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

FEB 21 1991

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: PP#4F3042 - Pendimethalin (Prowl®) on Tomatoes.
Review of the July 30, 1990 Amendment.
(No MRID Number) [DEB Nos. 7047 and 7048]
(HED Project No. 0-1932)

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and

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THRU: Richard D. Schmitt, Ph.D., Chief
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American Cyanamid Company has submitted this amendment consisting of a cover letter and a new Section B (new directions for use of Prowl® on tomatoes) in response to deficiencies outlined in the Residue Chemistry Chapter of the Pendimethalin Registration Standard dated May 10, 1984 and the Pendimethalin Registration Standard Update of March 19, 1990. CBTS (aka RCB) has previously recommended for the requested tolerance of pendimethalin in/on tomatoes (see memorandum PP#4F3042, L. Kutney, March 27, 1984); however, the Pendimethalin Registration Standard was issued before the tolerance was established. The Registration Standard identified a number of residue chemistry deficiencies, thus preventing establishment of the proposed tolerance. In the cover letter, the petitioner requests reactivation of the petition contending all deficiencies are resolved. The deficiencies identified in the Registration Standard are repeated below in the body of this review in the order they appeared in the Pendimethalin Registration Standard,



followed by the petitioner's response, and then by CBTS comments. Our conclusions and recommendation follow.

EXECUTIVE SUMMARY OF CHEMISTRY DEFICIENCIES

- Plant metabolism studies required.
- Livestock (ruminant and poultry) metabolism studies are necessary.
- Confirmatory analytical method needed.
- Multiresidue method data are needed.
- Livestock feeding studies should be presented.
- Tomato processing study should be performed.

CONCLUSIONS

1. CBTS Conclusion on Directions For Use

The petitioner has proposed an adequate set of directions for use of Prowl Herbicide (EPA Registration No. 241-243) on tomato fields to control various grasses and broadleaf weeds.

2. CBTS Conclusion on Nature of the Residue - Plants

CBTS reiterates that the nature of the pendimethalin residue in plants is not adequately understood. Additional plant metabolism studies are required in which pendimethalin, radiolabeled in the phenyl ring, is applied to plants at rates equal to or greater than the maximum application rate. High application rates are preferred to increase the level of radioactive material available for analysis and identification, provided there is no phytotoxicity. One plant metabolism study should be conducted on sweet corn with analysis of vegetative parts and grain from 1) plants treated preemergence and 2) plants treated postemergence. A second plant metabolism study is needed on a plant in which the edible portion grows in the soil. The deficiency remains unresolved and continues outstanding.

3. CBTS Conclusions on Nature of the Residue - Livestock

a. CBTS reiterates that ruminant metabolism study submitted in a co-pending petition does not define the nature of the residue. Measurable/detectable residues were found only in the caprine liver ranging from 0.08 ppm to

0.17 ppm from a 6.5 ppm dose of ^{13}C and ring-labeled ^{14}C -pendimethalin. Fractionation of the liver extracts revealed numerous free, unbound ^{14}C -components which were not characterized. CB reiterates the petitioner has not adequately characterized the nature of the residue in ruminants. CB suggests the petitioner repeat the HPLC identification step for all fractions containing 0.005 ppm radiolabeled residue characterizing major peaks using detectors that can elucidate organic structure, such as but not limited to MS, FTIR, FTUV, NMR, etc. The petitioner needs to confirm the presence of or absence of all metabolites identified in the rat metabolism study. Complete characterization of the caprine radiolabeled residue is essential for CB to ascertain the need for a ruminant feeding study. If caprine metabolism differs significantly from that in rats, then porcine ^{14}C -pendimethalin residue data are also necessary. This deficiency is not resolved and continues outstanding.

b. CBTS reiterates that poultry metabolism studies are required using laying hens dosed with ring-labeled ^{14}C -pendimethalin for at least 3 days at a level > 1.0 ppm, sufficient to have adequate radiolabeled material available for identification. The laying hens are to be sacrificed within 24 hours of the final dose. The distribution and characterization of at least 90+ percent of the radiolabeled residue need to be determined in eggs (white and yolk), muscle, fat, skin, and liver. The deficiency is not resolved and continues outstanding.

