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OFFICE CO

PP#6F1741. Pendimethalin in peanuts
Amendment of 4/29/80.

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and

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THRU: **Richard D. Schmitt, Acting Chief**
Residue Chemistry Branch (TS-769)

The amendment contains a peanut hull metabolism study, peanut residue data, and a tolerance proposal for residues of pendimethalin and its metabolites in or on peanut hulls at 0.25 ppm.

The amendment is in response to our memo of 5/25/76 (A. Smith) which raised questions on the nature of residues in the hull.

Conclusions

1. The nature of the residue in peanut hulls is adequately delineated. The significant components of hull residues are the parent compound pendimethialan (CL92,553) and its metabolites CL202,347; CL113,068; and, bound and free CL113,072. We query TOX on the toxicological significance of other metabolic components containing the pendimethalin moiety and which are present in trace quantities.

2. Adequate methods are available for the determination of residues of the parent pendimethalin and the metabolite CL202,347. However, validated analytical methods are needed for the metabolites CL113,068 and bound and free forms or CL113,072. Method trials may need to be conducted for these metabolites when the methodology is submitted.

3. The residue data are inadequate and do not reflect the significant components of the residue as noted in Conclusion 1. Residue data on hulls which have been analyzed for the metabolites CL113,068 and CL113,072 (bound and free). Additionally, the proposed tolerance should be revised to reflect the significant components of the hull residue.

4a. The absence of adequate residue data on the peanut hulls precludes valid conclusions on the transfer of pendimethalin residues to meat, and milk of livestock as warranted under §180.6(a). Livestock feeding studies may be required for any metabolites which are present in peanut hulls.

b. Since peanut hulls are not a poultry feed and since no detectable residues are expected in meat and soapstock, there will be no problem of secondary residues in poultry tissue and eggs.

Recommendation

We recommend against the proposed peanut tolerances. A favorable recommendation is contingent upon resolution of the deficiencies noted in Conclusions 2 and 3.

Peanut Hull Metabolism Study

Studies were performed in which peanuts were grown in soil treated with radiolabelled (C^{14}, C^{13}) pendimethalin. The peanuts were grown in the greenhouse or in the field. Pendimethalin was applied at a rate of 3.75 pounds per acre. The peanuts were harvested at maturity, and the hulls were analyzed for residues of pendimethalin and its metabolites.

The total radioactivity in the hull averaged 5.1 ppm. About 3.8 ppm (or, 75%) of the total activity in the hull was extracted. Of the extracted radioactivity, only 16% (0.68 ppm) was pendimethalin-related components. These compounds are identified as: the parent compound pendimethalin (CL92,553), and its metabolites; CL202,347, CL217,146, CL99,200, CL113,066, CL113,067, CL113,068, CL113,071, and CL113,072. The metabolites CL113,071, CL113,072, and CL217,146 are probably present in conjugated forms, and such components are freed through acid hydrolysis. (See the chart of chemical names for compound identification.)

About 40% of the extracted activity was associated with the aqueous phase, and the remainder was uncharacterized very polar material. This very polar activity was shown by two dimensional thin layer chromatography (TLC) to consist of more than 20 components. The activity in the aqueous phase consisted of at least 10 components in trace quantities. None of the components could be related to any of 55 compounds synthesized to contain the pendimethalin moiety.

The unidentified readioactivity is believed to be naturally-occurring plant components containing reincorporated radioactivity.

