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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MAY 15 1984

MEMORANDUM

SUBJECT: PP#4F3007 (Acc. Nos. 072212-072217 and 072219): CGA-64250 (Tilt) in Pecans. Evaluation of residue data and analytical method.

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Ciba-Geigy Corporation proposes a tolerance for residues of the fungicide CGA-64250, (1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl] methyl]-1-H-1,2,4-triazole; TILT®], and its metabolites, determined as 2,4-dichlorobenzoic acid and expressed as the parent compound, in or on pecans at 0.1 ppm.

This is the first permanent tolerance proposal for this chemical. A temporary tolerance (PP#1G2530) of 0.1 ppm in pecans has been approved by RCB (see memo of Linda S. Propst, 2/10/84).

Conclusions

1(a) The label statement on grazing should be changed to read, "Do not graze livestock in treated areas or cut treated cover crops for feed."

1(b) The application dosage should also be expressed as pounds active ingredient per 100 gallons of spray solution (consult EPA Pesticide Assessment Guidelines-Subdivision O- Residue Chemistry).

2(a) The nature of the residue in plants and animals is adequately understood.

2(b) 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 aminoacid conjugate of the triazole ring, 1,2,4-triazole-1-alanine. (All components are determined by the analytical methods.) RCB defers to TOX as to whether or not the residues containing the triazole moiety should be included in the tolerance expression for plant commodities.

2(c) Residues in animals (goats, rats, mice) 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. Although no feed items are involved in this petition, RCB defers to TOX as to whether or not the components containing the triazole moiety should be included in the tolerance expression for animal commodities to be considered in future proposed usages.

3(a) Two analytical methods are available for the determination of residues in crops. In one method residues

of the parent compound CGA-64250 and metabolites containing 2 and 3 rings (free and conjugated) are determined. The method's overall sensitivity is approximately 0.2 ppm. This level is greater than the proposed tolerance level of 0.1 ppm. The method is not sensitive enough to support the proposed tolerance. More important, however, if TOX declares that all triazole residues must be included in the tolerance expression, then this procedure, as validated, should not be considered for regulatory purposes.

3(b) The second method determines residue components containing the triazole ring as the dibromomethyl derivative. However, untreated samples yielded triazole equivalent residues up to 2.6 ppm which seriously interfere with the determination of triazoles from treatment with CGA-64250. Therefore, the method is not adequate for the determination of residues of CGA-64250; improvements are needed. Analytical methods must be submitted which determine residues of CGA-64250 and its metabolites at levels which reflect the residues expected from the proposed use. The methods must be capable of distinguishing between residues due to treatment and background components. After the petitioner has resolved those deficiencies relating to the analytical methodology and as to what the appropriate tolerance level should be (see Conclusion 4 below), RCB will request an EPA method trial.

4. The residue data generated by the triazole procedure (AG-357) show, for example, pecan meats containing as much as 12 ppm total residues after six 1x applications and observance of 30-day intervals. As a result, we defer to TOX for the toxicological significance of those residues containing the triazole moiety (1,2,4-triazole, etc.). If TOX declares that triazole residues must be included in the tolerance expression, and the petitioner chooses to improve the triazole procedure, then the tolerance expression should be expressed as "...combined residues of the fungicide CGA-64250,...., and its metabolites determined as 1,2,4-triazole and expressed as the parent compound, ...in or on pecans at ...ppm." At this time, it is not possible to reach a valid conclusion on an appropriate CGA-64250 (Tilt) tolerance for pecans.

5. No feed items are involved in this petition.

6. There are no Codex or international tolerances for CGA-64250 (see attached International Residue Limit Status sheet).

Recommendation

RCB recommends against the proposed tolerance of 0.1 ppm CGA-64250 (Tilt) in/on pecans. A favorable recommendation is contingent upon resolution of the questions raised in conclusions 1(a), 1(b), 2(b), 3(a), 3(b), 4.

The petitioner should be informed of the deficiencies.

Detailed Considerations

Formulation

CGA-64250 is formulated as Tilt® 3.6E Fungicide, an emulsifiable concentrate containing 47.6% active ingredient (a.i.) or 3.6 pounds per gallon, for use as a foliar spray on pecan trees.

[redacted] (memo of J. Worthington, 1/7/82). The impurities are not likely to produce a residue problem.

The formulation's inert ingredients are cleared for use under §180.1001.

Proposed Uses

Applications begin at prepollination when young leaves are unfolding. Continue while small nuts are forming, and repeat at 2-4 week intervals as needed. A maximum of six applications per growing season is permitted, and no application is to occur after shucksplit (an outer husk protects the developing pecan and splits at pecan maturity.). Additionally, grazing of livestock is not permitted in treated areas.

The grazing restriction is inadequate and should be changed to read, "Do not graze livestock in treated areas or cut treated cover crops for feed."

The following application rates are permitted in a minimum of 10 gallons of water per acre. For trees over 30 feet tall, use 102-153 grams a.i. (0.22-0.34 lb) per acre. For trees under 30 feet tall, use 77-115 grams a.i. (0.17-0.25 lb) per acre.

Information which may reveal the manufacturing process has been deleted.

The application rates should also be expressed in terms of pounds active ingredient per 100 gallons of spray solution (consult EPA Pesticide Assessment Guidelines - Subdivision O - Residue Chemistry).

Nature of the Residue

Metabolism studies are submitted with wheat, corn, grapes, lettuce, carrots, tomatoes, and peanuts which have been treated with radiolabeled forms of the fungicide chemical CGA-64250 (formulation name: Tilt®). The studies show that CGA-64250 is absorbed by plants from soil and foliar applications, metabolized, and translocated.

The major metabolic pathway of CGA-64250 is thru hydroxylation of the beta-carbon of the n-propyl side chain of the dioxolane ring. This hydroxylation yields four metabolites which form sugar (glucoside) conjugates. A minor metabolic pathway involves rupture of the dioxolane ring to yield the alkanol (a compound with a hydroxy group on the alkyl bridge between the dichlorophenyl and triazole rings). The alkanol also undergoes conjugation with sugars. (The sugar conjugates are freed thrugh enzyme or acid digestion.)