4. CBTS Conclusion on Residue Analytical Method

a. CBTS reiterates that a validated confirmatory method (mass spectrometry is suggested) for residues of pendimethalin, per se, and its metabolite CL-202,347 is necessary. This part of the deficiency is not resolved and continues outstanding.

b. CBTS reiterates that additional multiresidue method (MRM) validation data are necessary for the Food & Drug Administration (FDA) MRM's A thru E. Chromatographic data are required for pendimethalin and its alcohol metabolite for Protocol C. Representative samples of plant and animal tissues need to be analyzed by appropriate MRM protocols B, D, and E following the FDA decision tree for MRM testing. The protocols are found in FDA's PAM-I, Appendix II. This part of the deficiency is not resolved and continues outstanding.

c. CBTS reiterates that if radiolabeled validation of existing analytical methods for plants and animals indicates a major portion of the total radioactive residue is not recovered and identified by these methods, then radiolabeled

validation of any new proposed residue analytical method needed may be required. The deficiency is not resolved and continues outstanding.

5. CBTS Conclusion on Storage Stability Data

CBTS reiterates that data are needed reflecting the stability of pendimethalin and its 3,5-dinitrobenzyl alcohol metabolite (CL-202,347) in or on representative plants (such as root and tuber vegetables, legume vegetables, and cereal grains) and miscellaneous crops (e.g., cottonseed, peanuts, and sunflower/safflower seeds), and animal matrices stored at freezing temperatures for time intervals approximating those of the treated samples used to determine the magnitude of the residue. The sample storage conditions and intervals must be supplied for all previously submitted residue data for tomato commodities (raw and processed foods and feeds). Storage stability data are required for only those samples deemed to be useful for tolerance assessment. The purity of the reference standards used for fortification of samples, a complete description of the analytical methods (including extraction procedures), and any method validation data generated need to be provided. The deficiency is not resolved and continues outstanding.

6. CBTS Conclusion on Magnitude of the Residue - Meat/Milk/Poultry/Eggs

a. CBTS reiterates that a conventional ruminant feeding study may be necessary, depending on the results of the ruminant metabolism study in which lactating ruminants are dosed at 0.1, 0.3, and 1.0 ppm pendimethalin, per se, in the total diet, \geq three animals per dose group. The animals should be kept on the treated feed for 4 weeks. However, if residues have not plateaued in milk by the end of 4 weeks, then the feeding period should continue until a plateau is reached. Milk should be collected twice daily and residues determined therein. Animals must be sacrificed within 24 hours of the final dose, and residues determined in muscle, liver, kidney, and fat. The deficiency is not resolved and continues outstanding.

b. CBTS reiterates that a conventional poultry feeding study may be necessary, depending on the results of the poultry metabolism study in which laying hens are dosed at 0.1, 0.3, and 1.0 ppm pendimethalin, per se, in the total diet, \geq 10 hens per dose group. The laying hens should be kept on the treated feed for 4 weeks. However, if residues have not plateaued in eggs by the end of 4 weeks, then the feeding period should continue until a plateau is reached. Eggs should be collected at least daily and residues determined therein. The laying hens need to be

sacrificed within 24 hours of the final dose and residues determined in muscle, liver, skin, and fat.

c. If feeding studies become necessary, then at this time, CBTS reiterates that we will request residue data for residues of pendimethalin, per se, and its metabolite CL-202,347 in the conventional feeding studies. CBTS points out that residue data may need to be presented for any additional metabolite(s) of toxicological concern if the requested metabolism studies so identify.

d. CBTS reiterates that the present ruminant metabolism study indicates that residues of pendimethalin may occur in meat and meat byproducts. The petitioner should be advised that tolerances need to be proposed for these animal commodities if the requested pendimethalin metabolism and feeding studies so indicate the transfer of residues. The deficiency is not resolved and continues outstanding.

