester</p>		<p>Apple peel, flesh, foliage, and rinse Cucumbers and foliage Peanut nutmeat, hay, and vines Wheat forage, grain, hulls, and straw Rotated spinach, turnip root and leaves, and wheat forage and straw Goat milk, fat, kidney, liver, and muscle Hen egg yolk, muscle, fat + skin, and liver</p>
<p>CGA-331409</p> <p>(E,Z)-Methoxyimino-[2-[1-(3-trifluoromethyl-phenyl)-ethylideneaminoxymethyl]-phenyl]acetic acid methyl ester</p>		<p>Apple peel, foliage, and rinse Cucumbers and foliage Peanut hay and vines Wheat forage, hulls, and straw Rotated spinach, turnip root and leaves, and wheat forage</p>
<p>CGA-357261</p> <p>(Z,E)-Methoxyimino-[2-[1-(3-trifluoromethyl-phenyl)-ethylideneaminoxymethyl]-phenyl]acetic acid methyl ester</p>		<p>Apple peel, flesh, foliage, and rinse Cucumbers and foliage Peanut hay and vines Wheat forage, grain, hulls, and straw Rotated turnip leaves</p> <p><i>low roots</i> <i>17-11-2008</i></p>

Figure 1 (continued).

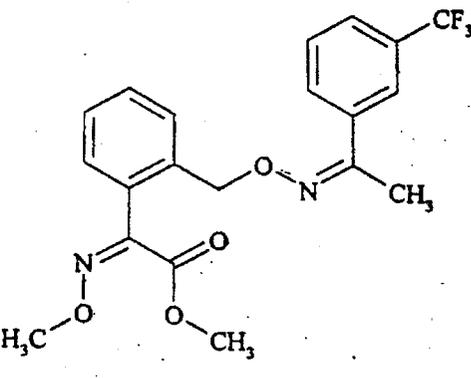
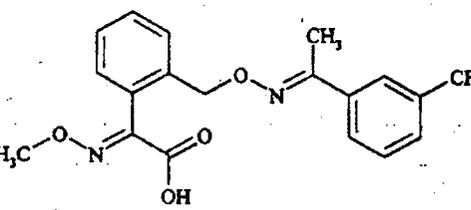
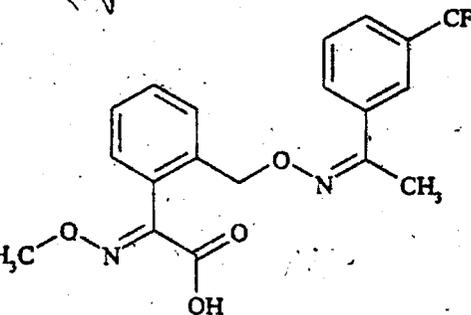
Common Name Chemical Name	Structure	Substrate
<p>CGA-357262</p> <p>(Z,Z)-Methoxyimino-[2-[1-(3-trifluoromethyl-phenyl)-ethylideneaminoxymethyl]-phenyl]acetic acid methyl ester</p>		<p>Apple peel, flesh, foliage, and rinse Cucumbers and foliage Peanut hay and vines Wheat forage, hulls, and straw Rotated spinach, turnip root and leaves, and wheat forage and straw</p>
<p>CGA-321113</p> <p>(E,E)-Methoxyimino-[2-[1-(3-trifluoromethyl-phenyl)-ethylideneaminoxymethyl]-phenyl]acetic acid</p> <p><i>(Includes malonyl glucose and sugar conjugates and hydroxy-CGA-321113 for peanuts)</i></p>		<p>Apple peel, flesh, and foliage Cucumbers and foliage Peanut nutmeat, hay, and vines Wheat forage, grain, hulls, and straw Rotated spinach, turnip root and leaves, and wheat forage and straw Goat milk, fat, kidney, liver, and muscle Hen egg white and yolk, muscle, fat + skin, and liver</p>
<p>CGA-373466</p> <p>(Z,E)-Methoxyimino-[2-[1-(3-trifluoromethyl-phenyl)-ethylideneaminoxymethyl]-phenyl]acetic acid</p>		<p>Apple peel, flesh, and foliage Peanut nutmeat, hay and vines Rotated spinach, and turnip root and leaves, and wheat straw</p>

Figure 1 (continued).