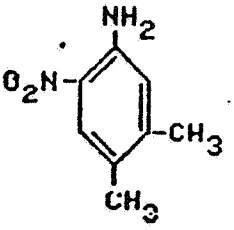
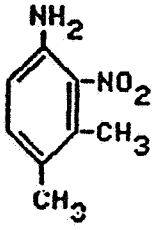
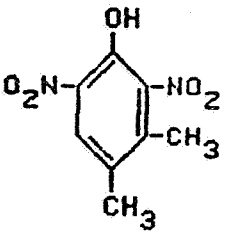
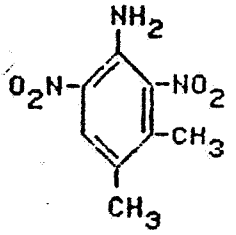
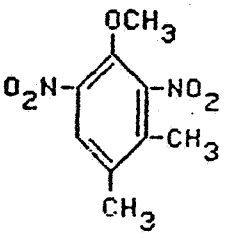
The petitioner contends that the significant components of the residue (based on quantities present) are: pendimethalin (CL92,553) and its metabolites CL202,347; CL217,146; and CL113,072. However, we find that the significant components are pendimethalin (CL92,553) and its metabolites: CL202,347; CL113,068; CL113,072. The metabolite CL217,146, as well as the reaminder not named here, were present at levels (<0.05 ppm) which are not likely to be detected by the residue method. The four components that we have listed represent about 80% of the identified components. Nevertheless, we defer to Toxicology as to the toxicological significance of the remaining components not listed by RCB, but which contain the pendimethalin moiety.

The peanut hulls were extracted by acid hydrolysis with dilute hydrochloric acid. Pendimethalin residues were characterized and determined using microchemical tests (acetylation with acetic anhydride and triethylamine; methylation with diazomethane), autoradiographic techniques with thin layer chromatography (TLC), high performance liquid "chromatography (HPLC)", and mass spectrometry.

The petitioner has not identified the major portion of the residue, but has demonstrated that the unidentified components are not likely to be pendimethalin-related compounds.

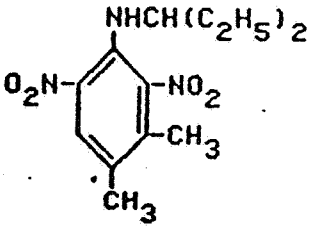
We conclude that the nature of the residue in peanut hulls is adequately delineated. The significant components of the residue are pendimethalin and its metabolites CL202,347; CL113,068; CL113,072.

TABLE OF COMPOUNDS CITED IN THIS REPORT

CL Number	Chemical Name	Structure
CL 16,528	3,4-Xylidine, 6-nitro-	
CL 16,529	3,5-Xylidine, 2-nitro-	
CL 18,231	o-Xylene, 4-hydroxy-3-5-dinitro-	
CL 84,846	3,4-Xylidine, 2,6-dinitro-	
CL 92,367	o-Xylene, 4-methoxy-3,5-dinitro-	

