

PMSD TSB



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, DC 20460

DEC 22 1988

OFFICE OF
PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP# 8F3655 (Prowl^R on Almonds) and Pendimethalin
Reregistration Requirements. Evaluation of Residue
Data and Analytical Methods and Letter Dated 2/4/87.
MRID Nos. 407034-00, -01, -02. DEB No. 4609.

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Tolerance Petition Section 2
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Health Effects Division (TS-769C)

THRU: Charles L. Trichilo, Ph.D., Chief
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TO: Robert Taylor/Vickie Walters, PM-25
Registration Division (TS-767C)
and
Toxicology Branch, HFM Support
Health Effects Division (TS-769C)

American Cyanamid Company is requesting the establishment of tolerances for the herbicide pendimethalin [N-1-(ethylpropyl)-3,4-dimethyl-2,6-dinitrobenzenamine] and its metabolite, 4-[(1-ethylpropyl)amino]-2-methyl-3,5-dinitrobenzyl alcohol in or on almonds and almond hulls at 0.05 ppm in the subject petition. This is the first tolerance request since the 3/29/85 issuance of the registration standard.

Tolerances for pendimethalin and its 3,5-dinitrobenzyl alcohol metabolite are established in 40 CFR 180.361 on several RACs at levels of 0.01 to 0.1 ppm. The tolerance for peanut hulls is established for the parent, the 3,5-dinitrobenzyl alcohol metabolite and the 2,4-dinitrobenzyl alcohol metabolite at 0.25 ppm. Tolerances are pending on barley, grapes, peas, safflower seeds, sugarcane, tomatoes and wheat, all at 0.1 ppm. Of the pending tolerances, DEB recommended against the proposed tolerances on peas (3F2792), grains (wheat and barley-3F2788) and grapes (4F3121) for several reasons including the need for additional residue data and animal metabolism data (see memos of

R. Perfetti-3/9/83, and E. Haeberer-8/20/84).

The Product Chemistry and Residue Chemistry Chapters of the Pendimethalin Registration Standard were issued on July 20, 1984 with an addendum issued on December 3, 1985. The reregistration guidance document was issued on March 29, 1985. Additional plant and animal metabolism study data were requested since terminal residues in both plant and animal metabolism studies previously conducted had not been adequately characterized. Additional residue data were also requested in support of existing tolerances on RACs.

Conclusions (Concerning PP# 8F3655)

1. Details of the manufacturing process and formulation intended for use on almonds have been adequately described. The impurities are not expected to present any residue problems.
2. The Section B/label does not specify whether the application is to be made before or after the bloom stage. The residue data should reflect the proposed use. Two of the three field trials reflected post harvest or dormant uses (see also conclusion 5).
- 3a. DEB will consider the nature of the residue to be adequately understood for this petition request only, since the proposed tolerance is at limit of sensitivity of the analytical methodology, and assuming that the proposed tolerance level is found to be appropriate. The residues to be regulated in plants are the parent and the 3,5-dinitrobenzyl alcohol metabolite. If the proposed tolerance level is found to be inadequate, then additional metabolism data will be needed to support this use.
- 3b. The nature of the residue in animals is not considered to be adequately understood. Although almond hulls are a cattle feed item, the dietary contribution from this particular use is not expected to be significant, assuming that the proposed tolerance level on almond hulls is adequate. If this is the case, additional animal metabolism data will not be required to support this petition. If the proposed tolerance is not found to be adequate, then animal metabolism studies and feeding studies may be required to support this use.
- 4a. DEB concludes that adequate analytical methodology is available for enforcing the proposed tolerances on almonds and almond hulls. Note that additional metabolism studies may be required. If these studies indicate the presence of new metabolites, then additional methodology may be

necessary.