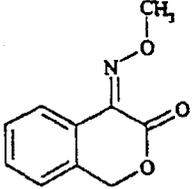
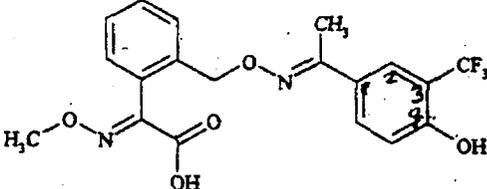
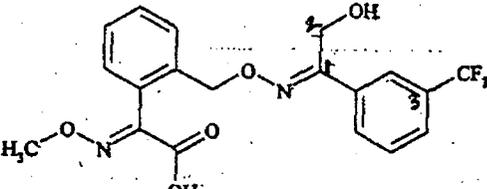
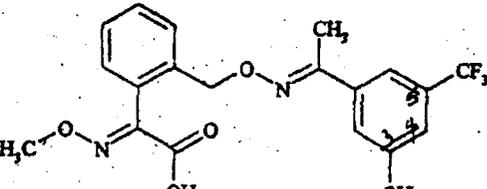
Common Name Chemical Name	Structure	Substrate
<p>CGA-320299</p> <p>Isochroman-3,4-dione-4-(O-methyl-oxime)</p>		<p>Apple flesh and foliage Rotated turnip root and leaves, and wheat forage and straw</p>
<p>NOA-417076 (Metabolite II_{22a})</p> <p>(E,E)-[2-[1-(4-hydroxy-3-trifluoromethyl-phenyl)-ethylideneaminoxymethyl]-phenyl]-methoxyimino-acetic acid</p> <p>(Including isomers II_{22a} and II_{22b} and respective sugar conjugates II_{10a}, II_{22a} and II_{10d})</p>		<p>Apple peel and flesh Cucumber and foliage *</p>
<p>Metabolite I₁₂ (plants) MET 2U (animals)</p> <p>{2-[2-Hydroxy-1-(3-trifluoromethyl-phenyl)-ethylideneaminoxymethyl]-phenyl}-methoxyimino-acetic acid</p> <p>(Including isomer I₁₀ (wheat only) and sugar conjugates II₁₁ and II₈ (wheat only))</p>		<p>Cucumber and foliage Wheat forage, grain, hulls, and straw Goat milk, fat, kidney, and muscle Hen egg white and yolk, muscle, fat + skin, and liver</p>
<p>NOA-414412 (Metabolite I₁₀)</p> <p>{2-[1-(3-hydroxy-5-trifluoromethyl-phenyl)-ethylideneaminoxymethyl]-phenyl}-methoxyimino-acetic acid</p> <p>(Including sugar conjugate II₁₀)</p>		<p>Cucumber and foliage Wheat forage, grain, hulls, and straw</p> <p><i>low acute</i> <i>NOA-414412</i></p>

Figure 1 (continued).