7. CBTS Conclusion on Magnitude of the Residue - Processed Food/Feed

Upon further consideration, CBTS now concludes that the petitioner needs to conduct a pendimethalin tomato processing study using tomatoes bearing detectable residues, or, if no residues are detected, then use tomatoes treated at the highest practical application rate. The tomatoes are to be processed by standard commercial operations into wet tomato pomace, dry tomato pomace, tomato juice, and tomato puree or tomato catsup. Pendimethalin and its metabolite residue data are needed for each of these processed tomato commodities. If pendimethalin residues concentrate, then appropriate food and/or feed additive tolerances need to be proposed.

RECOMMENDATION

CBTS cannot, at this time, recommend for the requested pendimethalin tolerance at 0.1 ppm on tomatoes for the reasons cited in our Executive Summary of Deficiencies and detailed in our Conclusions 2 through 7 above.

For further consideration of this petition, the petitioner needs to be advised to resolve these deficiencies.

DETAILED CONSIDERATIONSDIRECTIONS FOR USEPetitioner's Response

The petitioner has presented a revised label for use of Prowl® Herbicide (EPA Registration No. 241-243) containing 4 lb active ingredient/gallon, 42.3 percent of technical pendimethalin to control various grasses (e.g., barnyard grass, crabgrass, foxtail, Johnsongrass, etc.) and broadleaf weeds, (e.g., carpetweed, lambsquarter, pigweed, etc.) in tomato production.

CBTS Comments

The petitioner proposes applying Prowl® Herbicide to direct seeded tomatoes postemergence at blocking or thinning/lay-by as a directed ground spray in at least 10 gallons of water. Prowl® is applied to cover the soil between rows and beneath tomato plants in direct seeded tomatoes. Do not apply Prowl® directly to tomato foliage. Prowl® is mechanically incorporated into the top 1 or 2 inches of soil within 7 days of application.

The petitioner proposes applying Prowl® Herbicide to transplanted tomatoes preplant in at least 20 gallons of water by ground equipment, or at least 5 gallons of water in aerial application. Mechanically incorporate Prowl® into the top 4 to 6 inches of soil between 60 days of transplanting to immediately prior to transplanting. Set tomato transplants so that the roots are below the incorporation zone.

The rate of Prowl® application in Southern States, where there are no organic matter in soil restrictions ranges from 1 pint (0.5 lb. a.i. pendimethalin) per acre in coarse, sandy soils to 3 pints (1.5 lbs. a.i.) per acre in fine clay soils. In Northern States where soils contain 3 percent organic matter or less, the Prowl® application rate ranges from one pint (0.5 lb. a.i. pendimethalin) per acre in coarse, sandy soils to 3 pints (1.5 lbs a.i.) per acre in fine clay soils. For the Northern States where soils contain greater than 3 percent organic matter, Prowl® is applied at rates of 2 pints (1 lb. a.i.) per acre in course sandy loam soils to 3 pints (1.5 lbs a.i.) per acre in fine clay soils.

The petitioner has proposed an adequate set of directions for use of Prowl® Herbicide on tomato fields.

NATURE OF THE RESIDUE - PLANTS

Deficiency

The following additional data are required:

- o Data involving the reasonably complete characterization of the extractable and unextractable radioactive residues found in plant tissues as the result of the application of radiolabeled pendimethalin in a manner simulating a treatment regime registered for use. Representative crops (potatoes, soybeans, corn, etc.) for which pendimethalin formations are registered should be used.
- o Data depicting the distribution and metabolism of ¹⁴C-pendimethalin in or on mature plant parts from three dissimilar food crops (e.g., a root crop, oilseed crop, and a leafy vegetable). If metabolism is not similar in the three crops, additional studies using other crops may be required. A completely characterized test substance representative of technical pendimethalin (including impurities, if appropriate) used in the commercial formulations must be applied at levels sufficiently high to permit characterization of ¹⁴C-residues. Confirmation of the identities of residues using a suitable confirmatory method such as MS or HPLC is also required. In addition, representative samples from the tests must be analyzed using a currently accepted or proposed enforcement method in order to ascertain that this method will determine all possible metabolites of concern.

Petitioner's Response

The petitioner did not respond.

CBTS Comments

After a number of consultations with the petitioner, CBTS reiterates that the registrant should be informed that the plant metabolism data base for pendimethalin is not adequate. Although the available studies indicate that low levels of radioactivity are taken up from the soil into aerial parts of plants, these studies were conducted with pendimethalin radiolabeled in side chains as opposed to the phenyl ring. In addition, most of the studies were conducted using application rates lower than the maximum permitted on product labels.