- 4b. Pendimethalin has been successfully recovered via the FDA multiresidue protocol 4. The petitioner should conduct additional pesticide analysis for the 3,5-dinitrobenzyl alcohol metabolite through the appropriate MRM testing.
5. The residue data submitted here are inadequate to support any proposed use. Additional field trials (at least six) should be conducted in California. The additional 6 trials should match the timing on the revised label. Some of the additional studies should be conducted using exaggerated application rates. If the additional data show that the proposed tolerances are too low, additional plant metabolism data may be required.
6. The dietary burden to cattle from this proposed use appears to be very low. If no finite residues are to be found in almond hulls, then nondetectable secondary residues are expected to occur in meat and milk. Note that additional residue data are necessary to support the proposed tolerance on almond hulls. There is a restriction against grazing and feeding livestock in treated areas. If the proposed tolerance is later found to be too low, feeding studies as well as a metabolism study on lactating ruminants may be needed. Almonds and almond hulls are not poultry feed items, so no secondary residues are expected to occur in poultry or eggs.
7. There are no Codex, Canadian or Mexican tolerances for pendimethalin on almonds or hulls. Therefore, no compatibility problems exist.

Concerning Reregistration Requirements:

- I. DEB disagrees with the registrant's conclusion that additional plant metabolism data are not required. Better characterization of extractable and unextractable residues in plants is needed. A few representative crops for which pendimethalin formulations are registered should be used.
- II. The registrant is advised to conduct the additional ruminant metabolism study as required in the registration standard. We are especially concerned with residue identification in milk, muscle, fat, kidney and liver.
- III. The Pendimethalin Registration Standard states the following:

Due to the fact that residues in seed crops may concentrate during processing to oil to the extent of 6X for soybeans

and as much as 25X for corn, there is a concern that combined residues of pendimethalin and CL 202.347 (3,5-dinitrobenzyl alcohol metabolite) in processed oil may exceed the established tolerance of 0.1 ppm for the individual raw agricultural commodity. Since additional metabolism studies are requested, the request for an additional processing study for soybeans will depend upon the results of the final residues of concern. If requested, this processing study will be translated to cottonseed, peanuts, corn, sunflower seed, and may also be translated to support the pending safflower seed tolerance.

The plan to submit a corn processing study instead of soybeans to satisfy the processing residue data requirement relative to the concentrations of pendimethalin in the oils of cottonseed, peanuts, soybeans, sunflower seed and safflower seed tolerance is agreeable with DEB. These data should be submitted after the plant metabolism studies are completed. Levels of all residues of concern should be included in the report.

- IV. The plan for submission of additional residue data for soybean foliage is appropriate.

Recommendations

DEB recommends against the establishment of the proposed tolerances on almonds and almond hulls for reasons given in conclusions 2, 4b and 5. Note that the adequacy of the plant and animal metabolism data (conclusions 3a and 3b) as well as the analytical methodology (conclusion 4a) and feeding studies (conclusion 6) is conditional. A favorable recommendation from DEB is contingent upon satisfactory resolution of these deficiencies (conclusions).

DEB recommends that the registrant proceed with the submission of data requirements for reregistration purposes as previously outlined. Plant and animal metabolism data are still required as well as all other requirements as outlined in the Residue Chemistry Chapter of the Registration Standard and addendum No. 1.

DETAILED CONSIDERATIONS

Manufacture and Formulation

The formulation proposed for use on almonds is Prowl herbicide (EPA Reg. No. 241-243-ZA). Prowl contains 42.3% technical grade pendimethalin (4 lb ai/gal). All inerts in the formulation are cleared under 40 CFR 180.1001.

Technical pendimethalin is 91-94% pure. The manufacturing process was reviewed in conjunction with PP# 5F1556 and as part of the Registration Standard. The impurities present, including the N-nitroso contaminant, are not expected to present any residue problems (see memos of E.T. Haeberer dated 8/20/84 and G. Makhijani dated 6/25/86).

