PP# 5F1606

PP# 5F1606. CGA-24705 on Corn. Evaluation of analytical method and residue data.

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The Ciba-Geigy Corporation requests establishment of tolerances for residues of the herbicide 2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide and its metabolites determined as 2-([2-ethyl-6-methylphenyl]amino)propanol and 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone in or on the following raw agricultural commodities:

0.75 ppm--corn fodder and forage

0.05 ppm--fresh corn, including sweet corn (kernels plus cob with husks removed) and corn grain

0.02 ppm--eggs, milk, and the meat, fat, and meat byproducts of cattle, goats, hogs, horses, poultry and sheep.

The parent compound is known as CGA-24705. No trade name or common name has been proposed.

Temporary tolerances, on the above commodities and at the same levels now proposed, were established for residues of CGA-24705 and its metabolites converted to 2-([2-ethyl-6-methylphenyl]amino)-propanol in response to PP# 5G1553 on 3/20/75.

The tolerance proposal should include the phrase "and calculated as the herbicide" to clarify the basis.

Conclusions

1. The metabolism of CGA-24705 is adequately delineated in corn and in animals. Residues are primarily polar conjugates of those compounds shown in Figure 1.

Conclusions Cont.

2a. The analytical methods convert parent and various metabolites to 2-([2-ethyl-6-methylphenyl]amino)propanol (CGA-37913) and 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone (CGA-49751) using a 6N HCl refluxing hydrolysis step.

2b. Because the sensitivity of the method for CGA-49751 is only 0.10 ppm for corn grain and 0.04 ppm for animal tissues, the 0.05 ppm proposed tolerance level for corn grain and sweet corn (kernels + cob with husk removed) should be raised to 0.1 ppm and the 0.02 ppm level for milk, meat, etc. should be raised to 0.04 ppm.

2c. Our final judgement of the adequacy of the analytical method is dependent upon the results of a method trial in our laboratories.

3a. Residues of CGA-24705 will not exceed 0.10 ppm in corn grain and sweet corn (kernels plus cob with husk removed) or 0.75 ppm in corn forage, silage and fodder (and inferentially sweet corn cannery waste) from the proposed uses of either CGA-24705 alone or mixed with atrazine.

3b. Residues of atrazine from the prepacked mix or tank mix uses with CGA-24705 will not exceed the established tolerances (§180.220) for atrazine in corn.

3c. Since there are no detectable residues in corn grain, no above tolerance residues would be expected in corn byproducts.

4. Cattle and poultry feeding studies demonstrate that residues (if any) of CGA-24705 and its metabolites will be less than the method sensitivities (0.02 ppm for CGA-37913, 0.04 ppm for CGA-49751) in meat, milk, poultry and eggs from the feed use of residue-bearing corn grain, forage, silage and fodder. We recommend a method sensitivity level tolerance of 0.04 ppm to cover this §180.6 (a)(2) use.

5. EEE requirements concerning crop rotational restrictions necessary to prevent illegal residues in rotational crops must be satisfied.

Recommendations

We recommend against establishment of the proposed tolerances because of Conclusions 2b, 2c, and 5. The petitioner should be advised of these deficiencies. We also recommend that the tolerance proposal state "---for combined residues of the herbicide---and it metabolites determined as---and---and calculated as the herbicide in or on---"

Inert ingredient information deleted.

Detailed Considerations

Manufacture and Formulation

The manufacturing process has been detailed in our 2/12/75 evaluation of PP# 5G1553. The resulting technical material has a minimum purity of 90%. The impurities have been discussed in our review of 2/12/75 and are not expected to constitute significant portions of terminal residues of CGA-24705.

[redacted]

Proposed Use

CGA-24705 is applied as a preemergence herbicide to the soil surface at rates of 1 to 3 lbs. a. i./A; rates are dependent on soil type. The label states that small grains may be planted after corn harvest and any rotational crop may be planted the following spring.

A tank mixture of CGA-24705 plus atrazine is also proposed. Application rates for the mix are 1.25-2.0 lbs. a. i./A for CGA-24705 and 1.0-2.0 lbs. a.i./A for atrazine. These rates are lower than for either compound used alone. The following rotation restrictions apply to the tank mix: 1) do not make a second broadcast application (a second band treatment to untreated areas is allowed in the event of crop failure); 2) do not plant treated areas to any crop except corn until the following year; do not plant sugar beets, tobacco, vegetables, spring seeded small grains or small-seeded legumes and grasses the year following application; 3) if applied after June 10, do not rotate with crops other than corn or sorghum; 4) when rainfall is sparse and erratic or where irrigation is required, use only when corn or sorghum is to follow corn or a crop of untreated corn of sorghum can precede other rotational crops; 5) injury to soybeans may occur when planted the year following an application on soils having a calcareous surface layer.