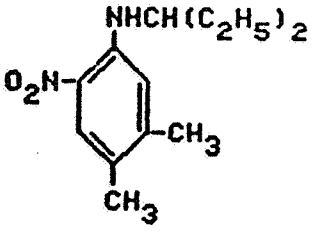
CL 92,553

2,6-Dinitrobenzenamine, N-(1-ethylpropyl)-3,4-dimethyl-



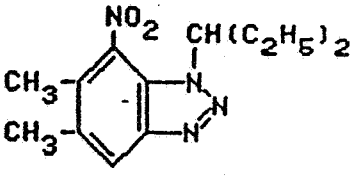
CL 94,049

3,4-Xylidine, N-(1-ethylpropyl)-6-nitro-



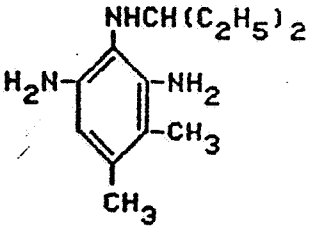
CL 94,163X

1H-Benzotriazole, 1-(1-ethylpropyl)-5,6-dimethyl-7-nitro-



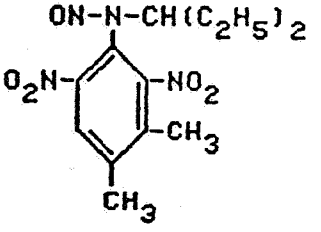
CL 94,211

o-Xylene-3,4,5-triamine, N^4-(1-ethylpropyl)-



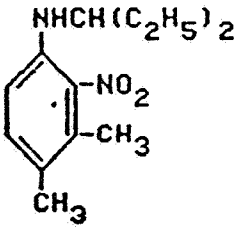
CL 94,269

3,4-Xylidine, N-(1-ethylpropyl)-2,6-dinitro-N-nitroso



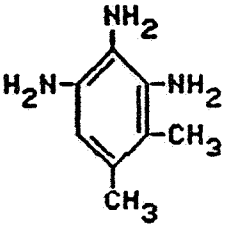
CL 94,492

3,4-Xylidine,
N-(1-ethylpropyl)-
2-nitro-



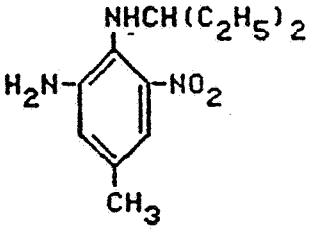
CL 94,707

3,4-Xylidine,
2,6-diamino-



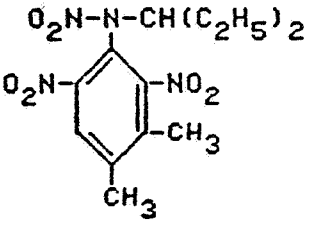
CL 94,756

o-Xylene-4,5-diamine,
N^4-(1-ethylpropyl)-
3-nitro-



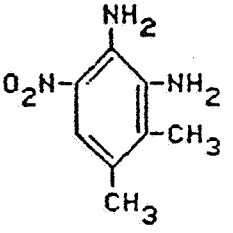
CL 94,801

3,4-Xylidine,
N-(1-ethylpropyl)-
N,2,6-trinitro-

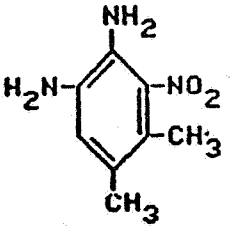


CL 94,992

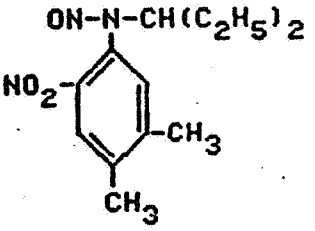
o-Xylene-3,4-diamine,
5-nitro-



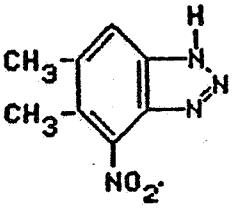
CL 94,994 — o-Xylene-4,5-diamine, 3-nitro-



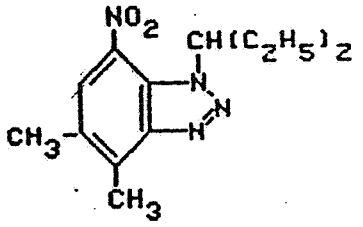
CL 99,157 — 3,4-Xylidine, N-(1-ethylpropyl)-6-nitro-N-nitroso-



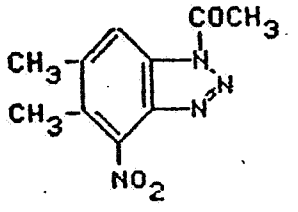
CL 99,336 — 1H-Benzotriazole, 5,6-dimethyl-4-nitro-

