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

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

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MEMORANDUM

Subject: PP#2F2601. Metolachlor in or on safflower seed. Evaluation of analytical methodology and residue data.

EPA Reg. No. 100-597. Request to amend the registration of Dual 8E Herbicide to permit its use on safflowers.

From: M. Nelson, Chemist
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Thru: Charles Trichilo, Chief
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To: Richard Mountfort, Product Manager #23
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Registration Division (TS-767)

and
Toxicology Branch
Hazard Evaluation Division (TS-769)

The Ciba-Geigy Corporation proposes a tolerance for combined residues of the herbicide metolachlor [2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide; trade name, Dual®; aka CGA-24705] and its metabolites determined as 2-[(2-ethyl-6-methylphenyl)-amino]-1-propanol [aka CGA-37913] and 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone [aka CGA-49751], each expressed as parent metolachlor, in or on the raw agricultural commodity safflower seed at 0.1 ppm.

The petitioner also requests the amended registration of the Dual 8E herbicide label (EPA Reg. No. 100-597) to permit the use of Dual 8E in safflower culture.

Tolerances are presently established (40 CFR 180.368) for aforesaid combined residues in or on field corn, peanuts, soybeans, and sorghum at levels ranging between 0.1-3 ppm. There are also tolerances established for secondary residues in meat, milk, poultry, and eggs at 0.02 ppm.

Additional tolerances are co-pending on sweet corn, popcorn, sunflower seed, flaxseed, cottonseed, potatoes, and seed and pod vegetables at levels ranging between 0.1-1 ppm.

There is also a rotational crop tolerance proposal pending which requests a 0.5 ppm level for rotational grain crop forage and fodder.

Conclusions

1. The nature of the residue in plants and animals is adequately delineated. The residue of concern is parent metolachlor and its metabolites determined as the hydrolysis products CGA-37913 and CGA-49751.

2. Adequate analytical methodology is available to enforce the proposed tolerance.

3a. Residues in safflower seeds are not expected to exceed the proposed tolerance (0.1 ppm). In fact, detectable residues were not encountered under proposed use (or 2X rate) conditions, and the proposed tolerance level merely reflects combined method sensitivity levels of the two hydrolysis products CGA-37913 (0.03 ppm) and CGA-49751 (0.05 ppm) rounded up to a convenient level (0.1 ppm).

3b. No detectable residues were found in any safflower fraction regardless of treatment rate (1X or 2X), thereby precluding the need for food or feed additive tolerances.

3c. Safflower seed forage and fodder is reportedly unpalatable to livestock. Therefore, neither a tolerance nor label feeding restriction for these commodities is needed.

4. The existing meat/milk/egg tolerances are adequate to cover secondary residues arising therein from both the proposed and registered uses.

5. The amended registration request to revise the Dual 8E herbicide label to permit use in safflower culture is supportable.

6. An International Residue Limit (IRL) Status sheet is attached. There is no IRL/Codex tolerance for metolachlor residues in or on safflower seed.

Recommendation

Toxicological considerations permitting, we recommend for the proposed tolerance and amended registration requested by the petitioner.

Detailed Considerations

Manufacture and Formulation

The manufacturing process and the composition of technical metolachlor are detailed in our (A. Smith) 4/2/79 review of PP# 8F2081, which see.

The technical product is typically ca 95% pure. The various impurities, reaction by-products, etc. are not expected to cause a residue problem.

The question of the possible presence of nitrosamines was considered in conjunction with PP# 7F1913 and was discounted as unlikely (ref. 9/6/78 review of D. Reed and W. Boodee).

Technical metolachlor is the active ingredient in Dual 8E Herbicide (EPA Reg. No. 100-597), an emulsifiable concentrate formulation containing 8 lbs ai/gal. It is this formulation which is proposed for use on safflowers.

The inerts in Dual 8E are all cleared for use under 40 CFR 180.1001 (c) or (d). See Section A of PP#1E2563 for a Confidential Statement of Formula.