Additional plant metabolism studies are required in which pendimethalin radiolabeled in the phenyl ring is applied to plants at rates equal to at least the maximum rates on product labels. Provided significant phytotoxicity does not occur, even

higher application rates (2X to 5X) are preferred to increase the level of radioactivity available for analysis and identification. One study should be conducted on sweet corn with analysis of vegetative parts and grain from 1) plants treated preemergence and 2) plants treated postemergence. A second plant metabolism study is needed on a plant in which the edible portion grows in the soil, such as potatoes or peanuts. The petitioner's report should include the percent of the total radioactive residue (TRR) for each plant part and the report should include the ppm value for the total TRR as well as each identified component of the TRR. The petitioner is expected to identify at least 90+ percent of the TRR. The petitioner is to confirm identities of all metabolites by a second technique.

Chemistry Branch I recently concluded that deficiencies in the knowledge of plant metabolism were not applicable for use on sugarcane (PP#2F2765, R. Cook, November 26, 1990). CBTS emphasizes that this decision applies only to sugarcane and is based on the low total activity (< 0.01 ppm) and long preharvest interval observed in that crop.

CBTS reiterates that the nature of the residue in plants is not adequately understood. The deficiency continues unresolved and remains outstanding.

NATURE OF THE RESIDUE - LIVESTOCK

Deficiency

The following data are required:

- o Metabolism studies utilizing ruminants - Animals must be dosed with ring-labeled [¹⁴C]pendimethalin for 3 days at a level (> 1.5 ppm) sufficient to make residue identification possible. Animals must be sacrificed within 24 hours of the final dose. The distribution and characterization of residues must be determined in milk, muscle, fat, kidney, and liver. If ruminant metabolism is found to differ significantly from that in rats, then swine metabolism data will also be required.
- o Metabolism studies utilizing poultry - Hens must be dosed with ring-labeled [¹⁴C]pendimethalin for 3 days at a level (> 1.0 ppm) sufficient to effect residue identification. Birds must be sacrificed within 24 hours of the final dose. Residues must be characterized and quantified in eggs, muscle, fat, kidney, and liver.
- o Metabolism studies utilizing ruminants and poultry - Animals must be dosed orally with ring-labeled

[¹⁴C]pendimethalin for a minimum of 3 days at a level sufficient to make residue identification and quantification possible. Eggs and milk must be collected twice daily during the dosing period. Animals must be sacrificed within 24 hours of the final dose. The distribution and identity of residues must be determined in eggs, milk, muscle, fat, kidney (except poultry), liver, and poultry skin. Representative samples from both of the studies must be analyzed using a suitable confirmatory method such as MS or high-pressure liquid chromatography. In addition, representative samples from these studies must be analyzed using a currently accepted or proposed enforcement analytical method in order to ascertain that the method is capable of adequately recovering and identifying all residues of concern. If the ruminant and/or poultry metabolism differs significantly from the rat data, then swine metabolism data will also be required.

Petitioner's Response

The petitioner did not respond.

CBTS Comments

CBTS reiterates that the nature of the pendimethalin residue in poultry is not adequately understood. CBTS reiterates that a poultry metabolism study using ring-labeled ¹⁴C-pendimethalin is necessary. The petitioner is reminded to identify at least 90+ percent of the TRR in any new poultry metabolism study. Current Branch policy as outlined and explained in Attachment 3 to the "Overview of Residue Chemistry Guidelines" clearly states that CBTS now requires a poultry metabolism study whenever a pesticide is to be applied to a crop having a poultry feed commodity listed in Table II of the Residue Chemistry Guidelines. For tomatoes, the feed item commodity listed in Table II is wet or dry pomace. Wet tomato pomace can be 2 to 3 percent of poultry diets. Thus, livestock metabolism studies are necessary.