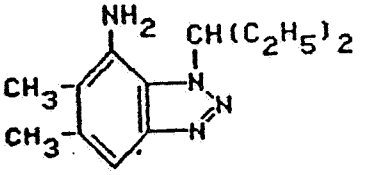
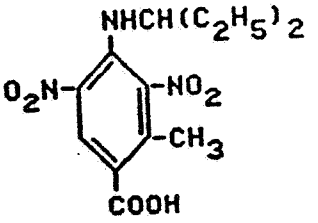
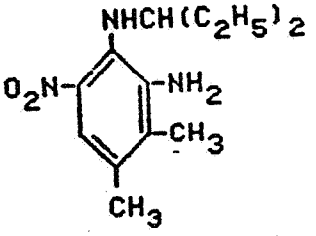
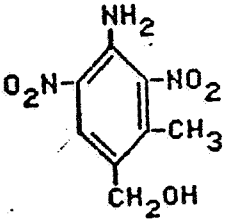
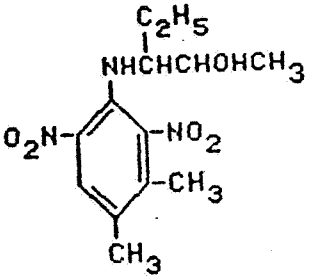


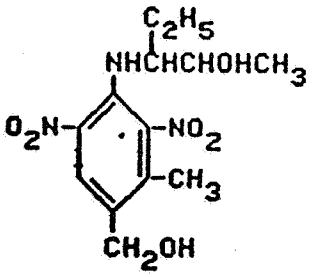
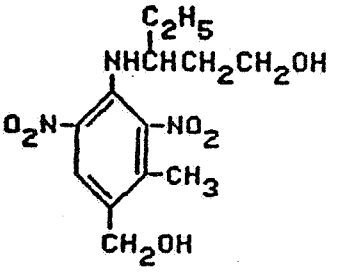
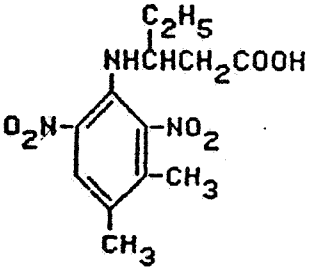
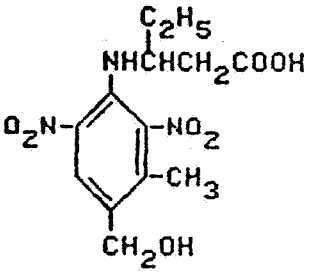
CL 99,474 — 1H-Benzotriazole, 1-(1-ethylpropyl)-4,5-dimethyl-7-nitro-

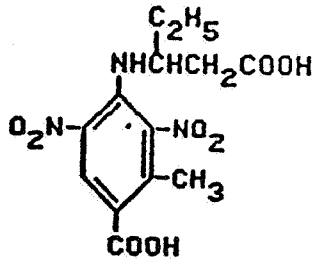
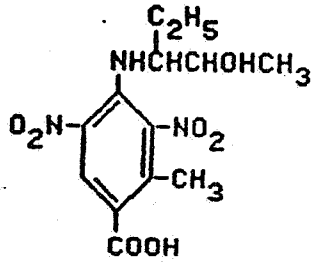
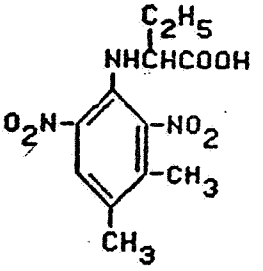
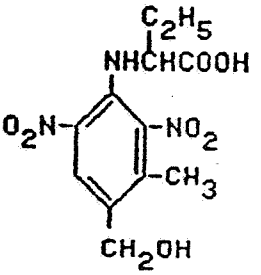