The fruits formed from growing plants further metabolize the translocated metabolites. The bridge between the dichlorophenyl and triazole rings is broken and yields the triazole ring as the major residue component. The triazole ring is conjugated with the amino acid alanine. (See the accompanying charts for chemical and structural identification of components of the residue.)

The various metabolism studies are discussed below.

Plant Studies

A study was carried out (Report No. ABR-80006) in which greenhouse grown peanut plants (grown in 10 quart aluminum pails) were treated with radiolabeled CGA-64250. One set of plants was treated with the C^{14}-label in the triazole ring, and another set was treated with the C^{14}-label in the phenyl ring. [redacted] The plants were spray-treated 3 times: two at a rate of approximately 0.31 lb act/A; one at a rate of approximately 0.21 lb. act./A. Samples were collected at various intervals following each treatment and analyzed for residues.

Aliquots of homogenized samples were combusted, and the total radioactivity was determined by liquid scintillation counting techniques (LSC).

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For characterization of the components of the residue, aliquots of homogenized samples were extracted to yield aqueous and organic fractions. Each fraction was examined by one-dimensional thin layer chromatography (TLC). A different extraction of a sample aliquot involved the use of a methanol/water solution and filtering. The filtrate was partitioned with hexane to remove colored pigments and other interferences. The filtrate was then extracted with ethyl acetate which was concentrated and examined by two-dimensional TLC.

Additional characterizations were performed using sulfuric acid reflux reactions, Kjeldahl reflux reactions, and enzymatic hydrolyses on a portion of the aqueous methanol fraction above. The methanol was evaporated, and the residue in the aqueous portion was extracted into methylene chloride. The methylene chloride was dried, concentrated, and examined by TLC. The aqueous fraction was also subjected to ion-exchange cleanup, and radioactivity determinations were performed on the eluate.

The study shows that peanut plants absorb, metabolize, and translocate CGA-64250 throughout the plant, the peanut shell, and the nutmeat.

The plants received the first treatment at 5 weeks after planting. Sample collection occurred on the day of treatment (0-day) and 5 and 7 weeks later. The second treatment occurred at 12 weeks after planting (7 weeks after first treatment). Sample collection occurred on the day of the second spraying and 5 weeks later. The third treatment occurred at 17 weeks after planting (5 weeks after second treatment), and sampling occurred on the day of treatment and 5 weeks later. (The same schedule of treatments was followed for each labeled compound.)

The plant was divided into stalk, shell, and kernel, and each part was examined for radioactivity. The activity for each plant part was further expressed as organic, aqueous, and nonextractable fractions. The total activity was expressed as CGA-64250.

The maximum level of radioactivity was noted following the first spray treatment with the phenyl labeled compound. The stalk had 19 ppm, and the level had decreased to 1 ppm at intervals of 35 days and 49 days. At the maximum radioactivity level, approximately 93% of the activity was accounted for. The organic phase had 83%, the aqueous phase had 1%, and 9% was unextracted. (This behavior is expected since only one day has elapsed following treatment, and less metabolism of the parent would be expected at this time than at any other time.) At 35-49 days after treatment, the radioactivity in

the stalk was 21-23% organo-soluble, 52-57% aqueous-soluble, and 12-13% unextractable. The data indicate that metabolism and/or degradation of the parent compound is occurring.

At one day after the second application, the stalks had 6 ppm CGA-64250 equivalent radioactivity. At 35 days the stalk had residues of 2 ppm, the shell had 0.05 ppm, and the kernel had 0.04 ppm. The radioactivity in the stalk at 1 day was 68% organo-soluble, 13% aqueous-soluble, and 8% unextracted. At 35 days the activity in the stalk was 20% organo-soluble, 66% aqueous-soluble, and 13% unextracted. Again, the change in the soluble activity in the fractions indicate the change in the component composition of the residues. At 35 days the activity in the shell was 31% organo-soluble, 50% aqueous-soluble, and 26% unextracted. The kernel at 35 days had 30% organo-soluble, 50% aqueous soluble, and 19% unextracted activity.

The activity levels following the third application were similar to those noted following the second application. At 1 day after the third application, the stalk had 6.5 ppm CGA-64250-equivalent radioactivity. The shell had 0.03 ppm, and the kernel had 0.03 ppm total activity. The characterization of the activity (organic and aqueous soluble; unextracted) in the stalk, shell, and kernel was similar to that noted at day 1 above.

At 14 days after the third application, the stalk had total radioactivity equivalent to 4.4 ppm. The phase distribution was: 25% organo-soluble; 54% aqueous-soluble; and, 14% unextracted. The shell had activity of 0.09 ppm of which 31% was organo-soluble, 36% aqueous-soluble, and 19% unextracted. The kernel had activity of 0.05 ppm of which 24% was organo-soluble, 61% was aqueous-soluble, and 14% unextracted.

When peanut plants were treated with triazole-labeled C^{14}-CGA-64250, the residue deposition pattern was similar to the phenyl-labeled CGA-64250 treatments discussed above. The stalk had the highest residue levels, and the residues decreased with time. Initially, the organo-soluble activity represented the maximum percentage of the total activity. The amount of organo-soluble activity decreased with time and the aqueous-soluble activity increased. The amount of unextracted radioactivity also increased with time.

The metabolic route involved the conversion of the parent compound, CGA-64250, to more polar compounds which were subsequently conjugated with sugars. The organo-soluble fraction contained the parent compound. This compound represented 18% of the total radioactivity in mature plants irrespective of the radiolabeled site. The metabolites in

the plant are also similar for the two radiolabelled compounds. The metabolism is more advanced in the peanut kernel than in the plant; little, if any, cleavage of the alkyl bridge between the dichlorophenyl and triazole rings is noted in the plant. This is not an unreasonable result. The metabolic process in the living plant is a continuous one, and application began long before the nuts were formed. As a result, the metabolites in the plant are translocated to the kernel and further metabolism occurs. The kernel contained a distribution pattern of 89% aqueous-soluble and 2% organo-soluble for the C^{14}-triazole label and 61% aqueous soluble and 24% organo-soluble for the dichlorophenyl label. These data indicate that the alkyl chain between the phenyl and triazole rings has been broken.