Nature of the Residues

Extensive metabolism studies using ^{14}C-ring-labeled CGA-24705 have been carried out with field and greenhouse grown corn, nutrient grown corn, leaf incubations and stem injected corn. The results from these studies were discussed in PP# 5G1553 (our evaluation of 2/12/75); some additional data, particularly on characterization and identification of these residues, have been submitted in this petition.

Nature of the Residues Cont.

The structures and code letters of the expected metabolites and moieties of CGA-24705 are shown in Figure 1. In summary, the studies indicate that residues of CGA-24705 in plants are present as glutathione, S-glucoside and O-glucoside conjugates of the various moieties shown. Evidence of Compounds M, N, and O (Figure 1) was found in the various tracer studies. When the metabolites from each of the TLC zones (in the residue characterization separation from the tracer studies) were subjected to the 6N HCl hydrolysis procedure used in the analytical method, all were converted to either CGA-37913 or CGA-49751, the two moieties which are determined by the analytical method and included in the tolerance.

From the field and greenhouse tracer studies at the application rate of 2 lbs, a.i./A, the total ^{14}C residues (expressed as CGA-24705) were: mature grain -- 0.02 ppm in the field and 0.05 ppm in the greenhouse; mature corn forage -- 0.17 ppm in the field and 0.72 ppm in the greenhouse.

The metabolism of CGA-24705 in corn is adequately defined.

Animal metabolism studies have been carried out in rats and goats using ^{14}C-CGA-24705 and in goats only using ^{14}C-corn-biosynthesized metabolites. These studies were detailed in our review of PP# 5G1553 (2/12/75). The studies show rapid elimination with only trace residues in tissues (liver). Comparison of the urine metabolites with those found in corn indicate that, although the conjugating natural compounds are different, the hydrolyzed pesticide moieties are similar in both corn and ruminants.

The animal metabolism of CGA-24705 is also adequately understood.

Analytical Methods

The original method, AG-265, which determined only those residues convertible to CGA-37913 was discussed in our review of PP# 5G1553.

The present method, AG-277, is a modification of AG-265 which includes partitioning, cleanup, derivitization and microcoulometric GLC steps for also determining residues converted to CGA-49751.

Residues of CGA-24705 in corn (grain, ears, forage, fodder and stover) are converted to a mixture of CGA-37913 and CGA-49751 by refluxing 16 hours with 6N HCl.

Analytical Methods Cont.

The filtered acid extract is partitioned with dichloromethane to extract the CGA-49751 into the organic phase. The aqueous phase containing CGA-37913 is made strongly basic with 50% sodium hydroxide and subjected to distillation-partition into isooctane using a Bleidner apparatus. The isooctane phase containing CGA-37913 is cleaned up using an alumina column. CGA-37913 is determined with a gas chromatograph equipped with a Coulson electrolytic conductivity nitrogen detector; it is quantified by comparison with the peak area of standard CGA-37913 and calculated as CGA-24705 using the 1.47 equivalence factor.

The dichloromethane phase containing CGA-49751 is washed with 5% sodium carbonate solution and further cleaned up using an alumina column. The chloroethanol derivative of CGA-49751 is formed by reaction with boron trichloride/2-chloroethanol at 90°C for 15 minutes. The derivative is partitioned into hexane and an aliquot is cleaned up using silica gel and alumina columns. A gas chromatograph equipped with a Dohrmann microcoulometric chloride detector is used for analysis. Peak area is compared to that of injections of standards of derivatized CGA-49751 and residues are calculated as CGA-24705 using the conversion factor of 1.13.

For CGA-37913, controls ranged from <0.05 ppm on many samples but ranged up to 0.1 ppm due to an interfering peak on about half of the samples. Recoveries for 64 samples of fodder, forage, grain or ears fortified at levels of 0.10 and 0.20 ppm ranged from 45 to 100% with an average of 65%. The method sensitivity is considered to be 0.10 for CGA-49751 (as CGA-24705).

The combined sensitivities are higher than the tolerance of 0.05 ppm being sought on corn grain. The residue data for corn forage (where residues are at detectable levels) indicate that the major portion of the residues are determined as CGA-37913; the tracer study indicates that total residues of CGA-24705 in the grain will be <0.05 ppm; the petitioner uses these arguments to justify the 0.05 ppm tolerance being below the combined method sensitivities. We conclude that the tolerance level for corn grain should be raised to 0.1 ppm to at least match the sensitivity of the least sensitive method (for CGA-49751).

The petitioner has demonstrated that the method is specific in the presence of most other pesticides (six were not available for testing) with established tolerances on corn. An alternate column liquid phase has been tested. We therefore judge that the method has adequate specificity.