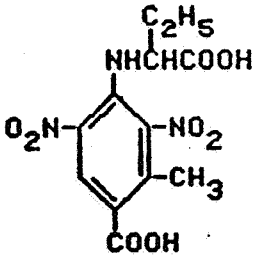
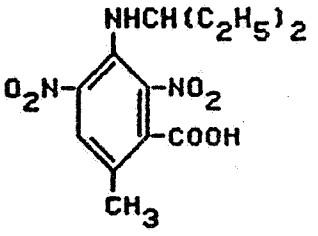
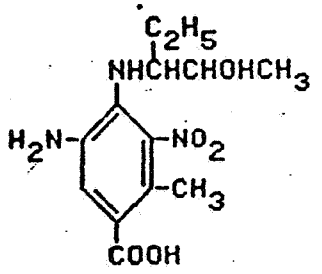
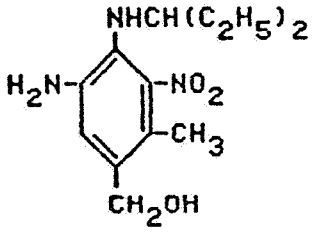
CL 99,530 — 1H-Benzotriazole, 1-acetyl-5,6-dimethyl-4-nitro-

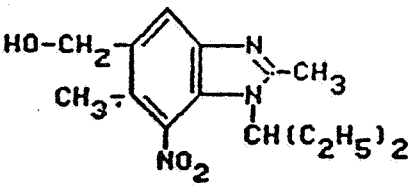
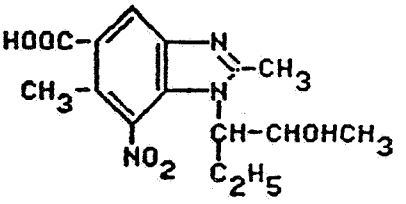
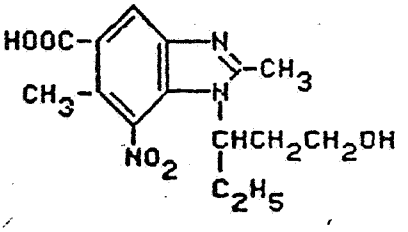
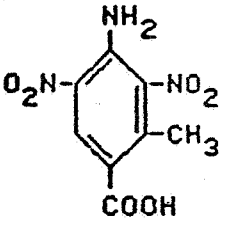


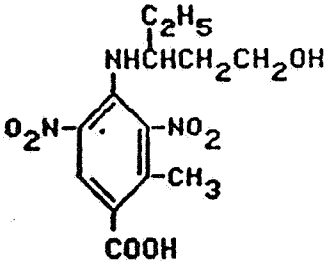
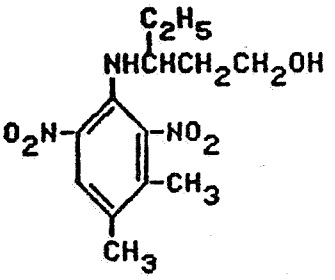
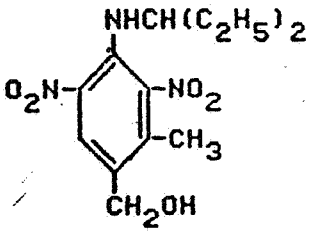
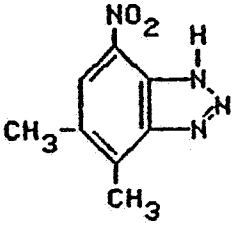
CL 99,863	1H-Benzotriazole, 7-amino-1-(1-ethylpropyl)-5,6-dimethyl-	
CL 99,900	o-Toluic acid, 4-[(1-ethylpropyl)amino]-3,5-dinitro-	
CL 105,908	o-Xylene-3,4-diamine, N^4-(1-ethylpropyl)-5-nitro-	
CL 113,065	Benzyl alcohol, 4-amino-2-methyl-3,5-dinitro-	
CL 113,066	2-Pentanol, 3-(2,6-dinitro-3,4-xylidino)-	