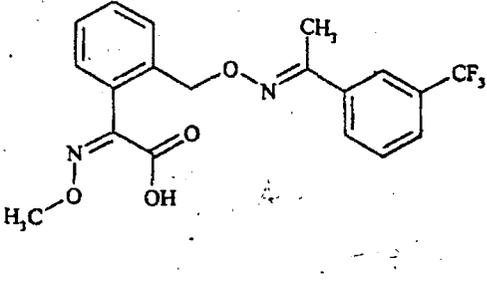
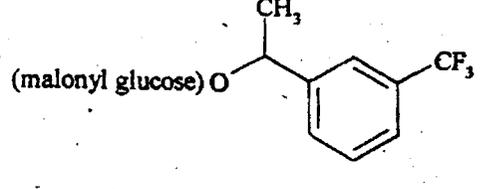
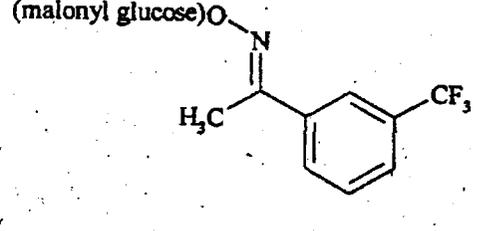
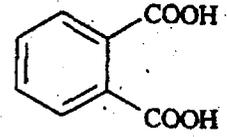
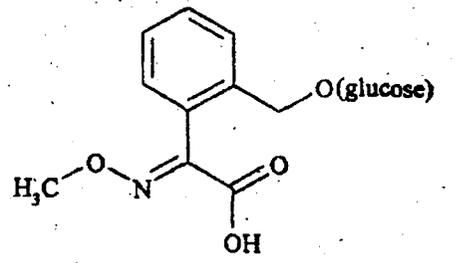
Common Name Chemical Name	Structure	Substrate
CGA-373465 (E,Z)-Methoxyimino-[2-[1-(3-trifluoromethyl-phenyl)-ethylideneaminoxyethyl]-phenyl]acetic acid		Peanut vines Rotated turnip root and leaves, and wheat forage
CGA-328365-malonyl glucose conjugate no chemical name provided		Peanut hay and vines
CGA-300624-malonyl glucose conjugate 1-(3-trifluoromethyl-phenyl)-ethanone oxime		Peanut vines
Phthalic acid		Peanut nutmeat, hay, and vines Rotated turnip root and leaves, and wheat forage
Metabolite A no chemical name provided		Peanut nutmeat, hay, and vines

Figure 1 (continued).

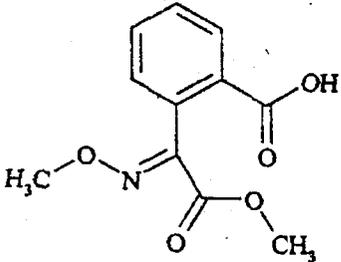
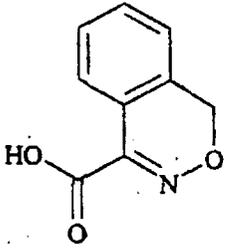
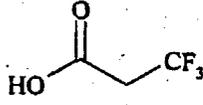
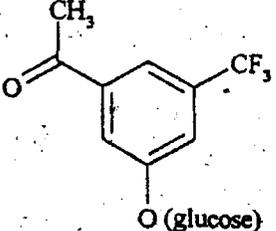
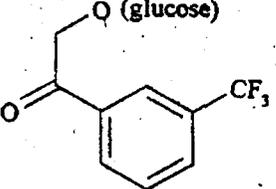
Common Name Chemical Name	Structure	Substrate
Metabolite B no chemical name provided		Peanut nutmeat, hay, and vines
WFH-IX-86 no chemical name provided		Peanut hay and vines
Trifluoroacetic acid		Peanut hay and vines Rotated spinach, turnip root and leaves, and wheat forage, grain, and straw
Metabolite A-7a no chemical name provided		Peanut hay and vines
Metabolite A-7b no chemical name provided		Peanut hay and vines

Figure 1 (continued).

Common Name Chemical Name	Structure	Substrate
NOA-413161 (E,Z)-{2-[carboxy-(3-trifluoromethyl-phenyl)-methyleneaminoxy-methyl]-phenyl}-methoxyimino-acetic acid		Wheat forage, grain, hulls, and straw
NOA-413163 (E,E)-{2-[carboxy-(3-trifluoromethyl-phenyl)-methyleneaminoxymethyl]-phenyl}-methoxyimino-acetic acid		Wheat forage, grain, hulls, and straw
CGA 357276 2-[1-(3-Trifluoromethyl-phenyl)-ethylideneaminoxymethyl]-benzonitrile		Goat liver ^b Hen egg white ^c and yolk, muscle, fat + skin, and liver
CGA 166988 3H-Isobenzofuran-1-one		Goat liver Hen muscle
NOA 417076 {2-[1-(4-Hydroxy-3-trifluoromethyl-phenyl)-ethylideneaminoxymethyl]-phenyl}-methoxyimino-acetic acid		Hen egg yolk

R = rel from DER #21

R

46

Figure 1 (continued).

