

PP# 601708. CGA-24705 on soybeans. Evaluation
of analytical method and residue data.

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JAN 29 1976

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The Ciba-Geigy Corporation requests establishment of temporary tolerances for combined 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 and calculated as the herbicide in or on soybean forage and hay at 1.25 ppm and soybeans at 0.1 ppm.

The parent compound is known as CGA-24705 and by the trade name, Dual.

Temporary tolerances, at levels of 0.75 ppm for corn forage and fodder, 0.05 ppm for corn grain and fresh corn, and 0.02 ppm for eggs, milk and the meat, fat and meat byproducts of cattle, goats, hogs, horses, poultry and sheep, were established in response to PP# 501553. These tolerances are for residues of CGA-24705 and its metabolites converted only to 2-((2-ethyl-6-methylphenyl)amino)propanol. They expire 3/20/76. Permanent tolerances for residues in the above commodities were proposed in PP# 5F1606, but denied because resolution of the following deficiencies was required: (1) restatement of the tolerance proposal, (2) higher tolerance levels to reflect the combined method sensitivity; and (3) resolution of EEE's questions regarding the rotational restrictions necessary to prevent residues in follow-up crops. The permanent tolerance proposal and methodology included all residues determined as the two compounds named in the present proposal rather than only the 2-((2-ethyl-6-methylphenyl)amino)propanol named in the earlier temporary tolerance on corn.

The presently proposed experimental program is for 600 gals. Dual 6E (3600 lbs a.i.) to be used on 1920 acres of soybeans in 30 states.

Conclusions

1. The metabolism of CGA-24705 is adequately delineated in corn, soybeans, and animals. The metabolic pathways are illustrated in Figure 1.

2a. The analytical methods convert parent and the expected 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 hydrolysis step.

2b. The methodology is adequate for enforcing this temporary tolerance.

3a. The proposed tolerance level of 1.25 ppm is adequate to cover residues of CGA-24705 in soybean forage and hay resulting from the proposed uses.

3b. The proposed tolerance of 0.1 ppm is adequate to cover resulting residues of CGA-24705 in soybeans and their fractions.

3c. Residues of linuron and metribuzin resulting from the proposed tank mixes with CGA-24705 are not expected to exceed the established tolerances for these compounds on soybeans and soybean forage and hay.

3d. For a permanent tolerance, additional residue data for the tank mix uses will be required for all three compounds on soybean forage, hay and beans.

4. The uses of CGA-24705 are classed as category 2 of 180.6(a). The temporary 0.02 ppm tolerance for residues in meat, milk, poultry and eggs, which expires 3/20/76, should be extended to cover these uses.

Recommendation

If toxicological considerations permit and if the contingency below is met, we recommend that the proposed tolerances be established.

CONTINGENCY In response to PP# 501553, a temporary tolerance of 0.02 ppm was established to cover residues of CGA-24705 (determined as CGA-37913) in eggs, milk, and the meat, fat and meat byproducts of cattle, goats, hogs, horses, poultry and sheep. This tolerance expires 3/20/76. It should be extended to cover possible residues resulting from these proposed soybean uses.

The petitioner should be advised that for a permanent tolerance we will require:

1. Additional residue data for CGA-24705, linuron and metribuzin on soybean forage, hay and soybeans to reflect the proposed tank mix uses.
2. A method trial in our laboratories of the methodology for crops and milk.

Inert ingredient information deleted.

Detailed Considerations

Manufacture and Formulation

The manufacturing process has been detailed in our evaluation of PP# 501553 (2/12/75). The purity of the technical product is 90% minimum. The impurities have been discussed in our review of 2/12/75 and are not expected to constitute significant portions of the terminal residues of CGA-24705.

CGA-24705 is formulated as an emulsifiable concentrate containing 6 lbs. a.i./gal. [redacted] inert ingredients of the formulation are cleared under Sec. 180.1001(c).

Proposed Use

CGA-24705 is applied as a preemergence herbicide to the soil surface at broadcast rates of 1 to 3 lbs. a.i./A; rates, are dependent on soil type. Proportionately lower rates may be used for band treatments.

The label bears the following directions: Do not make a second broadcast application. In case of crop loss, a second band treatment may be made to previously untreated soil. Fall seeded small grains may be planted after harvest. Any rotational crop may be planted the following spring. ?

Tank mixes of CGA-24705 with metribuzin and with linuron are proposed.

For the tank mix with metribuzin, application rates are 1.25-2.5 lbs. a.i./A. of CGA-24705 and 0.25-0.75 lbs. a.i./A. of metribuzin. The label bears a restriction against using treated vines for feed or forage and bears the same rotational restrictions as for CGA-24705 alone. Application rates for the tank mix with linuron are 1.25 - 2.5 lbs. a.i./A. for linuron. The additional label directions and restrictions are the same as those for CGA-24705 alone.