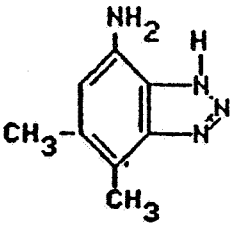
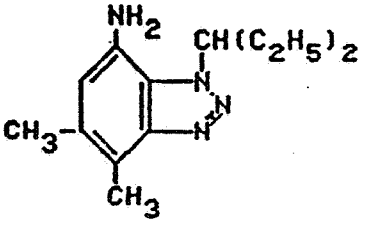
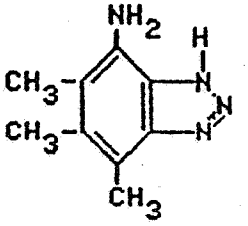
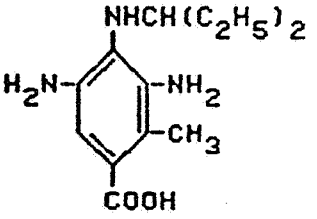
CL Number	Chemical Name	Structure
CL 113,067	Benzyl alcohol, 4-[(1-ethyl-2-hydroxypropyl) amino]-2-methyl- 3,5-dinitro-	
CL 113,068	Benzyl alcohol, 4-[(1-ethyl-3-hydroxypropyl) amino]-2-methyl- 3,5-dinitro-	
CL 113,069	Valeric acid, 3-(2,6-dinitro- 3,4-xylidino)-	
CL 113,070	Valeric acid, 3-[α^4-hydroxy-2,6- dinitro-3,4-xylidino)-	

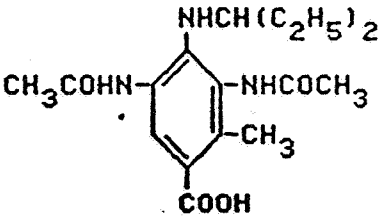
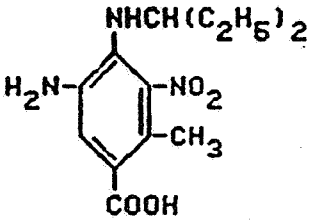
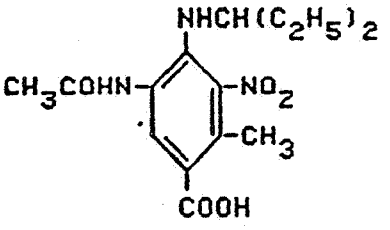
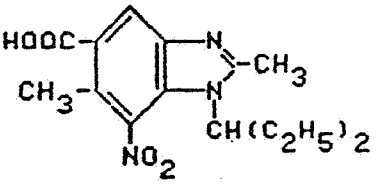
CL Number	Chemical Name	Structure
CL 113,071	o-Toluic acid, 4-{[1-(carboxymethyl)propyl]amino}-3,5-dinitro-	
CL 113,072	o-Toluic acid, 4-[(1-ethyl-2-hydroxypropyl)amino]-3,5-dinitro-	
CL 113,112	Butyric acid, 2-(2,6-dinitro-3,4-xylidino)-	
CL 113,113	Butyric acid, 2-(α^4-hydroxy-2,6-dinitro-3,4-xylidino)-	

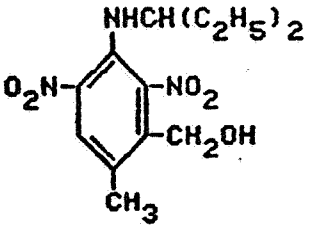
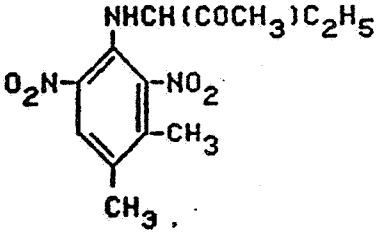
CL Number	Chemical Name	Structure
CL 113,114	o-Toluic acid, 4-[(carboxy-propyl)amino]-3,5-dinitro-	
CL 113,321	o-Toluic acid, 5-[(1-ethylpropyl)amino]-4,6-dinitro-	
CL 113,525	o-Toluic acid, 5-amino-4-[(1-ethyl-2-hydroxypropyl)-amino]-3-nitro-	
CL 113,527	Benzyl alcohol, 5-amino-4-[(1-ethylpropyl)amino]-2-methyl-3-nitro-	