The analytical methods for the determination of residues of CGA-24705 in meat, milk and eggs are similar to the method for corn but employ a more rigorous cleanup and use a mass spectrometer as the dectector. Detection limits are 0.006 ppm (as CGA-37913) and 0.01 ppm (as CGA-49751) in milk, and 0.02 ppm (as CGA-37913) and 0.04 ppm (as CGA-49751) in eggs, meat and poultry tissues. Once again, because of the less sensitive detection of CGA-49751 residues, we recommend that the milk, meat, poultry and egg tolerance level be raised to 0.04 ppm.

Residue Data

The data represent 12 studies in 6 states at application rates of 1X and 2 X the maximum proposed. Both field and sweet corn are represented. Irrigation was used in the Nebraska study. Samples of early forage, silage stage corn, fodder and grain or ear (sweet corn) samples were analyzed.

No detectable residues of CGA-24705 as CGA-37913 (<0.03 ppm) or CGA-49751 (<0.10 ppm) were found in any grain or fresh ear samples.

At the 1X rate, combined residues (as CGA-24705) of CGA-37913 and CGA-49751 ranged from <0.13 ppm to 0.90 ppm in ~~mature fodder~~. At the 2X rate corresponding combined residues were 0.13-0.64 ppm, 0.21-0.63 ppm, and 0.17-0.90 ppm.

early forage, 0.14 & 0.38 ppm in silage stage corn, and <0.03 ppm to 0.40 ppm in mature fodder,

For the combined use with atrazine at up to the proposed rates, maximum CGA-24705 residues were non-detectable (<0.03 ppm as CGA-37913, <0.10 ppm as CGA-49751) in corn grain and sweet corn ears and 0.73 ppm in corn fodder. Residues of atrazine were <0.05 ppm in corn grain and sweet corn ears and <0.10 ppm in all corn forage and fodder samples. Tolerances for residues of atrazine (§180.220) are established at 15 ppm for corn forage and fodder and at 0.25 ppm in sweet corn (kernels + cob with husk removed) and corn grain.

Since no detectable residues were found in corn grain we are not requiring data for corn byproducts, i.e., corn oil, meal, etc.

We would not expect residues in sweet corn cannery waste to exceed those in corn forage or fodder.

The residue data are adequate to support the proposed tolerance of 0.75 ppm for residues of CGA-24705 in corn forage and fodder.

Because of the method sensitivity of 0.10 ppm ofr residues determined as CGA-49751 we recommend that the tolerance level for residues of CGA-24705 in corn grain and sweet corn (kernels + cob with husk removed) be raised from 0.05 ppm to 0.10 ppm. The established tolerances for atrazine are adequate to cover residues resulting from the combined atrazine--CGA-24705 uses.

Meat, Milk, Poultry and Eggs

Cattle were fed at levels of 0, 0.2, 1.0 and 5.0 ppm of CGA-24705 in the total diet. If we consider corn forage or fodder as 100% of the diet, the levels represent exaggeration levels of 0.27X, 1.3X and 6.7X. Milk samples were collected at days 0, 1, 2, 7, 14, 21, and 28. Cows were sacrificed and tissue samples taken after 14, 21, and 28 days.

Only samples from the two highest feeding levels were analyzed. All residues in milk were less than the method sensitivity (0.006 ppm for CGA-37913, 0.01 ppm for CGA-49751). All residues in muscle, fat, liver and kidney were less than the method sensitivity (0.02 ppm for CGA-37913, 0.04 ppm for CGA-49751).

In the radiolabeled studies with goats, only trace activity at levels well below the above sensitivities were found in milk and tissues.

Chickens were fed at levels of 0, 0.1, 0.5, and 2.0 ppm in the total dry diet. Based oncorn grain constituting 100% of the diet, these feeding levels represent 2X, 10X and 40X exaggeration levels. Egg samples were taken on days 1, 3, 7, 10, 14 and 21. Chickens were sacrificed after 7, 14, 21 and 28 days for tissue analysis.

Only the two upper feeding level tissues and eggs were analysed. Residues as CGA-37913 in eggs, muscle and fat were <0.02 ppm. Residues of 0.02 ppm and 0.03 ppm CGA-37913 were found in liver from birds at the 0.5 and 2.0 ppm levels respectively. No detectable residues (<0.04 ppm) of CGA-49751 were found in eggs or any tissues.

The proposed uses are classed as §180.6(a)(2). A method sensitivity level (CGA-37913) tolerance of 0.02 ppm has been proposed for residues in eggs, milk, and the meat, fat, and meat byproducts of cattle, goats, hogs, horses, poultry and sheep. A tolerance level of 0.04 ppm, reflecting the less sensitive CGA-49751 method, would be more appropriate.

Other Considerations

EEE has indicated that longer crop rotational restrictions are required to prevent residues in rotational crops. Our favorable recommendation for the tolerance is contingent upon satisfying EEE's rotational requirements.

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