Proposed Use

Dual 8E is a selective herbicide recommended as a preplant incorporated or preemergence surface-applied treatment for control of most annual grasses and certain broadleaf weeds in safflowers.

Dual 8E Alone is to be applied at rates of 1-1/2 to 3 pints of formulation (i.e., 1.5 - 3 lbs ai) per acre, broadcast basis, with the rate dependent upon soil texture and percent of organic matter.

The possibility of tank-mixing for treatment of safflowers is not addressed on the label; therefore, it is presumably not endorsed for this crop.

Label Restrictions. Rotational Crops: 1) If treated crop is lost, corn, soybeans, peanuts, Concep®-treated grain sorghum, or safflower may be planted immediately. Do not make a second broadcast application of Dual 8E. If the original application was banded and the second crop is planted in the untreated row middles, a second banded treatment may be applied. 2) Small grains may be planted 4-1/2 months following treatment. Field corn, soybeans, sorghum, peanuts, safflower, root crops, and small grains may be planted the spring following treatment. Do not graze or feed forage or fodder from small grains to livestock. All other rotational crops may be planted 18 months after application without restriction.

Nature of the Residue

Radiotracer (ϕ- ^{14}C) metabolism data is available in our petition files from metolachlor studies on corn, soybeans, lettuce, and potatoes treated as target crops and carrots, soybeans, winter wheat, and oats grown as rotational crops in previously treated soils.

While no specific metabolism data is available for safflowers, we feel adequate data is available for other crops to allow us to conclude that safflowers would metabolize metolachlor in a similar manner.

Plants absorb, translocate, and metabolize metolachlor. The major pathway of metabolism in plants 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. A minor pathway involves a direct conjugation of metolachlor with glucuronic acid, followed by demethylation and conjugation of the hydroxy group with a neutral sugar.

The significant components of the residue in plants consist of parent metolachlor and its metabolites determined as the hydrolysis products 2-[(2-ethyl-6-methylphenyl)amino]-1-propanol (aka CGA-37913)and 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone (aka CGA-49751). The analytical methodology determines these components and their conjugates.

We consider the nature of the residue in plants (including safflowers, by translation of data from other crops) to be adequately understood.

Radiotracer (ϕ-^{14}C) metabolism data is also available in our files from metolachlor studies which have been conducted with rats and lactating goats and from a goat study using ^{14}C biosynthesized metabolites. Feeding study data is available from dairy cattle and poultry.

Metolachlor is ingested, rapidly metabolized, and almost totally eliminated by animals; there is only minor deposition of residues in tissues, milk, and eggs. Biosynthesized metabolites also pass through goats in a manner similar to metolachlor and are not accumulated in milk or tissues.

Comparison of metabolites found in urine with those found in plants (corn) indicate that, although the conjugating natural components in animals differ from those in plants, the hydrolyzed pesticide metabolic portions (aglycones) are similar. The significant components of the residue in animals are thus the same as those in plants.

We consider the nature of the residue in animals to be sufficiently delineated.

Analytical Methodology

Metolachlor residues determined as the hydrolytic moieties CGA-37913 and CGA-49751 were analyzed according to analytical method AG-338. Metolachlor residues are converted to CGA-37913 and CGA-49751 by refluxing with 6N hydrochloric acid overnight. CGA-37913 is determined as follows: An aliquot of the acid extract is basified with 50% (w/w) sodium hydroxide (19.4N) and CGA-37913 is partitioned into hexane. This fraction is subsequently chromatographed on an alumina cleanup column to remove interfering compounds. Final determination is performed on a gas chromatograph equipped with a Hall electrolytic conductivity detector specific for nitrogen or a N-P detector. The CGA-37913 residues are reported as metolachlor equivalents. The limit of detection is 0.03 ppm.