A tolerance of 0.1 ppm has been established for residues of metribuzin on soybeans resulting from preemergence use rates up to 1.0 lb a.i./A.

A tolerance of 1.0 ppm has been established for residues of linuron on soybeans, soybean forage and hay resulting from preemergence application rates up to 3.0 lbs a.i./A.

Nature of the Residue

The extensive ¹⁴C-tracer metabolism studies in corn have been discussed in PP# 501553 and PP# 6F1606. An additional study employing ¹⁴C-ring-labeled-CGA-24705 with soybeans is reported here.

In a greenhouse study, soybeans were grown to maturity in soil treated preemergence with 2 lbs. a.i./A of ¹⁴C-labeled CGA-24705. At maturity, the total activity (expressed as CGA-24705) was 2.66 ppm in the stalks, 0.17 ppm in beans of which 0.14 ppm was found in the meal and 0.01 ppm in the oil. We would expect residues from the greenhouse study to be higher than those encountered in the field.

Characterization of the residues by partitioning, ionic charge and TLC indicated that the metabolic pathways in soybeans are similar to those observed in corn.

The proposed metabolic pathways are illustrated in Figure 1. The major metabolites appear to be S-glucuronides with lesser amounts of O-glucuronides. Metabolites A, B, D and E accounted for 30, 15, 9 and 6%, respectively, of the activity in the soybeans and stalks.

In PP# 5F1606, it was shown that when each of the TLC zones (in the residue characterization separation) was subjected to the HCl hydrolysis procedure used in the analytical method, the residues were converted to either CGA-37913 (2-[(2-ethyl-6-methylphenyl)amino]-1-propanol) or CGA-49751 (4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone), the two moieties which are determined by the analytical method and included in the tolerance.

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

Animal metabolism studies have been carried out in rats and goats using ¹⁴C-CGA-24705 and in goats only using ¹⁴C-corn-biosynthesized metabolites. These studies were detailed in our review of PP# 5Q1553 (2/4/75). The studies show rapid elimination with only trace residues in tissues (liver). Comparison of the urine metabolites with those in corn indicate that, although the conjugating natural compounds are different, the hydrolysed pesticide moieties are similar in plants and ruminants.

The animal metabolism of CGA-24705 is adequately understood.

Analytical Methods

The analytical method is AG-286, "Analytical Method for the Determination of Residues of CGA-24705 Soybean Metabolites as CGA-37913 and CGA-49751 by Acid Hydrolysis." The method, is quite similar to AG-277 for residues in corn.

Residues of CGA-24705 in soybeans (forage, fodder, grain, meal, soapstock, hulls or oil) are converted to a mixture of CGA-37913 and CGA-49751 by refluxing overnight with 6 N HCl.

The filtered acid extract is partitioned with dichloromethane; CGA-49751 goes into the organic phase while CGA-37913 remains in the aqueous layer.

CGA-37913 is cleaned up using extraction from basic solution and alumina column chromatography. Gas chromatography employing a Coulson nitrogen detector is used for the determinative step; peak areas are compared to standard CGA-37913 injections and residues are calculated as CGA-24705 using the 1.47 equivalence factor.

CGA-49751 residues are cleaned up on an alumina column and derivatized with boron trichloride/2-chloroethanol. The derivative is partitioned into hexane and cleaned up on silica gel and alumina columns. Determination employs GLC equipped with a Dehrmann microcoulometric chloride detector; peak areas are compared to standards of derivatized CGA-49751 and residues are calculated as CGA-24705 using the conversion factor of 1.13. Alternatively, particularly for samples with high background, mass fragmentography detection may be used.

Samples fortified with CGA-49751 at levels of 0.05 - 0.1 ppm showed recoveries between 42% and 100% with an average of $66 \pm 13\%$ ($n=43$). Two controls in soybean forage were reported as less than 0.10 and 0.06 ppm; all others in forage and other fractions were less than 0.05 ppm. We consider the method sensitivity for CGA-49751 in soybeans to be 0.05 ppm.

Samples fortified with CGA-37913 at levels of 0.02 to 0.1 ppm showed recoveries between 55% and 100% with an average of $75 \pm 15\%$ ($n=27$). A few controls in soybean forage were reported as less than 0.08 and less than 0.10 ppm primarily because of small sample size; all others for forage, fodder, grain and fractions were less than 0.03 ppm.

The sensitivity of the method for CGA-37913 in soybeans appears to be 0.03 ppm.

The combined sensitivities for the two moieties in soybeans is less than 0.1 ppm.

The methodology for the determination of residues in tissues, eggs and milk was discussed in PP# 5F1606. The 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.

The residue method used for determining linuron residues from tank mix applications is listed in PAM II (Reidner, et. al., J. Agr. Food Chem 2, p 476 (1954)). Recoveries ranged from 83-124% from soybean forage fortified with 0.1 ppm of linuron.