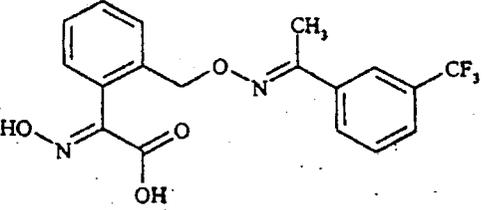
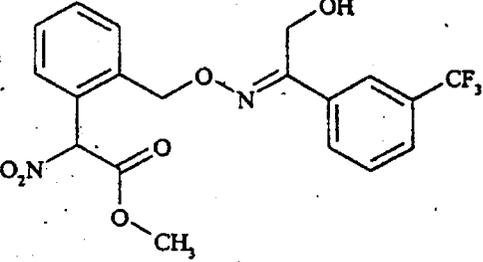
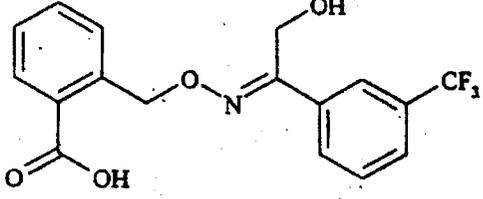
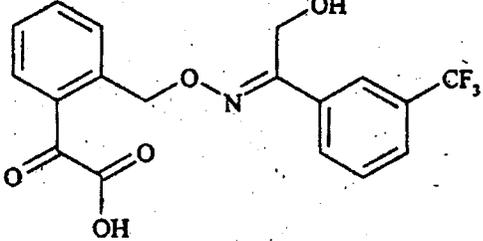
Common Name Chemical Name	Structure	Substrate
MET 1U Hydroxyimino-{2-[1-(3-trifluoromethyl-phenyl)-ethylideneaminoxymethyl]-phenyl}-acetic acid		Goat milk, fat, kidney, and muscle Hen egg white
MET 3U {2-[2-Hydroxy-1-(3-trifluoromethyl-phenyl)-ethylideneaminoxymethyl]-phenyl}-nitro-acetic acid methyl ester		Hen egg white, fat + skin, and liver
MET 4U 2-[2-Hydroxy-1-(3-trifluoromethyl-phenyl)-ethylideneaminoxymethyl]-benzoic acid		Hen liver
MET 5U {2-[2-Hydroxy-1-(3-trifluoromethyl-phenyl)-ethylideneaminoxymethyl]-phenyl}-oxo-acetic acid		Hen muscle and liver

Figure 1 (continued).

