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

AUG 15 1984

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: PP#4G3075. Tilt® on Small Grains. Evaluation of Residue Data and Analytical Method (100-EUP-69). (Accession Nos. 072487, 072488, 072556, 072557)

FROM: Lynn M. Bradley, Chemist
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THRU: Charles L. Trichilo, Chief
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and

Toxicology Branch
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The CIBA-GEIGY Corporation proposes temporary tolerances for combined residues of the fungicide CGA-64250, 1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-1H-1,2,4-triazole, and its metabolites determined as 2,4-dichlorobenzoic acid and expressed as the parent compound in or on the following commodities:

Kidney and liver of cattle, goats, hogs, horses, sheep, and poultry	0.1 ppm
Rice	0.1 ppm
Grain of wheat, barley, rye	0.1 ppm
Straw of wheat, barley, rye	1.5 ppm
Rice straw	3.0 ppm

No permanent tolerances have been established for CGA-64250. Permanent tolerance requests are in reject status for pecans (PP#4F3007, A. Smith, 5/15/84), bananas (PP#4E3026, K. Arne, 6/20/84), and for rice and rice straw, grain and straw of wheat, barley, and rye, and liver and kidney of cattle, goats, hogs, horses, sheep, and poultry (PP#4F3074, A. Smith, 7/12/84).

A temporary tolerance of 0.1 ppm for residues of the fungicide CGA-64250, 1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-1H-1,2,4-triazole and its metabolites containing the 2,4-dichlorobenzoic acid moiety in or on pecans was established pursuant to PP#1G2530. This tolerance and its associated experimental permit (100-EUP-70) expired on 12/31/83, and have not been renewed.

The experimental program proposed in connection with this petition is summarized below. A total of 3700 lb active fungicide is proposed.

Crop	Rice	Wheat	Barley	Rye
No. states	5	43	12	4
Acres	4000	16,875	2,175	200

NOTE TO PM: An experimental program of this size, especially for wheat, is not necessary to produce sufficient residue data. We question the need for such large acreage.

CONCLUSIONS

1a. The nature of the residue in plants and animals is adequately understood.

1b. Plant residues consist of the parent compound CGA-64250; free and conjugated metabolites containing the intact parent ring system (four hydroxylated derivatives of the parent compound, CGA-118241); free and conjugated components containing both the phenyl and triazole rings--CGA-91304, CGA-91305, and CGA-104284. The residues of the fruiting parts consist primarily of the amino acid conjugate of the triazole ring, 1,2,4-triazole-1-alanine. RCB defers to TOX as to whether or not the residues containing the triazole moiety are toxicologically significant. If so, then these components should be included in the tolerance expression for plant commodities.

1c. Residues in animals (goats, rats, mice) consist of the parent CGA-64250 and metabolites containing the intact parent structure with hydroxy groups, carboxylic acid groups, or hydroxy acid groups on the alkyl side chain of the dioxolane ring (CGA-118244, CGA-118245, CGA-121676, alpha-hydroxy-carboxylic acid). These components appear free and as glucuronide and sulfate conjugates. Lesser quantities of residue components consist of the intact dichlorophenyl and triazole-ring structure, i.e., CGA-91304 and CGA-91305. These components may contain hydroxy and methoxy groups on the phenyl ring and appear free and as glucuronide and sulfate conjugates. Meat (liver) and milk contain, in addition to traces of the above components, triazole (CGA-71019), triazolealanine conjugate, and possibly the acetyl derivative of triazolealanine (about 50% of milk

residues). In tissues, the triazole ring is conjugated with amino acids and possibly bound in protein linkages. Residues do not concentrate in the fat of meat or milk. RCB defers to TOX as to whether or not the components containing the triazole moiety are toxicologically significant. If so, then these components should be included in the tolerance expression for animal commodities.

2a. Three validated analytical procedures are available for the determination of residues in plant and animal commodities. One procedure determines the parent compound, CGA-64250, in plants. The method's sensitivity is about 0.1 ppm. The two remaining procedures determine the parent compound, free and conjugated metabolites containing the intact parent ring system, and free and conjugated components containing both the dichlorophenyl and triazole rings in plant and animal commodities. The methods are sufficiently sensitive for residue determinations in plant and animal commodities.