CGA-49751 is determined as follows: An aliquot of the acid extract is partitioned with dichloromethane to extract CGA-49751 into the non-aqueous phase. The dichloromethane-containing CGA-49751 is partitioned with a 5% sodium carbonate solution and chromatographed on an alumina column to remove interfering materials. CGA-49751 is converted to the chloroethanol derivative by reaction with boron trichloride/2-chloroethanol at 90°C for 15 minutes. The product is partitioned with hexane and chromatographed on a silica gel column followed by an alumina column. Modifications of the cleanup procedure, if any, are noted in the individual residue reports. Final determination is performed on a gas chromatograph equipped with an alkali flame ionization (N-P) detector operating in the nitrogen-specific mode. The CGA-49751 residues are reported as metolachlor equivalents. The limit of detection is 0.05 ppm.

Method AG-286 is the regulatory method in PAM II for metolachlor residues in corn, soybeans, sorghum, and peanuts, and is the analytical method which has previously undergone successful method trial (corn grain and beef liver) in re PP#5F1606 in our laboratories.

Method AG-338 is an updated version of the regulatory method and utilizes separate aliquots for the determination of CGA-37913 and CGA-49751.

Validation data for Method AG-338 for the various substrates (safflower seed, hulls, meal, crude oil, and soapstock) which were fortified at levels ranging 0.02-0.05 ppm of CGA-37913 and 0.05-0.1 ppm of CGA-49751 were submitted.

Recoveries ranged 70-100% for CGA-37913 and 56-100% for CGA-49751. Control values were below the limits of detection.

We conclude that adequate analytical methodology is available to enforce the proposed tolerance.

Residue Data

Three tests were conducted in the major safflower growing areas of the United States (CA and ND) using metolachlor alone (Dual 8E), and normal cultural practices. Rates used were 3.0 and 6.0 lbs. ai/A, which represent 1X and 2X, respectively, the maximum proposed use rate.

Samples of harvest seed were taken, frozen, and shipped to CIBA-GEIGY Laboratories in Greensboro, North Carolina. Representative sub-samples were taken and forwarded to a contract laboratory for analysis. Metolachlor analyses were performed by Craven Laboratories, Inc., Austin, Texas. One set of samples was also analyzed in CIBA-GEIGY Laboratories in Greensboro.

No residues (<0.08 ppm, which represents combined method sensitivities) were found in any seed sample regardless of location, treatment rate, or method of application. (See Table I, attached).

Based on the residue data presented in the petition, it is concluded that a residue tolerance of 0.1 ppm in or on safflower seed is adequate following a maximum label use rate (3.0 lbs. ai/A) application of metolachlor, either preplant incorporated or preemergence. The requested amended registration request is also supportable.

A large plot test in California provided sufficient treated seeds (both 1X and 2X) for fractionation. These samples were forwarded to the Food Protein Research and Development Center at Texas A&M University for commercial fractionation. A solvent extraction process was employed. Samples of hulls, meal, oil, and soapstock were forwarded to CIBA-GEIGY Laboratories for analysis.

No detectable residues were found in any safflower fraction regardless of treatment rate, thereby precluding the need for food or feed additive tolerances. (See Table II, attached).

No residue data or label feeding restriction was provided for safflower seed forage or fodder. The petitioner indicates this was because the forage and fodder of safflower are not fed to livestock. The Harris Guide and Morrison's Feeds and Feeding support this contention as does information in our Cultural Practices File which states, "...safflower seed has no feed byproducts (or forage) except for the meal derived from processing the oil. This is due to the fact that the plants are spiny and the plant material left after removal of the seed is unpalatable to livestock."

Residues in Meat, Milk, Poultry, and Eggs

Residue tolerances of 0.02 ppm for metolachlor and its metabolites expressed as parent compound have been established in milk, meat, poultry, and eggs (PP No. 7F1913).

Those tolerances are adequate to cover any secondary residues which might arise in those commodities as a result of: (1) ingestion of feed items (seeds, meal) derived from safflowers treated in accordance with the proposed use; and, (2) ingestion of feed items derived from the other tolerated crops (e.g., peanuts, soybeans, corn, etc.) listed in 40 CFR 180.368.

