UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

SUBJECT: PP#7F1918 Metolachlor on soybeans. Evaluation of analytical method and residue data. DATE: 14 JUN 1977

FROM: Donald Reed, Chemist, Chemistry Branch
Registration Division (WH-567)

TO: Product Manager No. 24 (H. Jacoby)
and Toxicology Branch

THROUGH: Chief, Chemistry Branch

The Ciba-Geigy Corporation requests establishment of a tolerance of 0.1 ppm for combined residues of the herbicide metolachlor: [2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl) acetamide] and its metabolites determined as (2-[(2-ethyl-6-methylphenyl)amino]-1-propanol) and (4-[2-ethyl-6-methylphenyl] -2-hydroxy-5-methyl-3-morpholinone), each expressed as parent metolachlor, in or on the raw agricultural commodity, soybeans.

Metolachlor is also known by the trade name, Dual, and as CGA-24705. ANSI has certified metolachlor as the common name for this chemical.

A permanent tolerance (§180.368) has been established at 0.1 ppm for residues of metolachlor and its metabolites in corn grain (excluding popcorn) in response to PP#5F1606. The rationale for establishing this tolerance was outlined in FR 41:178, 9/13/76.

In response to PP#6G1708, temporary tolerances were established on 4/23/76 at 0.1 ppm in soybeans, 1.25 ppm in soybean forage and hay, and 0.02 ppm in eggs, milk and the meat, fat and meat byproducts of cattle, goats, hogs, horses, poultry and sheep.

Conclusions:

1. The metabolism of metolachlor has been adequately delineated in corn, soybeans and animals. The general structure of the metabolic products is shown in Figure 1.

2(a) The analytical methods convert residues of the parent compound 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) (see Figure 1) using a 6N HCL hydrolysis step.

2(b) The methodology, although very time consuming, is adequate for enforcement of the proposed tolerance. The methods were tested with corn and liver in connection with PP#5F1606.

3(a) The proposed tolerance level of 0.1 ppm is adequate to cover residues of metolachlor and its metabolites in soybeans and their fractions (meal, oil, hulls, soapstock).

3(b) No tolerance has been proposed for soybean forage or hay including the fodder or straw left after harvesting the beans). The petitioner should either propose a tolerance for these items or place appropriate feeding restrictions on the label.

3(c) Residues of linuron and metribuzin resulting from the proposed tank mixes with metolachlor will not exceed the established tolerances of 1.0 and 0.1 ppm, respectively, for these compounds on soybeans.

4. The use is classed as §180.6(a)(2) and tolerances are required for residues in meat, milk, poultry and eggs.

5. Establishment of the previous permanent tolerance on corn grain was based upon the likelihood of there being no human or animal exposure to residues of metolachlor. This use on soybeans would be expected to result in some human exposure to small residues of metolachlor.

Recommendation:

We recommend against establishment of the proposed tolerance because of the deficiencies listed under conclusion 3b and 4.

The petitioner should be advised of these deficiencies.

DETAILED CONSIDERATIONS

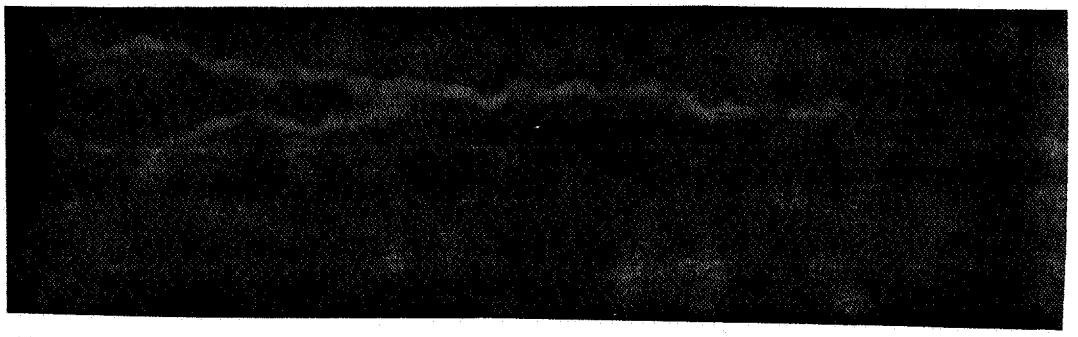
Manufacture and Formulations:

The manufacturing process has been detailed in our evaluation of PP#5G1553 (2/12/75). The purity of the technical product is now 95% in contrast to the 90% purity claimed in previous petitions. The impurities are:

[redacted]

Information about impurities deleted.