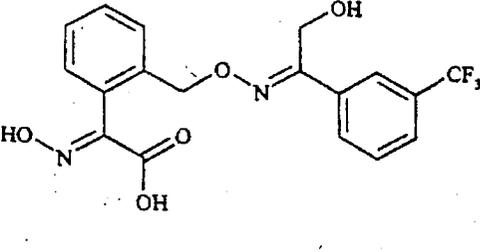
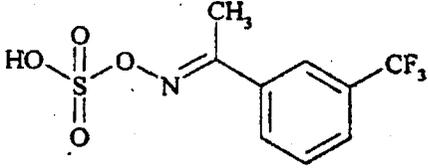
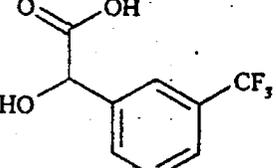
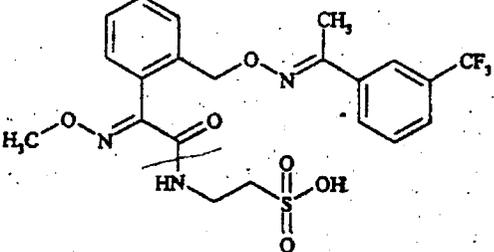
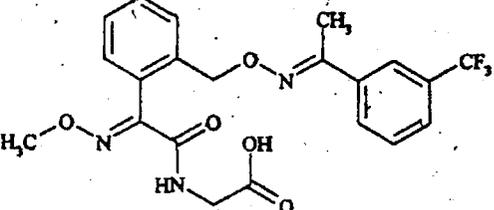
Common Name Chemical Name	Structure	Substrate
<p>MET 6U</p> <p>Hydroxyimino-{2-[2-hydroxy-1-(3-trifluoromethyl-phenyl)-ethylideneaminoxymethyl]-phenyl}-acetic acid</p>		<p>Goat milk and liver Hen egg white and liver</p>
<p>MET 11U</p> <p>Sulfuric acid mono-[1-(3-trifluoromethyl-phenyl)-ethanoneoxime]ester</p>		<p>Goat kidney</p>
<p>MET 12U</p> <p>Hydroxy-(3-trifluoromethyl-phenyl)-acetic acid</p>		<p>Goat milk, fat, and muscle Hen muscle and fat + skin</p>
<p>MET L7a</p> <p>Taurine conjugate of methoxyimino-{2-[1-(3-trifluoromethyl-phenyl)-ethylideneaminoxymethyl]-phenyl}acetic acid</p>		<p>Goat milk, kidney, liver, and muscle</p>
<p>MET L7b</p> <p>Glycine conjugate of methoxyimino-{2-[1-(3-trifluoromethyl-phenyl)-ethylideneaminoxymethyl]-phenyl}-acetic acid</p>		<p>Goat kidney, liver, and muscle</p>

Figure 1 (continued).