2b. The analytical methods do not determine components which contain only the triazole moiety. If TOX concludes that such components are toxicologically significant, then validated analytical methods which determine such components in plant and animal commodities should be submitted.

3a. The residue data for the plant and animal commodities do not reflect components containing only the triazole moiety. These components can comprise a significant portion of the fruiting parts of plants (e.g., grains) and eggs, milk, and meat. If TOX concludes that such components are toxicologically significant, then residue data for plant and animal commodities which reflect these components should be submitted.

3b. Grain processing studies indicate concentrations of residues in the milling fractions (bran, shorts) of wheat, barley, and rye, and in the milling fractions (bran, hulls, polishings) of rice. Therefore, food additive tolerances will be needed to cover residues in the grain milling fractions.

3c. Because of the questions raised on the residue data, RCB cannot reach valid conclusions on the adequacy of the proposed tolerances for the small grains and commodities of livestock. Petitioner should be advised that livestock tolerances should be expressed as residues in "meat, fat, and meat by-products of cattle, goats, hogs, horses, sheep and poultry." Method sensitivity tolerances will be necessary for those commodities not showing detectable residue levels.

3d. Should TOX determine that residue components containing only the triazole moiety are toxicologically significant, then tolerances for milk and eggs may be needed. Additionally, the tolerance expression for plant and animal commodities would need to reflect all components containing the triazole moiety. An appropriate an appropriate tolerance expression

to reflect total residues is as follows: "... combined residues of the fungicide CGA-64250, [chemical name], and its metabolites determined as 2,4-dichlorobenzoic acid and 1,2,4-triazole and expressed as the parent compound in or on ...."

RCB recommends against the proposed tolerances. A favorable recommendation is contingent upon resolution of the questions raised in Conclusions 2b, 3a, 3b, 3c, and 3d.

Regarding the status of our repeated deferrals to TOX regarding the significance of the residue components which contain only the triazole ring (petitions 4F3007, 4F3026, and 4F3074, as well as this temporary tolerance request), we have been advised that TOX is currently evaluating the triazolealanine compound (personal communication, W. Dykstra, 7/26/84), and there appears to be cause for concern. Our conclusions will await a formal answer from TOX.

DETAILED CONSIDERATIONS

Manufacture and formulation

Tilt®, an emulsifiable concentrate containing 3.6 lb/gal 1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-1H-1,2,4-triazole (41.8% active ingredient) is proposed for use as a fungicide on small grains.

The manufacturing process and technical grade CGA-64250 has been fully discussed in PP#1G2530 (J. Worthington, 1/7/82). The impurities are not likely to be a residue problem.

The formulation's inert ingredients are cleared for use under 40 CFR 180.1001(c) or (d).

Proposed Uses

Wheat, barley, rye Apply 50 gms a.i./A (1.76 oz a.i./A) in a minimum of 20 gal/A with ground equipment or 10 gal/A by air. Highest yields are normally obtained when Tilt is applied at the end of flag leaf emergence (growth stage 8), but application may be made earlier if disease symptoms appear. Apply before the boot splits and head emerges to avoid possible illegal residues. Only 1 application per season is permitted.

Rice Apply Tilt as an aerial spray in 5-10 gal water/A by either of the following schedules:

--75 gms a.i. (2.65 oz a.i.) per acre at time of first internode elongation (panicle initiation) and repeat

at time of booting before the boot splits and head emerges (2 applications totaling 150 grams or 5.3 oz).

--100-125 gms a.i./A (3.53 - 4.41 oz a.i./A) at internode elongation (panicle differentiation) (only one application allowed).

Nature of the Residue

The metabolism of CGA-64250 in plants and animals has been fully discussed in PP#4F3007 (A. Smith, 5/15/84). The conclusions are summarized here.