CL Number	Chemical Name	Structure
CL 113,529	5-Benzimidazolemethanol, 1-(1-ethylpropyl)-2,6-dimethyl-7-nitro-	
CL 113,530	5-Benzimidazolecarboxylic acid,1-(1-ethyl-2-hydroxypropyl)-2,6-dimethyl-7-nitro-	
CL 113,531	5-Benzimidazolecarboxylic acid,1-(1-ethyl-3-hydroxypropyl)-2,6-dimethyl-7-nitro-	
CL 202,078	o-Toluic acid, 4-amino-3,5-dinitro-	

CL Number	Chemical Name	Structure
CL 202,345	o-Toluic acid, 4-[(1-ethyl-3-hydroxy-propyl)amino]-3,5-dinitro-	
CL 202,346	1-Pentanol, 3-(2,6-dinitro-3,4-xylidino)-	
CL 202,347	Benzyl alcohol, 4-[(1-ethylpropyl)-amino]-2-methyl-3,5-dinitro-	
CL 202,348	1H-Benzotriazole, 4,5-dimethyl-7-nitro-	

CL Number	Chemical Name	Structure
CL 202,392	1H-Benzotriazole, 7-amino-4,5-dimethyl-	
CL 202,393	1H-Benzotriazole, 7-amino-1-(1-ethylpropyl)-4,5-dimethyl-	
CL 202,394X	1H-Benzotriazole, 7-amino-5,6-dimethyl-	
CL 206,920	o-Toluic acid, 3,5-diamino-4[(1-ethylpropyl)amino]-	

CL Number	Chemical Name	Structure
CL 206,921	o-Toluic acid, 3,5-diacetamido-4-[(1-ethylpropyl)amino]-	
CL 206,922	o-Toluic acid, 5-amino-4-[(1-ethylpropyl)amino]-3-nitro-	
CL 206,923	o-Toluic acid, 5-acetamido-4-[(1-ethylpropyl) amino]-3-nitro-	
CL 206,925	5-Benzimidazolecarboxylic acid, 1-(1-ethylpropyl)-2,6-dimethyl-7-nitro-	

CL Number	Chemical Number	Structure
CL 217,146	Benzyl alcohol, 3-[(1-ethylpropyl) amino]-6-methyl-2,4-dinitro-	
CL 233,752	2-Pentanone, 3-(2,6-dinitro-3,4-xylidino)-	

Analytical Methods

The petitioner attempted to develop a residue method for the determination of free and conjugated residues of the metabolite CL113,072. However, difficulties were encountered. Untreated peanut hulls had 0.1 ppm CL113,072-equivalent residues. Moreover, untreated (control) peanut hulls yielded a recovery of only 60% at a fortification level of 1.0 ppm.

The difficulty in validating the method at sufficiently low levels and the showing of a total residue level of only 0.15 ppm for CL113,072 convinced they petitioner that a residue method for the metabolite was not necessary. Therefore, work on method development for CL113,072 was not continued.

Residue methods were developed for the parent pendimethalin (C192,553) and its metabolites CL202,347 and CL217,146. These components are reported to represent about 72% of the identified components in the metabolism study.

Pendimethalin (CL92,553)

A ground hull sample (also foliage or hay) is extracted with aqueous acidic methanol and filtered. An aliquot of the filtrate is extracted with hexane (the remaining filtrate is saved for analysis for the metabolites CL202,347 and CL217,146).

The hexane phase is extracted with acetonitrile. The acetonitrile which contains CL92,553 is evaporated to dryness.

The residue is taken up with hexane and cleaned up on a Florisil column. CL92,553 is eluted from the column using an hexane/benzene solvent mixture. The solvents are evaporated, and the residue is taken up with benzene. The CL92,553 is determined by gas-liquid chromatagraphy using an electron capture detector (ECGC).