Information about impurities deleted



We would not expects these impurities to constitute significant portions of the terminal residue.

Metolachlor is formulated as Dual 6E, an emulsifiable concentrate containing 6 lbs a.i./gal. The three adjuvants of the formulation are cleared under 180.1001(c).

Proposed Use:

Metolachlor is applied either preplant incorporated or preemergence using either ground or aircraft spray equipment. Broadcast rates are 1.5 to 3 lbs a.i./A, depending on soil type, when only metolachlor alone is applied. For tank mixes with Sencor, Lexone or Lorox the following broadcast rates are specified:

1.25-2.5 lbs. a.i./A metolachlor+0.25-0.75 lbs. a.i./A Sencor 50WP or Lexone (Trade Names for metribuzin)

1.25-2.5 lbs. a.i./A metolachlor+0.5-1.5 lbs. a.i./A Lorox (Trade name for linuron)

The above rates for tank mixes are lower than the maximum rates specified when these compounds are used singly, i.e. 0.37-1.0 lb. a.i./A for Sencor or Lexone; up to 3 lb. a.i./A for Lorox. Tolerances have been established for residues in soybeans at ppm for linuron and 0.1 ppm for metribuzin.

The label bears a rotational crop restriction stating that if replanting is necessary, soybeans or corn may be replanted immediately; small grains may be planted in the fall following treatment and any crop may be planted the following spring.

Although no tolerances have been proposed for soybean forage, hay or fodder (straw), no restrictions against the feed use of these items has been included. Such restrictions are required if tolerances for these items are not proposed.

Nature of the Residue:

Extensive ^{14}C ring labeled metolachlor metabolism studies have been carried out in corn and soybeans. These studies have been described in detail in our evaluations of PP#'s 5G1553, 6F1606 and 6G1708. The metabolic pathways appear similar in soybeans and corn. The major pathway of metabolism involves conjugation with glutathione, formation of the mercaptan, conjugation of the mercaptan with glucuronic acid, hydrolysis of the methyl ether, and conjugation of the alcohol with a neutral sugar. The general structure of the metabolites is shown in Figure 1 as are the resulting products produced by the HCL refluxing employed in the analytical residue method. The HCL hydrolysis procedure was demonstrated to be effective in releasing the various metabolites in the corn tracer study, discussed in PP#5F1606.

The soybean study, in which soybeans were grown to maturity in a greenhouse in which the potted soil was treated preemergence with 2 lbs a.i./A of ^{14}C-ring labeled metolachlor produced total ^{14}C residues (expressed as metolachlor) of 2.66 ppm in the stalks and 0.17 ppm in the beans. Of the bean residues, 0.14 ppm was found in the meal and 0.01 ppm in the oil. We would expect residues in the greenhouse study to be higher than those encountered in the field.

The metabolism of metolachlor in soybeans is adequately defined.

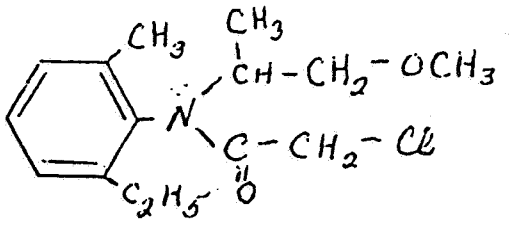
Animal metabolism studies have been carried out in rats and goats using ^{14}C-labeled metolachlor and in goats only using ^{14}C-corn-biosynthesized metabolites. These studies were detailed in our review of PP#5G1553. The studies show rapid elimination with only trace residues in tissue (liver). Comparison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

The metabolism of metolachlor in animals is adequately defined.