Qualitative and quantitative identification of the components of the residues were performed by liquid-liquid partitioning, enzyme digestion, ion exchange chromatography, thin layer chromatography (TLC), high performance liquid chromatography (HPLC), gas chromatography, and mass spectrometry (MS).

The residues in the mature stalk consist of 5 identified components with the intact parent ring system (i.e., dichlorophenyl, triazole, and dioxolane rings): the unchanged parent compound, CGA-64250, 1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-1H-1,2,4-triazole; 4 hydroxylated derivatives of the parent compound with the group designation of CGA-118241 (The hydroxylation is believed to be on the beta carbon of the alkyl chain on the dioxolane ring, and the 4 forms represent the cis/trans and D and L isomeric forms). These hydroxylated metabolites are also conjugated with sugars. The cis/trans isomers of the gamma-hydroxylated derivative, CGA-118242, are probably present, but at very low levels. A minor metabolic pathway yields the alkanol metabolite CGA-91305, alpha-(2,4-dichlorophenyl)-1H-1,2,4-triazole-1-ethanol. This compound has lost the dioxolane ring, and a hydroxyl group is at the 2-position on the alkyl bridge between the phenyl and triazole rings. This compound is also conjugated with sugars. These components represent 72-79% of the total C^{14}-activity in the mature peanut plant.

The major component of the peanut kernel is the triazole ring (about 50% of the activity), 1,2,4-triazole, which is conjugated with the amino acid alanine. The conjugate is designated RH-33968, (1,2,4-triazole-1-alanine). The petitioner states that the studies show no evidence of ring cleavage.

Additional studies with peanuts and tomatoes were carried out in support of the above findings. The studies are summarized below.

A field study was performed (Report No. ABR-81013) in which peanuts were grown in a small field plot and treated with 8 spray applications of C^{14}-triazole labeled CGA-64250 at two week intervals at a rate of 70 gm a.i./A (0.16 lb a.i./A). The soil had been treated twice at a rate of 0.375 lb a.i./A. Samples of the mature crop parts (stalks, shells, and kernels) were collected at 14 days after the last application.

The samples were analyzed as in the above study, and characterization of the residues were performed with the same techniques.

The results of this study were qualitatively the same as the above greenhouse study. However, the metabolism and/or degradation of CGA-64250 are more extensive. This is an expected result since more environmental factors are present which aid the breakdown of the chemical. For example, the conjugated triazole was 94% of the kernel activity as opposed to about 50% in the greenhouse study.

In order to confirm the identity of the major metabolite in peanut kernels, another study was performed (Report No. ABR-81031). Greenhouse grown peanuts were sprayed 8 times with C^{14}-triazole labeled CGA-64250 at 2-week intervals at approximately 0.16 lb a.i./A. Samples of peanuts were collected and analyzed for radioactivity as discussed in the above studies. In addition to previous analytical techniques used to characterize the residues, the analytical technique of infra-red spectroscopy (IR) was also used to aid in compound identification.

A second part of this study involved the use of tomato fruits to biosynthesize the alanine conjugate of the metabolite 1,2,4-triazole. Green tomatoes were treated with radiolabeled C^{14}-triazole by surface streaking and injection at levels equivalent to 20-30 ppm. The tomatoes were placed under fluorescent lighting (12 hours light and 12 hours dark cycles) for two weeks. The tomatoes were homogenized by blending with powdered dry ice. Aliquots of the homogenized sample were combusted and total radioactivity was determined by liquid scintillation counting techniques. The total activity was expressed as residues of CGA-64250.

The residue components were isolated and characterized by the same procedures and techniques used for peanuts. All of the tomato radioactivity was extractable. No free triazole was found. The alanine conjugate of 1,2,4-triazole was about 80% of the total radioactivity in the tomatoes.

The identity of the major component of the nutmeat residue as the alanine conjugate of 1,2,4-triazole was confirmed by comparison with a standard alanine triazole conjugate and the

alanine triazole conjugate isolated from tomatoes. The analytical techniques used liquid-liquid partitioning, cleanup on silicic acid and florisil columns, and formation of butyl and acetate derivatives to provide compound volatility. The component was qualitatively and quantitatively characterized with thin layer chromatography, gas chromatography, high performance liquid chromatography, mass spectrometry, and infra-red spectrometry.

Wheat

A metabolism study was submitted in which field grown wheat was treated with CGA-64250 (Project Report 36/79). A wheat crop was sprayed once with radiolabeled C^{14}-triazole-CGA-64250 [redacted] at a rate of 125 gms a.i./Ha (0.11 lb. a.i./A). Samples were collected over a period of 49 days after application and analyzed for radioactivity.

The radioactivity was measured by liquid scintillation counting techniques. The residue was cleaned up with a silica gel column and characterized with thin layer chromatography (TLC). The unextracted radioactivity was determined by combustion analysis. The residue components were further characterized and quantitated by gas-liquid chromatography (GLC), high performance liquid chromatography (HPLC), and high voltage electrophoresis. Conjugated components were released thru hydrolysis with hydrochloric acid.

The study shows that CGA-64250 is absorbed, metabolized, and translocated to the grain. After 11 days, the grain had residues of 0.2 ppm. At maturity (49 days), the grain had residues of 0.39 ppm. No parent compound was noted in the grain.

The straw had total activity equivalent to 1.42 ppm CGA-64250 at maturity (49 days) and the parent compound was at a level of 0.18 ppm (about 13% of the total activity). (An associated greenhouse study with wheat and CGA-64250 is reported to have yielded several unpolar metabolites which could be acetylated with acetic anhydride. One of these metabolites was probably the alkanol, CGA-91305. Additionally, there were indications that the n-propyl group on the dioxolane ring was oxidized.)

The residue characterization consisted primarily of showing that the radioactivity could be separated into three phases: unpolar (organo-soluble); polar (water soluble); and, unextracted. The organo-soluble activity was a maximum at 11 days and decreased thereafter. The water-soluble activity increased steadily from 50% at 11 days to 70% at 25 days.

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The unextracted residue increased from 0.4% at 1-day to 9% at 11 days, and 12% at 25 days.