Proposed Use

Prowl herbicide is to be applied for preemergence weed control in nonbearing and bearing almond trees in 20 or more gallon of water per acre using ground equipment. The recommended broadcast rate for short term control (4 months) is 2 qts Prowl/A (2 lb ai/A) and the rate for long term control (6-12 months) is 4-6 qts Prowl/A (4-6 lb ai/A). The spray is to be applied directly to the ground beneath the trees. There is a restriction against feeding forage and grazing livestock in treated fields.

The Section B/label does not specify whether the application is to be made before or after the bloom stage. The residue data should reflect the proposed use which needs to be clarified (see residue data section of this review).

Nature of the Residue

Plants

No new plant metabolism studies were submitted with this petition. Plant metabolism studies have previously been conducted on corn, cotton, dry beans, lima beans, peanuts, potatoes, beets, rice, snapbeans, soybeans, sugarcane and wheat and were reviewed in support of previous petitions and in preparing the registration standard. These studies indicate that pendimethalin is absorbed, translocated and metabolized in these plants.

In most of the existing plant metabolism studies, terminal residues were not characterized since the total radioactive residue levels were very low (<1.0 ppm). In the studies where sufficient radioactivity was present to allow for some characterization the only residues identified were the parent, the 3,5-dinitrobenzyl alcohol metabolite (CL 202,347), and to a

lesser extent and in only a few cases the 2,4-dinitrobenzyl alcohol metabolite. Application rates ranged from about 1.0 to 3.0 lb ai/A as soil, preplant, preemergence and post emergence applications.

DEB will consider the nature of the residue to be adequately understood for this petition request only, since the proposed tolerance is at limit of sensitivity of the analytical methodology, and assuming that the proposed tolerance level is found to be appropriate. The residues to be regulated in plants are the parent and the 3,5-dinitrobenzyl alcohol metabolite. If the proposed tolerance level is found to be inadequate, then additional metabolism data will be needed to support this use. See also the discussion under residue data that follows in this review.

Animals

No additional animal metabolism studies were submitted with this petition. Metabolism studies on goats, catfish, crayfish and rats have been reviewed in support of other petitions and in preparing the registration standard.

In the goat metabolism study (MRID No. 00067288) goats were fed radiolabeled pendimethalin at levels of 0.5, 1.5 and 20 ppm for 10 days. Total residues of ^{14}C -pendimethalin equivalents were monitored daily in milk, urine, feces and blood. The goats were slaughtered 2 hours after the last dose. The majority of the radioactivity ingested was excreted via the feces and urine with significant amounts present in the rumen and intestinal contents. Less than 0.1% of the dose was accounted for in tissues, milk and blood. Total ^{14}C pendimethalin equivalents in milk from the goat treated at 20 ppm were 0.01 ppm after the third day of treatment. Total ^{14}C pendimethalin equivalents were <0.01 ppm in leg and tenderloin muscle, brain, and back fat from all dosage levels. At the 20 ppm feeding level, total ^{14}C residues were 0.25 ppm in liver, 0.09 ppm in kidney, 0.01 ppm in heart and 0.03 ppm in omental fat. Residues in milk and tissues were not characterized.

The nature of the residue in animals is not considered to be adequately understood. Additional ruminant metabolism studies have been requested in support of other pending tolerances for pendimethalin and as a requirement for reregistration. Although almond hulls are a cattle feed item, the dietary contribution from this particular use is not expected to be significant (≤ 0.01 ppm), assuming that the proposed tolerance level on almond hulls is adequate (see the residue data discussion of this memo). If this is the case, additional animal metabolism data will not be required to support this petition. If the proposed tolerance is not found to be adequate, then animal metabolism studies and

feeding studies may be required to support this use. Regardless, animal metabolism data are needed to support the other pending pendimethalin tolerances and as indicated in the registration standard (see the discussion under other considerations in this review).