Analytical Methods:

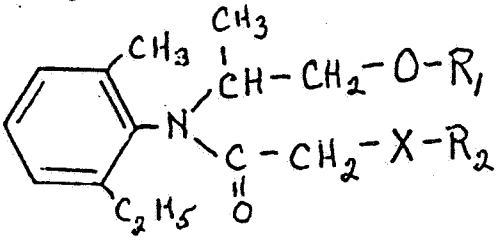
The analytical method, AG-286,"Analytical Method for the Determination of Residues of CGA-24705 Soybean Metabolites as CGA-37913 and CGA-49751 by Acid Hydrolysis," was discussed in detail in our evaluation of PP#6G1708. The sample is refluxed overnight with 6N HCL to convert the residues of parent and metabolites to the above compounds

Figure 1: Metolachlor Alteration



CGA-24705
(Metolachlor)

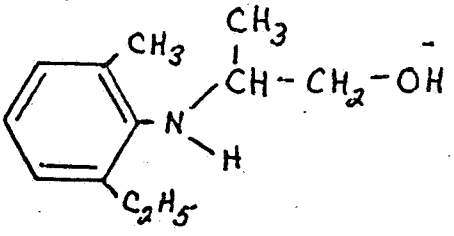
PLANT METABOLISM



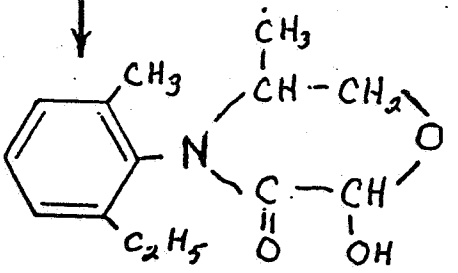
Where: R_1 & R_2 = methyl group or a natural product moiety (i.e. amino acids, sugars or sugar acids

X = O or S

METHOD CONVERSION
(Refluxing with HCl)



CGA-37913
2-((2-ethyl-6-methyl-phenyl)amino)-1-propanol



CGA-49751
4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone

(see Figure 1). After various partitioning and clean up steps, the CGA-37913 is determined by gas chromatography using a Coulson nitrogen detector; the CGA-49751 is derivatized, cleaned-up and determined by GLC using microcoulometric chloride detection. Both are calculated as metolachlor using the respective conversion factors of 1.47 and 1.13 for CGA-37913 and CGA-49751.

Samples fortified with CGA-49751 at levels of 0.05 - 0.1 ppm showed recoveries between 42% and 100% with an average of 66± 13% (n=43). Two controls in soybean forage were reported as <0.10 and 0.06 ppm; all others in forage and other fractions were <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% ± 15% (n=27). A few controls in soybean forage were reported as <0.08 and <0.10 ppm primarily because of small sample size; all others for forage, fodder, grain and fractions were <0.03 ppm.

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

The combined sensitivities for the two moieties in soybeans is <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 method, as applied to determining residues in corn grain, and a method for residues in tissues were subjected to method trials in connection with our review of PP#5F1606. The methods were judged acceptable, but quite time consuming (see evaluations of R.R. Watts, 7/28/76 and 7/29/76, PP#5F1606).

The method for residues in soybeans was tested by the petitioner for specificity with 54 of the 58 pesticides registered on soybeans. Furthermore, DC-200 and Carbowax 20M are alternative liquid phases for the GLC determinative steps. The methods possess adequate specificity and are judged adequate for enforcement of the proposed tolerances.

The residue analysis for linuron residues resulting from tank mix applications were performed by DuPont using a hydrolysis/extraction iodination/GLC procedure(see Barenok and Geissbuehler, "Specific Determination of Urea Herbicide Residues by EC Gas Chromatography After Hydrolysis and Iodine Derivative Formation, "Bulletin of Environmental Contamination and Toxicology, Vol 3, No. 1, pp 7-17, (1968)). Linuron recoveries on soybeans averaged 82% (range 68-95%) at fortification levels of 0.05 - 0.5 ppm. For soybean fodder, recoveries averaged 93% (range 84-100%) at levels of 0.2-2.0 ppm.

Residue analysis for metribuzin (Sencor, Lexone) and its metabolites were peformed by Chemagro using a modified version of the earlier Chemagro method detailed in PAM II. Recoveries of 79-108% were obtained for the parent and metabolite at levels of 0.05-0.10 ppm in the beans; recoveries were 54-93% in dry vines.

Residue Data:

Although the samples were stored frozen for periods up to one year, the storage stability of metolachlor residues has been demonstrated in corn fodder and grain samples. Since no significant loss of residues occurred during a 13 month storage period, we do not consider the storage stability of residues in frozen samples to constitute a problem.

Nine residue studies were carried out in eight states representing major soybean growing areas. Metolachlor was applied at rates of 2 to 6 lbs. a.i./A (0.67X to 2X the maximum proposed rate).