A second field study was performed using radiolabeled CGA-64250 and wheat (Project Reports: 17/80; 19/81; 36/81). In this study the form of radiolabeled CGA-64250 used was C^{14}-phenyl labeled CGA-64250. The treatment was the same as in the above study: A single spray application at 0.11 lb a.i./A. However, samples were collected at 41 days instead of 49 days after treatment.

The results of the two studies were compared. The metabolic pathways for the two labeled compounds was similar. The nature of the residue was different for the grain. Radioactivity in the grain was higher from the triazole labeled CGA-64250. (This result is not unexpected when considering previous plant studies above.)

Following residue characterization and component quantitation of the straw residues, the metabolic path is found to be essentially the same as in the previous plant studies. The residues consist primarily of the parent compound, CGA-64250, and four parent-like metabolites with hydroxylation on the alkyl group of the dioxolane ring (4 isomeric forms: free and as glucoside [sugar] conjugates). Additionally, the presence of phenolic products was indicated in minor quantities in hydrolysis fractions of straw and husks. (Hydrolysis of conjugated residues were performed by digestion with hydrochloric acid or the enzyme cellulase). For the grain, approximately 54% of the radioactivity was shown to be the alanine conjugate of 1,2,4-triazole (CGA-131013). The study conjectures that ring hydroxylated phenyl components could be present as a byproduct of dichlorophenyl metabolism.

Both studies with wheat support the peanut and tomato metabolism studies discussed earlier and show that CGA-64250 is absorbed, metabolized, and translocated by plants.

Grapes

A study was performed with radiolabeled CGA-64250 and grape vines (Project Reports 42/80, 20/81, and 40/81). Three grape plants were sprayed 4 times with C^{14}-triazole labeled-CGA-64250. The application rate was 2.5 gms a.i./100 l water (0.09 oz. a.i.) and applications were made at 14, 16, and 18-day intervals.

A grape fruit sample was taken at 30 days after the last treatment, and samples of grapes and leaves were taken at harvest (about 60 days after the last treatment). The samples were cleaned up, and the residues were characterized and

determined using the same analytical techniques that were used in all previous plant studies.

The results of the study confirm the findings of the preceding plant studies. Grape plants absorb, metabolize, and translocate the fungicide CGA-64250. The residues of the whole grape leaves, grape juice, and press cake consisted of the following identified components: the parent compound and the four beta-hydroxy isomers (hydroxylated on the alkyl group of the dioxolane ring), identified as CGA-118244, in free forms and as glucoside (sugar) conjugates; the alkanol, CGA-91305 (free and as glucoside conjugate). The grape juice had components which reflected residues in the grape. The major component was the amino acid conjugate of the triazole, 1,2,4-triazole-1-alanine (CGA-113013). However, in the whole grape, the major component was the parent compound. This is not unexpected since the growing fruit received some direct deposits as well as some residues through translocation.

The radioactivity described as unextractable in all studies increased slowly with time. This residue was not significantly affected by acid or enzyme digestion. No further characterization was performed on the unextractable activity which seldom rose above a level of 20% of the total activity in plants at harvest. Undoubtedly, some of the activity represents a reincorporation of the radiolabeled atoms into naturally-occurring plant constituents. The absence of additional characterization of this unextracted residue does not alter the fact that generally the nature of the residue in plants is adequately delineated.

Uptake of C^{14}-CGA-64250 residues by rotational crops (Report No. ABR-82007)

Winter wheat, lettuce, corn, and carrots were grown in the field plots in which peanuts had been grown for 2 weeks. The peanuts had been sprayed 8 times with C^{14}-CGA-64250 at a rate of 0.16 lb a.i./A and the soil had been treated twice at a rate of 0.375 lb a.i./A (See Report No. ABR-81013). The total radioactivity in the soil was determined and expressed as residues of the parent compound CGA-64250. The soil residue components were not individually identified. The study was performed to determine the uptake of residues of CGA-64250 by rotational crops.

The soil residues decreased slowly with time. The total residue can be expressed in terms of extractable residues (those extracted with the methanol/water solvent system) and unextracted or soil-bound residues. The level of solvent-extractable residues decreased with time and the soil-bound residues increased with time.

The study showed that soil residues are absorbed by crops planted in rotation with peanuts, and such residues are translocated throughout the plant and the plant fruits.

Following the peanut harvest, the field plot was rototilled and winter wheat was planted in a subplot. The following spring, crops of lettuce, corn, and carrots were planted in subplots.

The winter wheat crop was sampled at various intervals and analyzed for residues. Analyses and residue characterizations were performed using the techniques discussed under the peanut studies.

At the time of planting, the soil residue concentration was 1.52 ppm in the 0-3 inch layer. This level had decreased to 0.49 ppm at the end of the growing season for the rotational crops. Approximately 25% of the extractable residues were organo-soluble at the time of planting of the rotational crops. The organo-soluble residues decreased with time. This indicates that CGA-64250 and its metabolites were being metabolized and/or degraded. Limited characterization of the soil residues during the peanut growth shows the parent compound to be approximately one-half of the total soil radioactivity. During the planting of the wheat crop, the parent CGA-64250 was about one-third of the total soil radioactivity. This shows that the parent compound was present in the soil at the time of the wheat planting and in decreasing amounts during the growth of the rotational crops.

The winter wheat had total radioactivity levels of 1.66 ppm (stalks), 2.58 ppm (husks), and 7.39 ppm (grains) at maturity. The corn had 1.33 ppm (stalks), 2.31 ppm (cobs), and 13.18 ppm (kernels) at maturity. The mature lettuce had residues of 7.35 ppm; the carrot stalks had 5.87 ppm; and the carrot roots had 1.30 ppm total radioactive residues.

The radioactivity for the rotational crops was characterized. Approximately 65-99% of the total radioactivity was aqueous-soluble and only 0.2-4% organo-soluble for the stalks, whole plants, husk, cob, and lettuce head. The grain of wheat and corn had 85-89% aqueous-soluble and <0.1-0.2% organo-soluble activity. These data indicate that only a very small portion of the residues at harvest consists of intact free parent derivatives (i.e., all three ring systems present). The residues appear to consist of conjugated forms of metabolites of CGA-64250 and conjugates of 1,2,4-triazole. (This is based on the residue behavior noted in the peanut and tomato studies.)