Analytical Methodology

Acceptable GC methods are available for determining residues of pendimethalin and its 3,5-dinitrobenzyl alcohol metabolite in plants and their processed commodities. These methods are located in PAM II. Methods I and III determine the parent compound and Methods II and IV determine the alcohol metabolite. Each method involves solvent extraction, cleanup by solvent partitioning and Florisil column chromatography. Residues of the 3,5-dinitrobenzyl alcohol metabolite are similarly extracted with the addition of a derivatization step (acetic anhydride and pyridine). Determination is by GC with an electron capture detector. The method sensitivity is about 0.05 ppm for parent and metabolite.

DEB concludes that adequate analytical methodology is available for enforcing the proposed tolerances on almonds and almond hulls. Additional metabolism studies may be required. If these studies indicate the presence of additional metabolites, then additional methodology may be necessary.

Pendimethalin has been successfully recovered via the FDA multiresidue protocol 4. The petitioner should conduct additional testing for the 3,5-dinitrobenzyl alcohol metabolite through the appropriate MRM testing.

Residue Data

Three field trials were conducted in the state of California (MRID# 40703401). Prowl herbicide was applied postemergence as a 10 ft banded treatment and as a postemergence broadcast spray at 4 to 6 lb ai/A to vegetation/soil using ground equipment. Fruit was harvested 130 to 265 days after treatment. Nuts and hulls were separated and kept frozen at -20 F for no more than 36 days before analysis.

The samples were analyzed for the parent and the 3,5-dinitrobenzyl alcohol metabolite using methodology that was essentially the same as the enforcement method. Validation data were submitted (MRID# 4070342). Recoveries of the parent compound from almond kernels ranged from 87 to 112% over a fortification range of 0.05 to 0.5 ppm. Recoveries from almond hulls ranged from 71 to 97% over the same fortification range. Recoveries of the 3,5-dinitrobenzyl alcohol metabolite from

almond kernels ranged from 72 to 118% over a fortification range of 0.05 to 0.5 ppm. Recoveries of the metabolite from almond hulls ranged from 72 to 118% over the same fortification range. Residue levels in all samples were reported to be ≤ 0.05 ppm. Control sample responses averaged <0.003 to <0.008 ppm. Sample chromatograms of controls, standards and residue samples were supplied. Storage stability data were also submitted which support freezer stability of pendimethalin on almonds at -20°C for up to 12 months.

DEB does not consider the residue data submitted here as adequate to support any proposed use. The field trial conducted in Lodi, CA is the only field trial where application was near the bloom stage. One field trial is not enough to support this tolerance level. The other two trials appear to represent post harvest or dormant treatments rather than treatment near bloom. Additional field trials (at least six) should be conducted in California. Some of the additional studies should be conducted using exaggerated application rates. If the additional data show that the proposed tolerances are too low, additional plant metabolism data may be required. The application timing on the proposed label should be consistent with the residue data.

Meat, Milk, Poultry and Eggs

Almond hulls may comprise up to 25% of beef and dairy cattle diet. The dietary burden to cattle from this proposed use appears to be very low (≤ 0.01 ppm). If no finite residues were found in almond hulls, then nondetectable secondary residues are expected to occur in meat and milk. There is a restriction against grazing and feeding livestock in treated areas. Note that additional residue data are necessary to support the proposed tolerance on almond hulls. If the proposed tolerance is later found to be too low, feeding studies as well as a metabolism study on lactating ruminants may be needed. Almonds and almond hulls are not poultry feed items, so no secondary residues are expected to occur in poultry or eggs.

Other Considerations

An International Residue Limit Status sheet is attached to this review. There are no Codex, Canadian or Mexican tolerances for pendimethalin on almonds or hulls. Therefore, no compatibility problems exist.

Additional Comments, re: Pendimethalin Reregistration Requirements

American Cyanamid has also submitted for comment a letter from William A. Steller of American Cyanamid Company dated February 4, 1987, concerning the requirements for reregistration of pendimethalin. American Cyanamid disagrees with several of the conclusions in the registration standard review pertaining to the residue and metabolism section of the Residue Chemistry Chapter. The petitioner proposes to modify the data requirements in the following ways:

1. No additional plant or animal metabolism studies will be submitted to support the current tolerances for PROWL herbicide.
2. American Cyanamid Company will submit additional data to allay minor concerns for the potential of pendimethalin-related residues to occur at higher levels in processed commodities than the current tolerance of 0.1 ppm.