Plants (peanuts, wheat, corn, tomatoes, grapes, lettuce, carrots). Plant residues consist of the parent compound CGA-64250; free and conjugated metabolites containing the intact parent ring system (four hydroxylated derivatives of the parent compound, CGA-118241); free and conjugated components containing both the phenyl and triazole rings--CGA-91304, CGA-91305, and CGA-104284. The residue of the fruiting parts consists primarily of the amino acid conjugate of the triazole ring, 1,2,4-triazole-1-alanine. RCB again defers to TOX as to whether or not the residues containing the triazole moiety are toxicologically significant and, therefore, should be included in the tolerance expression for plant commodities. Radiolabeled studies on peanuts indicate that approximately 22% of the residue in the peanut plant contained only the triazole ring (PP#1G2530, J. Worthington, 1/7/82). Concern for the triazole-containing portion of the residue has arisen in connection with later petitions, since we recommended in favor of the temporary tolerance for pecans. We therefore continue to defer to TOX in this petition.

Animals (goats, rats, mice) Residues in animals consist of the parent compound CGA-64250 and metabolites containing the intact parent structure with hydroxy groups, carboxylic acid groups, or hydroxy acid groups on the alkyl side chain of the dioxolane ring (CGA-118244, CGA-118245, CGA-121676, alpha-hydroxy-carboxylic acid). These components appear free and as glucuronide and sulfate conjugates. Lesser quantities of residue components consist of the intact dichlorophenyl and triazole ring structure, i.e., CGA-91304 and CGA-91305. These components may contain hydroxy and methoxy groups on the phenyl ring and appear free and as glucuronide and sulfate conjugates. Meat (liver) and milk contain, in addition to traces of the above components, triazole (CGA-71019), triazolealanine conjugate, and possibly the acetyl derivative of triazolealanine (about 50% of milk residues). In tissues, the triazole ring is conjugated with amino acids and possibly bound in protein linkages. Residues do not concentrate in the fat of meat or milk.

RCB again defers to TOX as to whether or not the components containing the triazole moiety in eggs, milk, and meat are toxicologically significant and, therefore, should be included in the tolerance for animal commodities.

The nature of the residues in plants and animals is adequately understood. Plant and animal residues consist of the parent compound, CGA-64250, free and conjugated components containing the parent-ring structure, components containing the dichlorophenyl and triazole rings, and components containing the triazole ring.

Analytical Methods

One analytical method (Method No. AG-354, "Gas Chromatographic Determination of CGA-64250 Residues in Crops") entails initial extraction of a chopped sample by blending with a water/methanol solution and filtering. An aliquot of the extract is partitioned with an aqueous sodium chloride/ dichloromethane mixture. The dichloromethane phase containing the residues of CGA-64250 and its metabolites is filtered and evaporated to dryness.

The residue is cleaned up on an alumina column and eluted with an ethyl ether/hexane mixture which is then evaporated to dryness and the residue taken up in acetone. Quantitation is by gas chromatography using an alkali flame ionization detector which is sensitive to nitrogen.

The method determines the parent compound CGA-64250 only. The limit of detection is reported to be 0.05 ppm. Validation data are reported, consisting of recoveries at the 0.4 ppm level of an average of 118 $\pm$ 3% (soybean grain) and 94 + 4% (soybean fodder). The background level is reported to be <0.05 ppm. The method's sensitivity is about 0.1 ppm.

A second method, "Determination of Total CGA-64250 and CGA-64251 Residues in Crops by Conversion to 2,4-Dichloro-benzoic Acid Using Miniaturized Techniques and Analysis by Capillary Gas Chromatography" (Method No. AG-415), is also presented. This method is considered more useful for residue determinations, and is the one used for residue data submitted with this petition.

A macerated sample is refluxed with a concentrated ammonium hydroxide/methanol solution. The mixture is cooled and filtered. An aliquot is concentrated and refluxed with 70% nitric acid. The nitric acid reflux converts residues containing the 2,4-dichlorophenyl moiety to 2,4-dichlorobenzoic acid.