Further characterization and identification of the residues in wheat, lettuce, carrots, and corn confirm the above conclusion. The major component is the conjugated triazole: 1,2,4-triazole-1-alanine. The second major component is triazole-1-acetic acid which is believed to result from the alanine conjugate. These components make up 59-82% of the total radioactivity of wheat, lettuce, carrots, and corn.

A greenhouse study was performed in which a comparison was made of the plant absorption of C^{14}-phenyl labelled CGA-64250 and C^{14}-triazole labelled CGA-64250 (Report No. ABR-83030). One crop of peanuts was grown in soil treated with C^{14}-triazole labelled CGA-64250 and one crop of peanuts was grown in soil treated with C^{14}-phenyl labelled CGA-64250. The rate was 1.5 lb act/A in both cases. Following the harvest of the mature peanut crops, rotational crops of winter wheat and corn were planted in the treated soils and were grown to maturity.

The results of these studies were essentially the same as in the previous crop studies. Peanuts, wheat, and corn plants absorb residues of CGA-64250 and its metabolites from the soil, metabolize and translocate such residues throughout the plant and its fruiting parts. The residue levels in the plant stalks and straws were similar for both labelled compounds. The residue consisted primarily of the parent compound CGA-64250, its parent-like metabolites (4 isomers with the three rings intact and a hydroxy group on the beta carbon of the alkyl group on the dioxolane ring), sugar conjugates of these metabolites, and the alkanol metabolite (CGA-91305) with its sugar conjugate. The kernel and grain of plants grown in the soil treated with C^{14}-phenyl labelled CGA-64250 had lower residue levels than the kernel and grain of plants grown in soil treated with C^{14}-triazole labelled CGA-64250. This is a predictable result since previous studies have shown that the primary residue component of the fruit parts is the alanine conjugate of the intact triazole ring.

The cleanup procedures and analytical techniques used in this report were the same as those used in the studies discussed above.

This study confirms the findings on the nature of the residues of CGA-64250 in plant studies which are discussed above.

Storage Stability

Two studies were submitted in order to demonstrate that residues of CGA-64250 do not change appreciably under frozen storage. In one study, soybean fodder and grain samples were fortified with CGA-64250 at a level of 0.4 ppm, analyzed, and stored at 5°F for 6 months. An average of 82-89% CGA-64250 residues were recovered after 6 months. In the second study, field treated peanut fodder, shells, and nutmeats were analyzed for CGA-64250 residues and stored for 25 months at 5°F.

Prior to storage, residues were 7.6-13 ppm (fodder), 1.3-7.7 ppm (shells), and 0.15-0.67 ppm (nutmeats). At 25 months later, the percentages of the initial residues were 98-146% (fodder), 95-147% (shells), and 249-333% (nutmeats). The results for the peanut nutmeats are aberrant and may be disregarded in arriving at a conclusion.

In general, the studies show that residues in commodities held under frozen storage are not appreciably reduced.

Animals

Goats (Report Nos. ABR-80036 and ABR-81007)

A lactating goat was fed triazole-labelled C^{14}-CGA-64250 [redacted] equivalent to 4.53 ppm in the feed for 10 days. Samples of urine, feces, milk, and volatiles (carbon dioxide) were collected daily and analyzed for radioactivity. Blood samples were collected on alternate days for analysis. The animals (treated and control) were sacrificed at 27 hours after the last dose, and samples of tissues and intestinal contents were collected and analyzed.

Total radioactivity in the samples was determined by combustion analysis and liquid scintillation counting techniques (LSC). Samples were cleaned up by liquid-liquid partitioning and column chromatography techniques. Identification of components of the residues was performed with thin layer chromatography in 1- and 2-dimensions (TLC). The identified TLC zones were removed from the plates, cleaned up with methanol, and the radioactivity in each zone was determined by LSC. Additional characterizations were performed by refluxing the residues with 60% aqueous sulfuric acid. The resulting mixture was cleaned and examined for radioactivity as above. Chemical standards of compounds expected in the residues were used in the identification process. (The parent compound and metabolites containing the three rings are converted to CGA-58533, ketone, and the alcohol, CGA-77502, and its conjugates are converted to CGA-104284, alkene. See charts for structural identities.)

Approximately 90% (69% in the urine) of the radioactivity was excreted in the urine and feces. The rumen and intestinal content had about 2% of the total radioactivity, the blood had 0.12%, and the tissues had 0.04% of the total radioactivity. The radioactivity present as expired carbon dioxide and volatiles was below the detection limit of 0.01%, if present at all. The level of radioactivity in the milk averaged 0.18%. As a result, greater than 91% of the radioactivity is accounted for.

The parent compound CGA-64250 is ingested, metabolized, and excreted by the goat. Some radioactivity is deposited in

Information which may reveal the manufacturing process has been deleted

tissues and some is excreted in the milk. The residue level for milk plateaued at an average level of 0.015 ppm on the third day of feeding. The maximum level of residues in the tissues was noted in the liver (0.096 ppm) and the kidney (0.029 ppm). The fat had less than 0.008 ppm, the muscle had 0.009 ppm, and the tenderloin had 0.011 ppm.

Characterization of the urine, milk, feces, and liver residues showed no parent compound to be present. In the urine, about 75% of the components are shown to be compounds with the three rings intact. About 17% of the urine residue consists of compounds with only the dichlorophenyl and triazole rings present. The study indicates that, like plants, the major metabolic path involves oxidation of the n-propyl side chain of the dioxolane ring. However, metabolism in the goat yields carboxylic acids instead of alcohols.

The components of urine residue were divided into four groups. Group I consists of 3 compounds numbered 10, 15, and 17. The group I compounds are sulfate (no. 10 and 15) and glucuronide conjugates (no. 17). Group II consists of components 9, 11, 12, 13, 14, and 16. The major component in this group is no. 12 which represents 6% of the total radioactivity. This component is probably a triazole metabolite where the bridge between the phenyl and triazole rings is broken. Further, the triazole may be conjugated. The group II metabolites are possibly a collection of components with both triazole and phenyl rings (e.g., alkanol) and triazole ring only.