The method is reported to have a sensitivity of 0.05 ppm CL92,553. Untreated (control) peanut hull samples had <0.05 ppm CL92,553-equivalent residues. Control hull samples were fortified with CL92,553 at levels of 0.05-1.0 ppm. Recoveries were 76-130%.

Metabolites (CL202,347 and CL217,145)

The initial extraction and cleanup is the same as in the above procedure. A ground hull sample is extracted with aqueous acidic methanol and filtered. An aliquot of the filtrate is extracted with hexane.

The hexane phase is extracted with acetonitrile which is evaporated to dryness.

The residue is treated with acetic annydride which forms acetylated derivatives with the metabolites. The derivatives are extracted into hexane, and the solution is evaporated to dryness.

The residue is is taken up in hexane and cleanup on a florisil column. The metabolites are eluted with benzene. The matabolites are determined by ECGC as separate components.

The validated sensitivity of the method is 0.05 ppm for CL202,347 and 0.1 ppm for CL217,146. Control hull samples had 0.004-0.008 ppm CL202,347-equivalent residues. Control samples were fortified with CL202,347 at levels of 0.05-1.0 ppm. Recoveries were 71-98%. Control samples, fortified with CL217,146 at levels of 0.1-2.0 ppm, yielded recoveries of 82-108%.

The methods appear to be adequate for the determination of residues of pendimethalin and its metabolites (CL202,347 and CL217,146) in peanut hulls.

The methods are essentially the same as those submitted for the determination of pendimethalin and the metabolite CL202,347 in peanuts and peanut foliage and hay. The methods were successfully tested on cottonseed at levels of 0.05 ppm and 0.1 ppm (PP#5F1556) with these 2 components.

We have indicated (see Metabolism Study) that the significant components of the residue in hulls is expected to be the parent pendimethalin (CL92,553) and its metabolites CL202,347, CL113,068, and CL113,072 (bound and free forms). As a result methods which determine these components should be submitted. The methods should be validated for these components at the levels that they are likely to occur. Method trials may need to be conducted on these additional components of the residue.

Residue Data

Samples of peanut hulls were obtained from crops in Alabama, North Carolina, and New Mexico. The crops were grown in soil which had received single preplant treatments at rates of 1.0-2.0 lb act/A (up thru 2X maximum proposed rate); a preplant application of 0.75 lb act/A plus a 0.75 lb act/A application at cracking (10 days later); and, a preplant application at 1.0 lb act/A plus a postemergence application at 1.0 lb act/A (20 days later).

Combined residues of pendimethalin and its 2 metabolites (CL202,347 and CL217,146) were <0.25 ppm from all treatments. The crops were harvested at intervals of 140-192 days after the last treatment. (Only single preplant applications are proposed.)

The residue data do not reflect the significant components of the residue in the peanut hulls. We consider the significant components of the residue to be the parent compound (CL92,553) and its metabolites CL202,347, CL113,068 and CL113,072. The residue data for CL92,553 and the metabolite CL202,347 are acceptable. The petitioner should submit data on hulls which have been analyzed for residues of CL113,068 and CL113,072 (free and bound).

Meat, Milk and Eggs

The absence of adequate residue data on the peanut hulls precludes a valid conclusion on the transfer of pendimethalin residues to meat, milk of livestock as warranted under §180.6(a).

Since peanut hulls are not a feed item and since no detectable residues are expected in meal and soapstock, there will be no problem of secondary residues in poultry tissue and eggs.

TS-769:RCB:Smith:gs:X77324:CM#2:RM810:9/22/80
cc:RF, Circ., Smith, Watts, FDA, TOX, EEB, EFB, PP#6F1741
RDI:R.S. Quick:9/18/80:R.U. Schmitt:9/19/80