The mixture is cooled, and the 2,4-dichlorobenzoic acid residues extracted into a diethyl ether/hexane solution. The extract is evaporated to dryness and treated with a diazomethane

partitioned into the acetonitrile. The acetonitrile is evaporated to an aqueous solution which is treated with concentrated nitric acid and digested overnight. The mixture is cooled and partitioned into a hexane/ethyl ether mixture which is evaporated to dryness.

The residue is treated with a diazomethane solution which forms the methyl derivative of dichlorobenzoic acid. The solvent is evaporated, and the residue is cleaned up on a silica gel column and eluted with an ethyl ether/hexane solvent mixture. (For liver samples an additional cleanup with an aluminum oxide column is performed.) The eluate is concentrated, and the residue is determined by gas chromatography using an electron capture detector. The residues are expressed as the parent compound CGA-64250. The method determines residues of CGA-64250 and its metabolites which contain the 2,4-dichlorophenyl moiety. The method does not determine metabolites which contain only the triazole moiety.

Control samples had no detectable CGA-64250-equivalent residues--milk, <0.01 ppm, and liver and eggs, <0.05 ppm. Control milk, tissues, and egg samples were fortified with CGA-64250 at levels of 0.01-2.0 ppm. Overall recoveries were 51-94%. The method sensitivities for the various commodities are milk, 0.01 ppm; eggs, 0.05 ppm; and meat, 0.05 ppm. For further discussion on the method's deficiencies relative to metabolites containing only the triazole moiety, see Meat, Milk, Poultry, and Eggs.

If TOX concludes that components containing only the triazole moiety are toxicologically significant, then such components must be included in tolerance proposals. Residue methods which determine such components will then be required. The method must be properly validated for the significant components of the residues in eggs, meat, milk, and crops.

Residue Data

Wheat Crops were grown in Ohio (2.3%), New York (0.2%), Illinois (2.6%), North Carolina (0.3%), Mississippi (0.3%), Minnesota (5.7%), and Kansas (16%). (The numbers in parentheses represent percentages of total U.S. annual wheat harvest). These 7 states represent approximately 27% of the total U.S. annual wheat harvest.

Samples of winter wheat grain and straw were obtained from crops which had been treated as proposed and at the proposed rate. The grain had no detectable residues (<0.05 ppm) at 49-80 days after treatment (PHI). The straw had residues of 0.08-0.79 ppm during the same PHIs.

Four processing studies were conducted altogether. The first was on grain samples obtained from crops which had received

two applications (0.5X or 1X, 28 days apart) were harvested at 54 days after the last application. The grain had no detectable (<0.05 ppm) residues. The processing fractions (germ, shorts, bran, flour) also had no detectable residues (<0.05 ppm).

Grain samples obtained from crops which had received two applications (0.5X plus 1X or 1X plus 2X, 19 days apart) were harvested 42 days after the last application. The grain had no detectable residues (<0.05 ppm). The shorts, germ and flour also had no detectable (<0.05 ppm) residues. The bran had residues of 0.11-0.13 ppm.

Grain samples from crops which had received single applications at 1X or 2X the proposed rate were harvested at 49 days after treatment. The grain and flour had no detectable residues (<0.05 ppm). Residues in the processing fractions were shorts, <0.05-0.08 ppm, and bran, <0.05-0.09 ppm.

The most useful study was on samples from crops which had received single applications at 2X and 4X the proposed rate. At the 2X rate, residues in grain were 0.15 ppm at a 29-day PHI. Residues in the processing fractions were bran, 0.54 ppm; shorts, 0.19 ppm; flour, <0.05 ppm. At the 4X rate residues in the grain were 0.29 ppm and residues in the processing fractions were bran, 1.4 ppm; shorts, 0.20 ppm; flour, <0.05 ppm. Only this study has detectable residues in the grain and demonstrates that residues in the grain are concentrated in the bran (3.6X-4.8X) and the shorts (1.3X). No concentration of residues occurs in the flour. The other studies show no concentration in the germ and support the residue concentration in the bran and shorts. The maximum concentration factors noted are for bran (5X) and shorts (1.3X). We note that residues containing only the triazole ring are not measured.

Since residues are concentrated in the processing fractions bran and shorts, a food additive tolerance is needed to cover excess residues in these items. The level needed to cover residues in bran and shorts is not calculated here because of questions on the residue components. (These questions will be discussed after discussion of data for all crops.)

Barley Crops were grown in California (12%), North Dakota (25%), and Nebraska (0.5%). These states make up 38% of the total annual U.S. harvest.

Sample were obtained from crops which had been treated as proposed and at the proposed rate. The grain had no detectable (<0.05 ppm) residues at PHIs of 39 and 69 days. Barley straw had residues of 0.07-1.0 ppm at PHIs of 39 and 69 days.

No residue data are submitted which show if barley grain residues are concentrated in its processing fractions. However, since the grains of barley and wheat are similar, the results

of the wheat processing studies can be extended to include barley. Therefore, a concentration of residues is expected in the bran of barley (5X). No concentration of residues is expected in the flour or hulls of barley milling fractions. A food additive tolerance is need to cover residues in barley grain milling fractions.

Rye No residue data for rye grain or straw are submitted. For the purpose of this temporary tolerance, we will translate residue data from the other small grains to rye.

Rice Crops were grown in Arkansas (33.9%), Louisiana (22.7%), and Mississippi (5.8%). These states account for approximately 62% of the total annual U.S. rice grain harvest.

Samples were collected from crops which had received one (1X-2X proposed rate) or two (1X-3.3X proposed rate) foliar applications. No residues were detected (<0.05 ppm) in the grain from the proposed rates and PHIs of 53-80 days. The straw had residues of 0.05-2.08 ppm from the proposed rates and at PHIs of 53-80 days. A rate of 128 gms a.i./A yielded grain residues of 0.37-0.44 ppm at 20-26 days. The straw had residues of 5.7-7.4 ppm under the same conditions.

The exaggerated rate (2X) showed grain residues of <0.05 ppm and straw residues of 0.09 ppm at a PHI of 67 days. At PHIs of 20-26 days, the grain had residues of 0.65-1.3 ppm and the straw had residues of 12-15 ppm.

Rice grain which had no detectable residues (<0.05 ppm) were processed to hulls, bran, and polishings. No detectable residues were noted in the bran or polishings. However, the hulls had residues of <0.05-0.08 ppm. When considered alone, the residue data indicate no significant concentration of residues in the rice milling fractions (bran, hulls, polishings). However, when compared with the results for wheat milling fractions and considering the meager data, it is reasonable to assume that rice grain residues could be concentrated in the milling fractions upon processing. As a result, a food additive tolerance will be needed to cover excess residues in rice grain milling fractions (bran, hulls, polishings).

The residue data for barley, rice, and wheat do not include components containing only the triazole moiety (for example, triazolealanine). RCB has indicated (see Nature of the Residue) that fruiting parts of plants will contain the amino acid conjugate triazolealanine in significant quantities. RCB is requesting TOX's opinion on the toxicological significance of the triazole component of the residue in the grains of barley, rice, and wheat. If TOX concludes that these components are toxicologically significant, then additional residue data for barley, rice, and wheat grains and straw must be submitted. These data should also include analyses for components containing only the triazole moiety. The tolerance proposals should then

be changed to reflect total residues of CGA-64250 and its metabolites, including all components containing the triazole moiety as well as those containing the 2,4-dichlorophenyl moiety.

In view of the foregoing, valid conclusions on the adequacy of the tolerance levels for barley, wheat, rye, and rice are not possible.

Meat, Milk, Poultry, and Eggs

Livestock Feeding Studies Cows (Report No. ABR-83091) Lactating cows were fed CGA-64250 in the daily diet at levels of 15, 75, and 150 ppm for periods up through 28 days. The animals were milked daily, and milk samples were collected at intervals of 0, 1, 4, 7, 12, 14, 21, and 28 days. The samples were analyzed for total residues of CGA-64250. The animals were sacrificed at 14, 21, and 28 days during the study period. Tissue samples were collected and examined for residues of CGA-64250.

Sample analyses of milk and tissues for the parent compound only were performed by using the extraction procedure of Method No. 359 and the determinative procedure of Method No. 354. Milk samples were initially extracted by shaking with acetonitrile, and tissue samples were initially extracted by homogenizing with an 80% acetonitrile/water mixture. The extracts from milk or tissues were partitioned with hexane to remove fats. The extracts were evaporated to dryness and cleaned up on an alumina column.

The parent compound, CGA-64250, is determined by gas chromatography using an alkali flame ionization detector which is sensitive to nitrogen. The limits of determination are reported to be 0.01 ppm for milk and 0.05 ppm for tissues.

Total residues of CGA-64250 and its metabolites which contain the 2,4-dichlorophenyl moiety were determined as follows. The initial extraction was the same as above. However, no alumina column cleanup was included. The extract from the hexane partitioning is concentrated to the aqueous phase and refluxed with nitric acid for 16 hours. (The parent and the metabolites are converted to 2,4-dichlorobenzoic acid.) The mixture is cooled and diluted, and the residues are extracted with ethyl ether in hexane. The extract is evaporated to dryness and methylated with diazomethane. The derivative is cleaned up on a silica gel column. (For liver, an additional cleanup with an alumina column is necessary.)

The residue is determined by gas chromatography using an electron capture detector. Residues are expressed as CGA-64250-equivalent residues. The limits of determination are reported to be 0.01 ppm for milk, 0.1 ppm for kidney, and 0.05 ppm in other tissues.

In milk, no residues were noted at the 15 ppm feeding level. Total residues of <0.01-0.08 ppm were noted at the 75 ppm feeding level and plateaued on day 7 at 0.08 ppm. At the 150 ppm feeding level, total residues were <0.01-0.11 ppm and a plateau was reached on day 14 at 0.11 ppm. No residues of the parent compound were reported for any feeding level.

Residues were found in all tissues (tenderloin, round, kidney, liver, omental fat, perirenal fat) and at all feeding levels. Maximum residue levels were noted in the kidney and liver. The reported residues for all tissues are summarized below.

Tissue Residues Found (ppm)

TISSUE	FEEDING LEVEL (PPM) 15	75	150
Kidney	0.56-0.63	3.0-4.7	5.0-6.5
Liver	0.50-0.81	2.7-4.3	4.6-5.6
Fat	<0.05 (ND)*	0.07-0.23	0.13-0.26
Round	<0.05 (ND)*	0.05-0.11	0.11-0.18
Tenderloin	<0.05 (ND)*	<0.05-0.08	<0.09-0.13

*ND means no detectable residues.

Poultry (Report No. ABR-83092). Laying hens were fed CGA-64250 in their daily ration at levels of 7.5, 37.5, and 75 ppm for 28 days. Samples of eggs were collected daily for analysis. Chickens were sacrified at weekly intervals and samples of tissues were taken for analysis. All samples were analyzed for total residues of CGA-64250 and its metabolites as the methyl ester of 2,4-dichlorobenzoic acid and reported as CGA-64250 equivalents. Some samples were also analyzed for residues of the parent compound CGA-64250.

Analytical Method No. AG-359 is used to determine total residues of CGA-64250 and its metabolites containing the dichlorophenyl moiety. Egg samples are extracted by shaking with acetonitrile. Poultry tissues are extracted by homogenizing with an acetonitrile/water mixture. An aliquot of the mixture is extracted with hexane and concentrated to the aqueous phase. The aqueous phase is refluxed with nitric acid to convert parent and metabolites containing the dichlorophenyl moiety to 2,4-dichlorobenzoic acid. The mixture is cooled, diluted, and residues extracted into ethyl ether/hexane. The extract is evaporated to dryness and the 2,4-dichlorobenzoic acid is methylated with diazomethane. The derivative is cleaned up

on a silica gel column, and the residues are determined by gas chromatography using an electron capture detector. The limits of determination are reported as 0.10 ppm for liver and 0.05 ppm for eggs and other tissues.

The parent compound in eggs and tissues were determined using the above initial extraction procedure. The ethyl ether/hexane phase which contains CGA-64250 is evaporated to dryness and the residue is cleaned up on an alumina column. The parent compound, CGA-64250, is determined by gas chromatography using an alkali flame ionization detector which is sensitive to nitrogen. (This determination procedure is that of Analytical Method No. AG-354.) The limit of determination is reported to be 0.05 ppm for eggs and tissues.

No residues of the parent compound were found in eggs at any feeding level. No residues of parent and metabolites were noted (<0.05 ppm) from the 7.5 ppm feeding level. At the 37.5 ppm feeding level, detectable residues (0.13 ppm) appeared on the third day of feeding and reached a maximum of 0.18 ppm on the 14th day of feeding. Residues on day 28 were 0.06 ppm. At the 75 ppm feeding level, residues first appeared on day 3 (0.06 ppm). Residues reached a maximum of 0.37 ppm on day 21 and were 0.22 ppm on day 28.

No residues of the parent compound, CGA-64250, were found (<0.05 ppm) at any feeding level in any tissue (breast plus thigh, liver, fat, skin). No residues were found in any tissue (except liver) at the 37.5 ppm feeding level. Residues in the liver were <0.10-0.16 ppm. At the 75 ppm feeding level, residues were noted in all tissues--breast plus thigh (<0.05-0.07 ppm), liver (0.30-0.47 ppm), fat (0.05-0.11 ppm), and skin (0.05-0.07 ppm).

The residue results for milk, eggs, and tissues reflect only components which contain the dichlorophenyl moiety. However, metabolism studies with goats (see Nature of the Residue) show that milk and tissue residues contain significant quantities of components containing the triazole ring only (e.g., triazolealanine and, possibly, an acetyl derivative of trizolealanine). The analytical method use for milk and tissue analysis does not determine residues of triazolealanine. As a result, the residue levels reported for milk, eggs, cow, and poultry tissue in the above feeding studies do not reflect significant portions of the residues expected to occur in eggs, milk, and tissues after ingestion of residues of CGA-64250 and its metabolites.

We defer to TOX as to whether residue components containing only the triazole ring are considered toxicologically significant. If TOX determines that such components are toxicologically significant, then the components must be included in the tolerance proposals. This would require analyses of eggs, milk, and tissues of cows and poultry for residues of triazolealanine and other components

containing only the triazole ring. Until TOX determines whether the triazole components are significant, we will continue to be unable to reach valid conclusions on the expected residue levels due to the absence of analyses for components containing only the triazole ring.

The grains and grain mill fractions of barley, rice, rye, and wheat and the straw and forages are livestock feed items. As a result, it is necessary to consider the residues contributed from the livestock ingestion of the feed items. However, RCB has concluded (see Residue Data) that the level of residues in the feed items cannot be determined due to inadequate residue data.

Residue data deficiencies preclude valid conclusions on residue levels likely to occur in eggs, milk, meat, fat, and meat by-products of livestock. The feeding studies reviewed above are sufficient to indicate that residues might occur, however. Any commodities not expected to contain analytically detectable residues will require a tolerance at the level of method sensitivity. Commodities having significant residue levels will require tolerances at appropriate levels. Assuming that the triazole-only-containing components are determined to be toxicologically significant, an appropriate tolerance expression to reflect total residues is as follows: "... combined residues of the fungicide CGA-64250, [chemical name], and its metabolites determined as 2,4-dichlorobenzoic acid and 1,2,4-triazole and expressed as the parent compound in or on ...." Additionally, the tolerance expression for meat should be revised to reflect all meat products, i.e., " ... meat, fat, and meat by-products of cattle, goats, hogs, horses, sheep, and poultry".

cc: R.F., Circu, Reviewer, EAB, EEB, TOX, PP#4F3075
RDI: ARR:8/13/84:RDS:8/13/84
TS-769:RCB:CM#2:RM810:X737:Lynn Bradley:Edited by:wh:8/14/84