Group III consists of components 7 and 8 and these compounds are probably hydroxy carboxylic metabolites with all three rings present. Group IV consists of components 5 and 6. The components of this group resemble the alkanol, olefin, and ketone structures. Metabolite no. 5 is the major component in goats' urine.

The milk was divided into fractions of fat, whey, and casein. The major portion of the activity was in the whey (74-86%) which is the water portion of the milk. The casein had 15-18% and the fat had 1-2.5%. The study shows that residues are not preferentially transferred to fat, and therefore do not concentrate in fat. In whole milk, approximately 11% of the radioactivity is in the conjugated forms. The components of the residue consist of those of groups I and II (described above).

Characterization of the liver residue shows that 80-90% of the activity is conjugated probably with amino acids and/or bound to proteins by peptide bonds. The parent compound CGA-64250 and the alpha and beta-hydroxy metabolites (oxidation of the propyl side-chain of the dioxolane ring) are not detected in milk or liver. The following components are

probably present in liver and milk: a small amount of the alkanol, CGA-91305 (3-6%); metabolites containing all 3 rings (oxidation on alkyl group on dioxolane ring, i.e., acids and hydroxyacids), 13-16%; triazole and possibly the acetyl derivative of the conjugate triazole-1-alanine. The metabolites containing the triazole ring represent about 50% of the total activity in milk. The ketone is probably present in milk and liver.

In summary, goats metabolize CGA-64250 to carboxylic acid derivatives of the parent compound by oxidation of the alkyl group on the dioxolane ring. These components are further detoxified through conjugation with sugars and sulfate and excreted. Metabolites containing both the phenyl and triazole rings represent greater than 90% of the radioactivity in the goat urine and 19% in milk and liver. The major portion of residues in milk and liver are components containing only the triazole ring. The major component in milk (50% of the residue) is probably the acetyl derivative of the triazole-1-alanine conjugate. In milk and liver, the bridge between the phenyl and triazole rings has been broken, and the triazole ring is conjugated with amino acids and bound in protein linkgages.

Most of the milk residue (74-86%) partitions into the whey, and only a maximum of 2.5% is in the fat. As a result, the study shows that residues do not concentrate in the fat of milk.

Studies were performed with the chemical CGA-64251. However, this petition involves only CGA-64250. As a result, only studies with CGA-64250 are being reviewed at this time.

Rats (Project Report Nos. 24/79, 35/79, 9/81, 1/83, 11/83, 24/83)

Studies are presented in which rats and mice (male and female) were orally administered single or multiple doses of radiolabelled (triazole- or phenyl-label) C^{14}-CGA-64250 at levels of 0.5-50 mg/kg. (This dose range includes the feeding of single oral doses of the plant conjugate C^{14}-triazolealanine as well.) The urine and feces samples were collected daily and examined for radiolabelled residues which were qualitatively and quantitatively characterized. At the end of the feeding, the animals were sacrificed, and tissue samples were taken for analysis.

Total radioactivity in samples was determined by combustion and quantitation of the activity by liquid scintillation counting (LSC) techniques. Samples were cleaned up by the liquid-liquid partitioning and column chromatography. Residue components were identified using thin layer chromatography (TLC), gas chromatography (GLC), mass spectrometry (MS),

electrophoresis, and nuclear magnetic resonance (NMR). Additionally, chemical derivatization, acid and enzyme hydrolyses, and sulfuric acid digestion were also used to aid in characterization of the residues. (These are essentially the same techniques used in the goat studies above.)

Rats and mice ingest, absorb, metabolize, and excrete residues of CGA-64250. Greater than 95% of the radioactivity is excreted in the urine and feces. A small portion of the parent compound is unchanged: about 3% of the dose is found in the feces and none in the urine. Less than 1% of the radioactivity is eliminated as carbon dioxide.

The metabolic pathway involves hydroxylation of the propyl side chain on the dioxolane ring resulting in the alpha and beta hydroxy derivatives. These alcohols are oxidized to the diols (alpha and beta diols; beta and gamma diols). The alcohols and/or diols are oxidized to monocarboxylic acids, or hydroxy acids. The alcohols, acids, diols, and hydroxy acids are conjugated as glucuronides and sulfate esters.

The dioxolane ring is metabolized, possibly to carbon dioxide, resulting in two-ring compounds of the alkanol and ketone types. Metabolites are then formed from the alkanol and ketones through hydroxylation of the phenyl ring by replacement of a chlorine in either 2- or 4-position or hydroxylation at the 5-position. Methylthiolation of the phenyl ring also occurs, but the position on the phenyl ring is not determined. The various hydroxy and acid groups are also conjugated to form glucaronides and sulfates.

The amino acid conjugate, 1,2,4-triazole-1-alanine, was fed to male and female rats and mice in single doses (as C^{14}-triazole label). Within 24 hours 95-105% of the dose had been excreted and primarily in the urine. Trace residues (<0.02 ppm) were noted in the tissues from the high dose levels (50 mg/kg), but none from the low dose (0.5 mg/kg) level. Up to 86% of the dose is excreted unchanged. The urine residue consisted primarily of triazole-1-alanine (69-86%) and N-acetyl-triazolealanine (8-19%).

Analytical Methods

The method used for residue determinations is Method No. AG-356 entitled "Determination of Total CGA-64250 Residues in Crops by Conversion to 2,4-Dichlorobenzoic Acid and Analysis by Gas Chromatography Mass Spectrometry." The method determines the parent compound CGA-64250 and its metabolites containing 2 and 3 rings (free and conjugated). Different samples require different initial extractions. These processes and the resulting determinations are discussed below.

TILT CGA-64250 Reviews

The next 7 page(s) is/are not included in this copy of the TILT reviews.

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 product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commerical/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

_✓_ Detailed methods and results of a registrant submission.

___ Duplicate pages.

The information not included generally is considered confidential by product registrants. If you wish to obtain the information deleted, please contact the individual who prepared this response to your request.