In a related co-pending petition (PP# 3F 2788) the petitioner presented the results of a caprine metabolism study using ¹³C and ¹⁴C-ring labeled pendimethalin. Measurable or detectable residues were found only in caprine liver ranging from 0.08 ppm to 0.17 ppm from a 6.5 ppm dose. Trace amounts were also detected in caprine kidney (about 0.02 ppm) and in caprine milk <0.01 ppm. Fractionation of various liver extracts revealed numerous free, unbound ¹⁴C-components in the 0.005 ppm to 0.025 ppm range which were not characterized. CB suggests the petitioner repeat the HPLC identification step for all fractions containing 0.005 ppm and above, characterizing the major peaks using detectors that can elucidate organic structure such as but not limited to MS, FTIR, FTUV, NMR, etc. This information is

essential for CB to ascertain the need for a ruminant feeding study. The petitioner needs to confirm the presence of or absence of all metabolites identified in the rat metabolism study. If the ruminant metabolism study differs significantly from the rat metabolism, then a ¹⁴C-ring labeled pendimethalin porcine metabolism study is necessary.

CBTS reiterates the above deficiencies. They remain unresolved and continue outstanding.

RESIDUE ANALYTICAL METHOD

Deficiency

The following additional methods are required:

- o A validated confirmatory method (MS is recommended) for residues of pendimethalin, per se, and its metabolite (C-202,347).
- o Representative samples of plant and animal tissues containing residues of pendimethalin and its 3,5-dinitrobenzyl alcohol metabolite must be analyzed by multiresidue protocols C and E from PAM Vol. I, Appendix II.
- o If radiolabeled validation of existing analytical methodology for plants and animals (refer to "Qualitative Nature of the Residue in Plants" and "Qualitative Nature of the Residue in Animals" for additional details) indicates a major portion of the total radioactive residue is not recovered and identified by these methods, radiolabeled validation of any new proposed analytical methodology will be required.

Petitioner's Response

The petitioner did not respond.

CBTS Comments

CBTS reiterates the above deficiencies. They continue unresolved and remain outstanding.

After reconsideration on the requirements for MRM testing CB now concludes that additional MRM validation data are necessary for FDA MRM's A thru E. Chromatographic data are required for pendimethalin and its alcohol metabolite for Protocol C. Representative samples of plant and animal tissues need to be analyzed by appropriate MRM Protocols B, D, and E following the FDA decision tree for MRM testing. The protocols are found in

FDA's PAM-I, Appendix II. This part of the deficiency is not resolved and continues outstanding.

STORAGE STABILITY DATA

Deficiency

The following additional data are required:

- o Data reflecting the stability of pendimethalin and its 3,5-dinitrobenzyl alcohol metabolite (C 202, 347) in or on representative plants [such as root and tuber vegetables, legume vegetables, cereal grains, and miscellaneous crops (cottonseed, peanuts, and sunflower seed)] and animal samples stored at freezing temperatures for time intervals approximating those of the treated samples used to determine the magnitude of the residue.
- o The sample storage conditions and intervals must be supplied for all required and previously submitted residue data for plant commodities (raw and processed foods and feeds). Storage stability data in support of previously submitted residue data are required for only those samples deemed to be useful for tolerance assessment. The purity of the reference standards used for fortification of samples, and a complete description of the analytical methods (including extraction procedures) and method validation data used to supply other data in MRID No. 405351-01 must be provided. For additional guidance on conducting storage stability studies, the registrant is referred to an August 1987 Position Document on the Effects of Storage Validity of Pesticide Residue Data available from NTIS under order No. PB 88112362/AS.

Petitioner's Response

The petitioner did not respond.

CBTS Comments

CBTS reiterates the above deficiencies. They continue unresolved and remain outstanding.