Analysis were performed for both CGA-37913 and CGA-49751. No detectable residues (<0.05 ppm) as CGA-49751 were found in any of the soybean samples. Residues as CGA-37913 in the soybeans ranged from <0.03 to 0.09 ppm at application rates up to 5 lbs a.i./A (1.7X). The maximum residue of 0.09 ppm resulted from a 3 lb. a.i./A application in the Indiana study. At the 2X application rate of 6 lbs a.i./A, residues ranged from <0.03 to 0.21 ppm. We conclude that the proposed tolerance level of 0.1 ppm is adequate to cover residues of metolachlor and its metabolites in soybeans.

Fractionation studies were performed at Texas A & M on soybeans from three of the studies. No detectable residues of CGA-37913 (<0.03 ppm) or CGA-49751 (<0.05 ppm) were detected in any fractionation

sample (meal, crude and refined oil, soapstock) from treatment rates ranging from 2 to 5 lbs a.i./A. At the 6 lbs a.i./A rate (2X), the only finite residue found was in soybean meal where 0.04 ppm CGA-37913 was detected. In one of the three tests, hulls contained 0.03 and 0.06 ppm CGA-37913 from treatment rates of 2.5 and 5.0 lbs a.i./A respectively. Soybean hulls from all other tests contained <0.03 ppm CGA-37913 and <0.05 ppm CGA-49751.

As mentioned in the Nature of the Residue, the fractionation of beans treated with labeled metolachlor also indicated that residues would not concentrate in the meal or oil. We conclude that the proposed 0.1 ppm metolachlor tolerance level is adequate to cover any residues in soybean fractions (hulls, meal, oil, soapstock) as well as in the beans themselves.

The petitioner has not proposed a tolerance for soybean forage, hay or fodder (straw). A small amount of residue data for these items has been included in this petition. More comprehensive data was presented in PP#6G1708 where a temporary tolerance of 1.25 ppm was established for soybean forage and hay. If the petitioner does not wish to propose a permanent tolerance for the forage and hay or fodder, the label should bear a restriction against the feeding of these items.

The residue data for tank mixes with linuron or metribuzin indicates that residues of these compounds will not exceed their respective tolerances of 1.0 and 0.1 ppm. Only one detectable residue, 0.11 ppm linuron, of these compounds was found in all of the tank mix studies.

Residues in Meat, Milk, Poultry and Eggs:

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

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

In a cold study, 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 (<0.02 ppm CGA-37913, <0.04 ppm CGA-49751) were found in eggs, muscle or fat. Residues of 0.02 ppm and 0.03 ppm of CGA-37913 were found in liver from birds at the 0.5 and 2.0 ppm levels respectively.

From the feeding of soybean meal, hulls and soapstock bearing residues of 0.1 ppm, the residue level in the total diet could approach 0.04 ppm for cattle and 0.02 ppm for poultry. The feeding levels (4.7 ppm in goats, 0.5 ppm in chickens) at which barely detectable residues were found in the above feeding studies thus represent exaggerations of ca. 100X for ruminants and 25X for poultry. In the case of ruminants, however, the question of proposing tolerances or appropriate feeding restrictions for soybean forage and hay has not been addressed. Allowing the feeding of soybean forage or hay (including the fodder or straw from the bean harvest) would result in an exaggeration factor of about 10X.

We class these uses as Category 2 of 180.6(a). Although residues in meat, milk, poultry and eggs resulting from these uses would be below the level of detectability, we cannot say with assurance that there will not be any residues in these items. if present

Other Considerations:

The tolerance for metolachlor on corn grain (PP#5F1606) was established before all current toxicological requirements were met, on the basis that there would be no human exposure to residues of metolachlor. (No residues were found in corn grain at exaggerated rates; feeding restrictions were proposed for corn fodder and forage to avoid residues in meat and milk).

In this petition for soybeans, the petitioner has also tried to build a case that this use would result in no human exposure to residues of metolachlor. The basis here is less clear cut than in the corn petition. Actual residues approaching 0.1 ppm occur in soybeans. Although the fractionation data indicate that little of the residues transfer to the primary human food, soybean oil, exposure to some residues are likely. This might

occur from products such as soybean based meat extenders as well as from small residues in the oil. In addition, there is the possibility that the livestock feed use of soybean fractions (not to mention the forage and hay) may lead to small, non-detectable residues in meat, milk, poultry and eggs (§180.6(a)(2)).

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