Residue Data

Residue studies were carried out in six states representing major soybean growing areas. Application rates of 2 to 6 lbs a.i./A (0.67 to 2X) are represented.

Although most samples were analysed within several months of collection, the petitioner has submitted data showing that both fortified and field incurred residues were stable in corn samples during 13 months of frozen storage.

Total residues (sum of residues converted to CGA-37913 and CGA-49751) of CGA-24705 in soybean forage ranged from 0.28 to 1.01 ppm from the maximum proposed application rate of 3 lbs a.i./A. PHI's of 30-92 days were represented. At the 2X exaggeration rate total residues ranged from 0.49 to 1.76 ppm.

Total residues in soybean hay at PHI's of 122-194 days ranged from less than 0.10 to 0.84 ppm at rates up to the maximum proposed 3.0 lbs a.i./A. At exaggerated rates of 4.06 lbs a.i./A, residues ranged from 0.14 to 2.46 ppm.

The proposed tolerance level of 1.25 ppm is adequate to cover residues of CGA-24705 in soybean forage and hay resulting from the proposed use.

Total CGA-24705 residues in soybeans were all less than 0.08 ppm (less than 0.03-0.03 ppm as CGA-37913; all less than 0.05 ppm as CGA-49751) from application rates up to 4 lbs a.i./A (1.3X). Detectable CGA-37913 residues of 0.05 and 0.08 ppm (total CGA-24705 residues of less than 0.10 and less than 0.13 ppm) were found in beans treated at exaggerated rates of 5 and 6 lbs a.i./A. Fractionation studies were performed on all bean samples. One detectable residue of 0.04 ppm (as CGA-37913) was found in the meal from beans treated at 6 lbs a.i./A (2X). All other samples of meal, crude and refined oil, soapstock and solvent had no detectable residues.

The proposed tolerance of 0.1 ppm for residues of CGA-24705 in soybeans is adequate to cover residues resulting in the beans or their fractions.

Four forage residue studies have been submitted for the proposed tank mix with linuron. Total residues of CGA-24705 ranged from 0.15 to 0.54 ppm in forage treated with 2.5/1.5 lbs a.i./A CGA-24705/linuron. This represents the maximum proposed rates for the tank mix. Linuron residues were less than 0.10-0.35 ppm. A tolerance of 1.0 ppm has been established for residues of linuron in soybean forage and hay.

No residue data have been submitted for the CGA-24705/mesbuzin tank mix. Application rates for both compounds in the tank mix are lower than those for the compounds applied singly; therefore, we expect no problem of excessive residues from the mix.

For a permanent tolerance we will need additional residue data for soybeans and soybean forage and hay representing residues of CGA-24705, linuron and metribuzin resulting from the two tank mixes.

Residues in Meat, Milk, Poultry and Eggs.

Cattle were fed at levels of up to 5 ppm of CGA-24705 in the total diet for 28 days. No detectable residues were found in milk (less than 0.006 ppm CGA-37913, less than 0.01 ppm CGA-49751) or in any of the tissues (less than 0.02 ppm CGA-37913, less than 0.04 ppm CGA-49751).

Total ¹⁴C residues (calculated as CGA-24705) were determined in the goat metabolism study where 4.7 ppm of ¹⁴C-CGA-24705 was fed for 10 days. Activity levels were 0.01 ppm in milk, 0.003 ppm in kidney, 0.07 ppm in liver, and less than 0.006 ppm in other tissues. The activity was not characterized. In addition, no detectable ¹⁴C residues resulted in milk or tissues from feeding ¹⁴C-labeled corn biosynthesized metabolites to goats.

Chickens were fed at levels of 0, 0.1, 0.5 and 2.0 ppm in the total dry diet for 28 days. No detectable residues (less than 0.02 ppm CGA-37913, less than 0.04 ppm CGA-49751) were found in eggs, muscle or fat. 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.

The maximum feeding levels in all the above studies represent exaggeration factors in excess of 10 for the residues which might be present in the total diet of cattle or poultry from the proposed use on soybeans. Residues resulting in meat, milk, poultry or eggs would be well below the method sensitivity, but the similar uses on corn have been classed as 180.6(a)(2).

The petitioner previously proposed a method sensitivity tolerance in meat, milk, poultry and eggs (PP# 501553 and 5F1606) but has not proposed one here. A 0.02 ppm temporary tolerance for residues of CGA-24705 (determined as CGA-37913) in eggs, milk and the meat, fat and meat byproducts of cattle, goats, hogs, horses, poultry and sheep was established in response to PP# 501553 and expires 3/20/76. We recommend that this tolerance be extended to cover any possible residues resulting from this use on soybeans.

Other Considerations

EEC has determined that an 18 month crop rotation restriction is required to prevent residues in rotational crops.

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