MAGNITUDE OF THE RESIDUE - MEAT/MILK/POULTRY/EGGS**Deficiencies**

The following data are required:

- o Lactating ruminants must be dosed with 0.1, 0.3, and 1.0 ppm pendimethalin per se (\geq three animals/dose group) in the total diet until residues plateau in milk or for 28 consecutive days if no residues are detected in milk. Milk samples must be obtained twice daily. Animals must be sacrificed within 24 hours of the final dose and residues in tissues (muscle, liver, kidney, and fat) determined.
- o Poultry must be dosed with 0.1, 0.3, and 1.0 ppm pendimethalin per se (\geq 10 hens/dose group) in the total diet. Egg samples should be collected twice daily and analyzed for residues; dosing should continue until residues in eggs plateau or for 28 days if residues are nondetectable. Hens should be sacrificed within 24 hours of the final dose and residues determined in muscle, fat, kidney, liver, and other edible tissues.
- o Since the residues of concern in animal products have not been delineated, at the present time we require data reflecting residues of pendimethalin, per se, and its metabolite CL-202,347. Other residues may need to be sought if requested metabolism studies so indicate.
- o The available goat metabolism study (see Nature of the Residue in Animals) indicates that residues of pendimethalin may occur in meat and meat byproducts of food animals. Tolerances must be proposed for these food commodities if the above-required data so indicate.

Petitioner's Response

The petitioner did not respond.

CBTS Comments

CBTS reiterates the above deficiencies. They continue unresolved and remain outstanding.

CBTS points out that in the "Overview of the Residue Chemistry Guidelines" current Branch policy is that animals should be kept on the treated feed for 4 weeks. However, if residues have not plateaued in eggs or milk by the end of 4 weeks, then the feeding period should continue until a plateau is reached.

MAGNITUDE OF THE RESIDUE - PROCESSED FOOD/FEED**CBTS Comments**

In our previous review by L. Kutney on March 27, 1984, CBTS (aka RCB) concluded that since field trial residue data showed no detectable residue (< 0.05 ppm) and the radio-labeled study showed no detectable residues (< 0.01 ppm) in tomatoes, no processing study or FAT's were needed. Upon further consideration, CBTS now concludes a pendimethalin tomato processing study is necessary. This study should be conducted to address considerations noted below.

Based on the requirements as stated in the Residue Chemistry Guidelines, the petitioner needs to conduct additional tomato crop field trials with pendimethalin at the proposed use rate and/or highest practical application rate. If detectable residues are found in the raw agricultural commodity (RAC) tomatoes, then a processing study is necessary; and if the data show a concentration of residues, then a Food/Feed Additive Tolerance (FAT) is required. Residue data are necessary for wet and dry tomato pomace, tomato juice, and tomato puree or catsup.

If exaggerated rate data are available and there are detectable residues, then samples should be used for a processing study. If residues concentrate on processing, then the concentration factor should be applied to the RAC tolerance to arrive at a FAT.

If pendimethalin exaggerated application rate residue data are available and there are no detectable residues in the RAC tomatoes, then no FAT is required provided that:

1. The application rate is exaggerated by at least the critical concentration factor,
2. The crop field trial data are sufficiently representative of the major tomato growing regions so that any reasonable potential for detectable residues has been realized, and
3. The exaggerated rate was not unrealistically high. The level of exaggerated application acceptable will depend on the use.

If application of the highest practical exaggerated pendimethalin rate results in no detectable residues and the level of exaggeration is less than the theoretical concentration factor, then the tomatoes are to be processed. If no detectable residues are found in the processed tomato juice, catsup or puree, or wet and dry tomato pomace, then no FAT is required. If any processed commodities contain any pendimethalin and its metabolite residues, then a FAT is required. In cases where the

raw tomatoes contain no detectable pendimethalin residues, the processing study will indicate only that the minimum concentration factor is the ratio of the concentration in the processed commodity to the limit of detection (not quantification) in the RAC. CBTS will evaluate all available data in determining what is the appropriate concentration factor. This will include, at a minimum, the metabolism studies and chromatographic support data for the RAC. In some cases, it may be possible to estimate residue levels from chromatograms where the response is below the limit of reliable quantitation, but nonetheless indicates a "true residue."

H-7509C:CBTS:Reviewer(FDG):CM#2:Rm814B:557-0826:JOB:
64800:I:WP5.0:C.Disk:02/05/91:C:wo:DD:aw:ed:fdg:2/7/91.

CC: R.F., Circ(7), Reviewer(FDG), PP#9F3042, Pendimethalin Reg.Std.
File, PIB/FOD(Furrow).

RDI:SecHd:RSQuick:2/21/91:BrSrSci:RALoranger:2/21/91.