Since corn grain has the lowest percent of oil of any of the RACs this commodity will be assayed by a newly developed more sensitive method to demonstrate that residues of pendimethalin after application at the label rate are so low in corn grain that if it all concentrated in the oil the residue would not exceed 0.1 ppm in corn oil.

3. American Cyanamid Company will submit additional residue data for soybean foliage to demonstrate that current tolerance for soybean foliage is adequate.

DEB disagrees with the registrant's conclusion that additional plant metabolism data are not required. These issues were addressed in the addendum to the Residue Chemistry Chapter issued on December 3, 1985, and our conclusions still stand. Better characterization of extractable and unextractable residues in plants is needed. A few representative crops for which pendimethalin formulations are registered should be used. A thorough examination of the residue patterns in plants could also aid in the establishment of future tolerances, such as the proposed use on almonds. We note that proposed use on almonds is for a maximum of 6 lb ai/A, which is higher than the current registered uses.

The registrant is also advised to conduct the additional ruminant metabolism study as required in the registration standard. Here again characterization of residues was not adequate in the previous study. We are especially concerned with residue identification in milk, muscle, fat, kidney and liver. We note also that ruminant animal metabolism data are required in support of pending tolerance requests.

The plan to submit a corn processing study instead of soybeans to

satisfy the processing residue data requirements relative to the concentration of pendimethalin in the oils of cottonseed, peanuts, soybeans, sunflower seed and safflower seed is agreeable with DEB (see footnote 14, Residue Chemistry , Guidance for Reregistration). These data should be submitted after the plant metabolism study is complete. Levels of all residues of concern are included in the report.

The plans for submission of additional residue data for soybean foliage is appropriate (see footnotes 15 and 16, Residue Chemistry, Guidance for Reregistration).

Attachment: International Residue Limit Status Sheet

TS769C:DEB:SHW:shw-12/13/88:CM2:RM810:X1439

cc: RF, Circ, Willett, Reg. Std File, PP#8F3655, PMSD (Eldredge)

RDI: JHOnley, 12/21/88; RALoranger, 12/21/88

INTERNATIONAL RESIDUE LIMIT STATUS1. ^{over} 12/8/88CHEMICAL Pendimethalin

CODEX NO. _____

CODEx STATUS:☒ No Codex Proposal
Step 6 or above

Residue(if Step 8): _____

| <u>Crop(s)</u> | <u>Limit</u> <u>(mg/kg)</u> |
|----------------|--------------------------------|
|----------------|--------------------------------|

PROPOSED U.S. TOLERANCES:Petition No. 8F3655RCB Reviewer S.H. Willett 12-8-88Residue: parent - N-(1-4-[(1-ethylpropyl)-3,4-dimethyl-
2,6-dinitrobenzenamine + metabolite]

| <u>Crop(s)</u> | <u>Limit</u> <u>(mg/kg)</u> |
|----------------|--------------------------------|
|----------------|--------------------------------|

| | |
|--------------|------|
| Almonds | 0.05 |
| Almond hulls | 0.05 |

CANADIAN LIMITS:☒ No Canadian limit

Residue: _____

| <u>Crop(s)</u> | <u>Limit</u> <u>(mg/kg)</u> |
|----------------|--------------------------------|
|----------------|--------------------------------|

MEXICAN LIMITS:☒ No Mexican limit

Residue: _____

| <u>Crop(s)</u> | <u>Limit</u> <u>(mg/kg)</u> |
|----------------|--------------------------------|
|----------------|--------------------------------|

NOTES:* 4-[(1-ethylpropyl)amino]-2-methyl-
3,5-dinitrobenzyl alcohol