Other Considerations

An International Residue Limit (IRL) Status sheet for metolachlor is attached to this review. There is no established IRL or Codex proposal (step 6 or above) for metolachlor residues in/on safflower seed.

Attachments (3)

cc: cc: R.F., Circu, Reviewer, PP# No., FDA, TOX, EEB, EFB, Randy Watts
TS-769:Reviewer:Nelson:RCB:CM#2:RM:810 x77377:Date:2/9/82
RDI:Section Head:RSQ:Date:1/25/82:RDS:Date:1/25/82

INTERNATIONAL RESIDUE LIMIT STATUS

CHEMICAL Metolachlor

PETITION NO 2F2601

CCPR NO. none

Codex Status

[✓] No Codex Proposal
Step 6 or above

Proposed U. S. Tolerances
for 180.368

Residue (if Step 9): _____

Residue: metolachlor plus metabolites determined as CGA-37913 + CGA-49751.

Crop(s)	Limit (mg/kg)
none	

Crop(s)	Tol. (ppm)
Safflower seed	0.1

CANADIAN LIMIT

Residue: _____

Crop	Limit (ppm)
none (on above commodities)	

MEXICAN TOLERANCIA

Residue: _____

Crop	Tolerancia (ppm)
none	

Notes:

TABLE I: METOLACHLOR RESIDUES IN SAFFLOWERS RESULTING FROM PREEMERGENCE OR PREPLANT INCORPORATED APPLICATIONS OF DUAL 8E

Test No. Location	Rate lbs. ai/A	Date Applied	Type of Application	Interval (Days)	Crop Fraction	Rep	Residue (ppm) CGA-37913*	Residue (ppm) CGA-49751*
6133 CA	3.0	4/23/80	PPI	140	Seed	I	<0.0084	<0.013
						II	<0.0084	<0.013
	6.0 (2X)			140	Seed	I	<0.0084	<0.013
						II	<0.0084	<0.013
6140 CA	3.0	4/22/80	PPI	134	Seed	I	<0.03	<0.05
						II	<0.03	<0.05
	3.0	4/23/80	PRE	133	Seed	I	<0.03	<0.05
						II	<0.03	<0.05
6207 ND	3.0	4/29/80	PPI	128	Seed	I	<0.03	<0.05
						II	<0.03	<0.05
	6.0 (2X)			128	Seed	I	<0.03	<0.05
	3.0	5/1/80	PRE	126	Seed	I	<0.03	<0.05
						II	<0.03	<0.05
	6.0 (2X)			126	Seed	I	<0.03	<0.05

*Residues reported as metolachlor equivalents.
Value in parenthesis indicates relationship to maximum use rate.

TABLE II. RESIDUES IN SAFFLOWER SEED FRACTIONS RESULTING FROM COMMERCIAL FRACTIONATION

Test No. - AG-A 6133 II
Location - California
Mode of Application - PPI
Treatment Rates - 3.0 lbs. ai/A, 6.0 lbs. ai/A
Place of Fractionation - Food Protein Research and Development Center, Texas A&M University

	Residue (ppm)			
	3.0 lbs.		6.0 lbs.	
	CGA-37913	CGA-49751	CGA-37913	CGA-49751
Seeds (small subsamples)	<0.0084*	<0.013*	<0.0084*	<0.013*
Seeds (from large batch sent to TX A&M)	<0.03	<0.05	<0.03	<0.05
Hulls	<0.03	<0.05	<0.03	<0.05
Solvent extracted meal	<0.03	<0.05	<0.03	<0.05
Crude oil	<0.03	<0.05	<0.03	<0.05
Refined oil	<0.03	<0.05	<0.03	<0.05
Soapstock	<0.03	<0.05	<0.03	<0.05

Note: Residues are expressed as metolachlor equivalents.

*Analyses were pushed beyond the normal limits of detection to determine the presence of any residue. The screening level for each particular analysis is given.