Pecan Nutmeats

A sample is extracted by blending with methanol:water (80:20) and filtering. An aliquot of the filtrate is washed with hexane which is discarded. The aliquot is concentrated and mixed with concentrated nitric acid for reflux.

Pecan Shells

A ground sample in water is initially extracted by direct mixing with concentrated nitric acid and refluxed. (This step converts residues to 2,4-dichlorobenzoic acid.)

Following sample reflux, the cooled sample is diluted with water, and the residues are partitioned into dichloromethane which is filtered and evaporated to dryness.

The residue is treated with a diazomethane ethyl ether solution which forms the methyl ester derivative of 2,4-dichlorobenzoic acid. The ethyl ether is evaporated.

The residue is cleaned up on a silica gel column and eluted with an ethyl ether:hexane (1:19) solvent system. The eluate is evaporated, taken up with hexane and determined by gas chromatography and mass spectrometry. Quantitation of the residue is performed through the use of a standard 2,4-dichlorobenzoic acid methyl ester. The results are expressed as CGA-64250 equivalents.

The residue components determined by the methods are as follows: the parent compound CGA-64250; the beta and gamma hydroxy derivatives of the parent and their conjugates (CGA-118244 and CGA-118245); the olefin, CGA-104284; the ketone (CGA-91304) and the alkanol (CGA-91305) and their conjugates. These comprise the plant residue components which have both the dichlorophenyl and triazole rings as part of their structures.

Untreated (control) samples of pecan nutmeats had no detectable (<0.02 - <0.05 ppm) CGA-64250 equivalent residues. Control nutmeat samples were fortified with the parent compound CGA-64250 at levels of 0.05-2.0 ppm. Recoveries were 51-89%.

Control samples of pecan shells had 0.07-0.16 ppm CGA-64250 equivalent residues. Control samples were fortified with the parent compound CGA-64250 at levels of 0.1-0.5 ppm. Recoveries were 67-112%.

The control samples were fortified with the parent compound only. However, the major portion of the residue determined by this method has the parent-like structure (i.e., three intact rings) and the remainder has the two-ring structure which

includes the dichlorophenyl ring. Because of the severity of the digestion conditions (approximately 70% nitric acid mixture under heat for 16 hours), the dichlorophenyl moiety of all components is expected to be converted to the benzoic acid derivative. The method's sensitivity is reported to be approximately 0.1 ppm.

However, since control values range up through 0.16 ppm and recovery values have a lower limit of 51%, the overall sensitivity is about 0.2 ppm.

Additionally, a determinative GLC procedure using an electron capture detector is available for confirmation purposes (Method No. AG-359).

Pesticide chemicals with registered uses on pecans and peanuts were tested with the method to determine if the chemicals interfered in the determination of residues of CGA-64250 and its metabolites. No interferences were noted. The method has adequate specificity.

A second method is submitted which determines total residues of CGA-64250 as 1,2,4-triazole (Method No. AG-357). This method determines combined residues of CGA-64250 and its metabolites containing the triazole moiety. This includes essentially all significant residue components of crops, both free and conjugated.

A ground sample is refluxed with a solution of concentrated ammonium hydroxide/methanol, cooled, and filtered. An aliquot of the filtrate is concentrated and refluxed with a mixture of sulfuric acid:nitric acid:water (2:1:1). The mixture is cooled and washed with dichloromethane.

The solution is treated with solutions of sodium bromide and sodium bromate which convert the triazole to 3,5-dibromo-1,2,4-triazole. The derivative is extracted into ethyl acetate which is evaporated to dryness.

The residue is taken up with a hexane/toluene solution, cleaned up on a silica gel column, and eluted with a diethyl ether/toluene solvent. The eluate is treated with diazomethane which converts the residue to a methyl derivative.

The methyl derivative is determined by gas chromatography using a flame ionization detector (GLC-FID) which is specific for nitrogen. The residue may also be determined by a combined gas chromatography-mass spectrometry (GLC-MS) procedure which could serve as a confirmatory step. Residues are expressed in terms of the parent compound CGA-64250.

The method's sensitivity is reported to be about 1 ppm.

Untreated (control) pecan nutmeat samples had CGA-64250-equivalent residues of 0.14-2.5 ppm with the GC-FID procedure and 0.16-2.6 ppm by the GC-MS procedure. Control nutmeat samples were fortified with the parent compound CGA-64250 at levels of 2.0-20 ppm and analyzed. Recoveries were 31-85% for the GC-FID procedure and 32-112% for the GC-MS procedure.

The recovery of CGA-64250 from fortified controls was similar for the two procedures. However, the recoveries were generally low and erratic. Generally, it would be expected that the recovery of CGA-64250 would increase with increasing fortification levels. This was not noted. Again, it is expected, under give conditions, that controls would yield similar background levels. The wide variations in background levels for controls do not support this expectation. Apparently, the content of the interfering plant component(s) varies within samples taken from the same prepared batch. This result appreciably affects the level of CGA-64250 recovered from a fortified sample. As a result, the method's reliability is seriously reduced. This leads to considerable doubt on the level of residues found in treated pecan nutmeat samples by the method and both determinative steps.

The high levels of background response have been noted in other crops (rice, soybeans, peanuts as well as pecans). These levels are <0.1-3.5 ppm. A study (Report No. ABR-83047) was performed in order to establish the amount of background which could be contributed by the triazolealanine metabolite. Untreated (control) peanut nutmeat samples were analyzed with the residue method (AG-357) and background levels of triazole were equivalent to 0.66 ppm CGA-64250 residues.

Control peanut nutmeat samples were then fortified with radiolabelled C^{14}-triazolealanine. The fortified samples were then analyzed by the methods used in the metabolism studies to characterize radiolabelled residues. The samples were extracted by blending with a methanol/water mixture. The blended mixture was filtered, and the methanol was evaporated. The aqueous phase was partitioned with hexane, concentrated and held for further characterization.

The concentrate was cleaned up on a silicic acid column. The eluate fractions containing radioactivity were pooled, concentrated, and characterized with thin layer chromatography (TLC). The radioactive areas were removed and extracted with a methanol/water solvent system and evaporated to dryness.