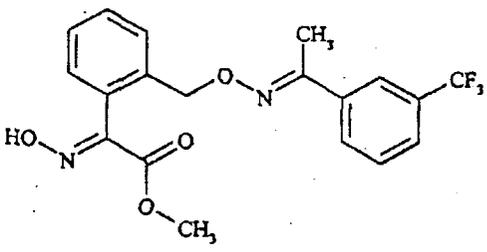
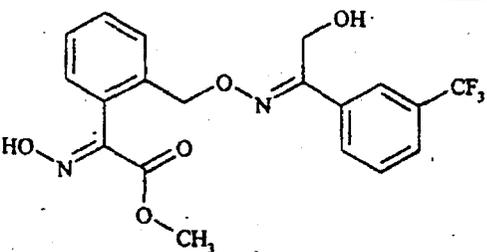
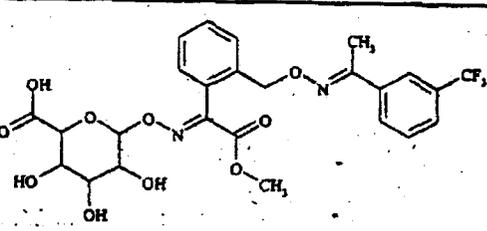
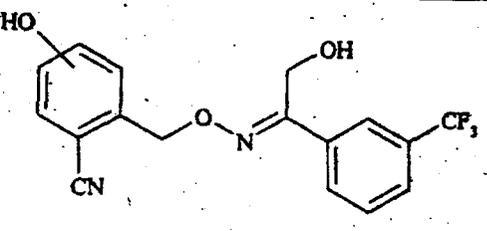
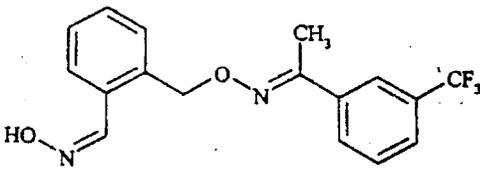
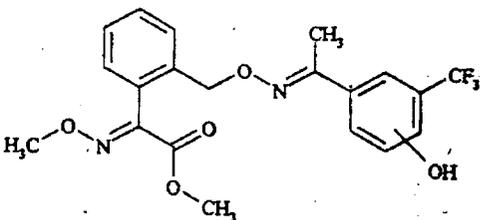
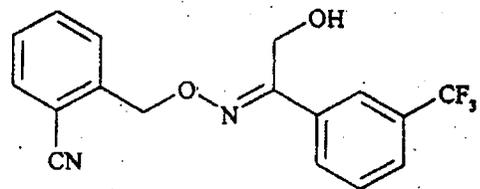
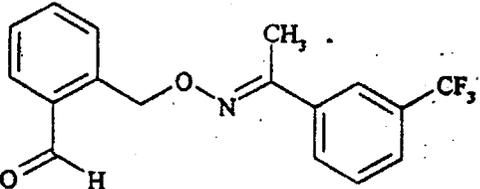
Common Name Chemical Name	Structure	Substrate
<p>MET 2F</p> <p>Hydroxyimino-{2-[1-(3-trifluoromethyl-phenyl)-ethylideneaminoxymethyl]-phenyl}-acetic acid methyl ester</p>		<p>Goat milk and liver Hen egg yolk, muscle, fat + skin, and liver</p>
<p>MET 3F</p> <p>Hydroxyimino-{2-[2-hydroxy-1-(3-trifluoromethyl-phenyl)-ethylideneaminoxymethyl]-phenyl}-acetic acid methyl ester</p>		<p>Goat milk</p>
<p>MET 1G</p> <p>Glucuronic acid conjugate of hydroxyimino-{2-[1-(3-trifluoromethyl-phenyl)-ethylideneaminoxymethyl]-phenyl}-acetic acid methyl ester</p>		<p>Goat kidney and liver Hen egg yolk, muscle, fat + skin, and liver</p>
<p>EW1b</p> <p>Hydroxy-2-[2-hydroxy-1-(3-trifluoromethyl-phenyl)-ethylideneaminoxymethyl]-benzonitrile</p>		<p>Hen egg white^d and yolk,^d muscle,^d fat + skin,^d and liver</p>

Figure 1 (continued).

Common Name Chemical Name	Structure	Substrate
EW11 2-[1-(3-Trifluoromethyl-phenyl)-ethylideneaminooxymethyl]-benzaldehyde oxime		Hen liver
MET L13b {2-[1-(Hydroxy-5-trifluoromethyl-phenyl)-ethylideneaminooxymethyl]-phenyl}-methoxyiminoacetic acid methyl ester		Hen egg white and yolk, muscle, fat + skin, and liver
MET L14 2-[2-Hydroxy-1-(3-trifluoromethyl-phenyl)-ethylideneaminooxymethyl]-benzonitrile		Hen muscle, fat + skin, and liver
MET L24 2-[1-(3-Trifluoromethyl-phenyl)-ethylideneaminooxymethyl]-benzaldehyde		Hen liver

- a Quantitative results were not reported.
- b This metabolite was only found in goat liver following microwave-assisted extraction of nonextractable residues; the petitioner concluded (based on a control experiment) that this compound resulted from the thermal decarboxylation of CGA 321113.
- c The petitioner believes that the presence of this metabolite in egg white is a result of degradation of MET 1U, or a conjugate of MET 1U, during sample workup.
- d The metabolite termed MET EW1 was identified in this tissue. When MET EW1 was isolated from liver it was determined to consist of two compounds, EW1a and EW1b; EW1b was present at about twice the level of EW1a. EW1b was identified but EW1a could not be identified.



13544



003328

Chemical:	Invalid PC Code
PC Code:	129112
HED File Code	21400 MARC
Memo Date:	07/13/99
File ID:	DPD257835
Accession Number:	412-01-0084

HED Records Reference Center
01/23/2001



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