The residue was taken up with methanol and treated with derivatizing reagents which formed the n-butyl ester/N-trifluoroacetyl derivative of the triazole alanine compound.

The residue was then examined by High Performance Liquid Chromatography (HPLC) and combined Gas Chromatography/Mass Spectrometry techniques (GC/MS). Radioactivity determinations were carried out through Liquid Scintillation Counting techniques (LSC). Quantitation of the residue component was performed using a standard triazolealanine which was treated in the same manner as the fortified samples.

The overall recovery of the added radiolabelled material was 9.3%. As a result, the triazolealanine compound represented about 10% of the total triazole background in the peanut kernel.

In view of the foregoing, it is reasonable to conclude that background levels in samples examined with the triazole procedure are due largely to the presence of natural plant constituents.

In summary, the analytical method (No. AG-356) is available for the determination of residues of CGA-64250 and its metabolites containing the 2- and 3-ring structures. However, its overall sensitivity is about 0.2 ppm instead of the reported 0.1 ppm. Most important, however, if Tox declares that all triazole residues must be included in the tolerance expression, this procedure should not be considered further for regulatory purposes. The analytical method which determines residues of CGA-64250 and its metabolites as the triazole (Method No. AG-357) does not have adequate sensitivity for the determination of residues at the proposed tolerance level of 0.1 ppm. (The method's sensitivity is reported to be about 1 ppm; however, validation data indicate a much higher level of about 3 ppm.)

The fruit portions of plants have been shown to consist largely of triazolealanine. As a result, the method (AG-357) which determines components containing the triazole moiety must be sufficiently sensitive and reliable to determine such components at levels likely to result in pecan nutmeats from the proposed use.

The analytical methods are not adequate for the determination of residues of CGA-64250 and its metabolites at the proposed tolerance level (0.1 ppm). After the petitioner has resolved deficiencies concerning the analytical methodology and the appropriate expression for the tolerance (see Residue Data section of this review), then RCB will request an EPA method trial.

Residue Data

Samples of pecans were collected from orchards in Alabama (4.8%), Oklahoma (2.2%), Georgia (50.4%), Louisiana (1.9%), Texas (19.4%), and New Mexico (11.2%). The numbers in parentheses

represent each state's contribution to the total United States pecan production. These states make up approximately 90% of the total annual pecan production for the U.S.

The samples were collected from crops which had received the proposed foliar spray applications (6-10 applications were made) at rates of 150 gms a.i./A (1X) and 300 gms a.i./A (2X). Samples of pecans were collected at intervals of 7-60 days (PHIs) after the last treatment. Samples of nutmeats and shells were analyzed by the two residue methods and the results are discussed below.

Residues determined as 2,4-dichlorobenzoate

Residues in the nutmeats were none detected (ND, <0.1 ppm) at both the 1X and 2X rates and all PHIs (7-60 days). The shells had residues of ND (<0.1 ppm) - 0.17 ppm from the 1X rate and all PHIs (7-14 days). At the 2X rate, residues in the shells were ND -0.47 ppm at 7-14 days after the last treatment.

Residues determined as 1,2,4-triazole

Residues in the nutmeat were 1.9-14 ppm at 7-8 days, 2-12 ppm at 14-21 days, and 0.7-12 ppm at 30-60 days from the 1X rate. At the 2X rate, residues in the nutmeat were 3.7-42 ppm at 7-8 days and 3.7-17 ppm at 14 days.

The data from the two procedures show that combined residues of CGA-64250 and its metabolites will greatly exceed the level of the proposed tolerance (0.1 ppm).

The petitioner's proposal is expressed as a tolerance for residues of CGA-64250 and its metabolites, determined as 2,4-dichlorobenzoic acid and expressed as the parent. This expression does not adequately reflect residues likely to result from the proposed use.

The plant metabolism studies (see Nature of the Residue) show that fruiting portions of plants contain significant levels of residues containing only the triazole moiety (e.g., 1,2,4-triazole-1-alanine). The pecan is the fruiting portion in this proposal, and therefore the pecan is expected to contain some triazole residues as a result of the proposed use.

The residue data generated by the triazole procedure (AG-357) show, for example, pecan meats containing as much as 12 ppm total residues after six 1X applications and observance of 30-day intervals. As a result, we defer to TOX as to whether or not these residues containing the triazole moiety (which include 1,2,4-triazole, etc.) should be included in the tolerance expression. If TOX indicates that triazole

residues must be included in the tolerance expression and the petitioner chooses to improve the triazole procedure, then the tolerance expression should be expressed as "... combined residues of the fungicide CGA-64250 and its metabolites determined as 1,2,4-triazolé and expressed as the parent compound," in or on pecans at-ppm. At this time, it is not possible to reach a valid conclusion on an appropriate CGA-64250 tolerance for pecans.

Meat, milk, and eggs of livestock (cattle, goats, hogs, horses, poultry, and sheep)

No feed items are involved in this petition, and the label contains a restriction on the grazing of livestock in treated areas. Therefore, no residues are likely to result in eggs, milk, meat, fat, and meat byproducts of cattle, goats, hogs, horses, poultry, and sheep from the proposed use [§180.6(a)(3)].•

cc: R.F.
Circu
Reviewer
TOX
EEB
EAB
Petition No. 4F3007
FDA
Robert Thompson

RDI:Section Head:RSQ:5/7/84:RDS:5/7/84
TS-769:Reviewer-AS:pjb:RM-810:CM#2:5/9/84:Client's Disk:Part II of II
Edited by Wh:5/14/84

A. Smith

INTERNATIONAL RESIDUE LIMIT STATUS

CHEMICAL CGA-64250 (TILT®)

PETITION NO. 4F3007

CCPR NO.

Codex Status

/ X / No Codex Proposal Step 6 or above

Proposed U.S. Tolerances

1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-1-H-1,2,4-triazole

Residue (if Step 9):

Residue:

Crop(s)	Limit (mg/kg)

Crop(s)	Tol. (ppm)
Pecans	0.1

CANADIAN LIMIT

Residue:

Crop	Limit (ppm)
None	

MEXICAN TOLERANCIA

Residue:

Crop	Tolerancia (ppm)
None	

Notes: