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

NOV 8 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP #8F3663. (DEB # 4297) DPX-M6316 (Pinnacle™) on Soybeans. Evaluation of the Analytical Method and the Residue Data. MRID Nos. 407378-01

FROM: Cynthia Deyrup, Ph.D., Chemist
Tolerance Petition Section 2
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

THRU: Charles L. Trichilo, Ph.D., Chief
Dietary Exposure Branch
Health Effects Division (TS-769)

TO: Robert Taylor, Product Manager No. 15
Registration Division (TS-767)

and

Toxicology Branch
Hazard Evaluation Division (TS-769)

Pinnacle™ or DPX-M6316 [methyl 3-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]-sulfonyl]-2-thiophenecarboxylate] is a herbicide for which E.I. du Pont de Nemours and Company (Inc.) is proposing a permanent tolerance of 0.10 ppm on soybeans.

Permanent tolerances for residues of DPX-M6316 have been established in/on wheat and barley grain at 0.05 ppm and in/on wheat and barley straw at 0.10 ppm under 40 CFR 180.439.

Conclusions

1a. The product chemistry of DPX-M6316 was discussed in DEB's memos of 2/12/87, 12/24/87, 4/1/88, and 5/3/88 in conjunction with PP #6F3431 (memos of C. Deyrup).

DEB concluded that the petitioner would need to submit

analyses determining the levels of the impurities designated Y and Z in the technical, once commercial production has begun. In its 12/24/87 review, DEB also stated that if the submitted analyses of technical DPX-M6316 were of material produced with Semiworks equipment, analyses of batches of technical material would also be needed after commercial production had begun.

Therefore, analyses of DPX-M6316, reflecting determinations of the impurities Y and Z, are now required, if DPX-M6316 is in commercial production.

1b. If the batch analyses of Pinnacle™, submitted with PP #8G3602, are of material produced with Semiworks equipment, additional analyses of batches of Pinnacle™ will be required after commercial production has begun.

2. DEB concludes that the nature of the residue is adequately understood. The residue of concern is the parent, DPX-M6316.

3a. DEB concludes that the nature of the residue in ruminants is adequately understood.

3b. The maximum dietary exposure for poultry would be 0.06 ppm in poultry consuming barley and soybeans, based on the limit of determination for these commodities (0.50 x 0.02 + 0.50 x 0.05). Up to now, no detectable residues have been found on poultry feed items, and poultry metabolism studies are not needed at this time. If the petitioner should propose a use which results in the occurrence of residues of concern in poultry feed items, poultry metabolism studies would be needed.

4. The petitioner will need to submit standard curves to demonstrate the linearity of the detector response at the levels investigated.

5. DEB concludes that the storage stability data adequately support the residue data.

6a. No standard curves have been submitted so that DEB could validate the determination of the analyte. Therefore at this time DEB can make no judgment on the adequacy of the residue data.

6b. DEB would not expect residues of DPX-M6316 in the oil to exceed the proposed tolerance of 0.1 ppm, <u>provided that the requested standard curves support the methodology used to generate the residue data.</u>

7. The proposed use would fall under 180.6(a)(3). There is no reasonable expectation of finite residues in meat, milk, poultry, and eggs.

8. Neither Codex, Mexico, nor Canada has established tolerances for residues of DPX-M6316 on soybeans. There will be no compatibility problem.

Recommendations

DEB could recommend for establishing the proposed tolerance of 0.1 ppm DPX-M6316 on soybeans after the deficiencies cited in Conclusions 1a, 4, 6a, and 6b have been resolved. The petitioner should be made aware of Conclusion 1b.

Note: The format of PP #8F3663 was clear, concise, and easy to follow. The descriptions of the metabolism studies were especially well organized; the raw data (in dpm) and sample calculations led directly to the contribution each component made to the total radioactive residue.

Detailed Considerations

Manufacturing and Formulation

The product chemistry of DPX-M6316 was discussed in DEB's memos of 2/12/87, 12/24/87, 4/1/88, and 5/3/88 in conjunction with PP #6F3431 (memos of C. Deyrup).

DEB concluded that the petitioner would need to submit analyses determining the levels of the impurities designated Y and Z in the technical, once commercial production has begun. In its 12/24/87 review, DEB also stated that if the submitted analyses of technical DPX-M6316 were of material produced with Semiworks equipment, analyses of batches of technical material would also be needed after commercial production had begun. Therefore, analyses of DPX-M6316, reflecting determinations of the impurities Y and Z, are required, if DPX-M6316 is in commercial production.

The formulation to be used on soybeans is Pinnacle, a 25% dry flowable formulation; the inerts in this formulation have been cleared for use on crops under 40 CFR 80.1001(c) or (d). If the batch analyses of Pinnacle™, submitted with PP #8G3602, are of material produced with Semiworks equipment, additional analyses of batches of Pinnacle™ will be required after commercial production has begun.

Proposed Use

Soybeans are to be treated with Pinnacle at the rate of 0.0625 oz ai/A. Soybeans may be treated after the first trifoliate leaf has fully expanded up to 60 days before harvest. The herbicide may be applied by ground equipment (in a minimum of 10 gal/A) or aerially (in a minimum of 5 gal/A). Applications of Pinnacle must include am EPA-approved surfactant at rates of 0.125% v/v. The addition of liquid nitrogen fertilizer at the rate of 1 gal/A is required for

the control of certain species.

There is a restriction against allowing livestock to graze or forage the treated crop; hay or straw from treated areas may not be fed to livestock.

Nature of the Residue

Wheat metabolism studies had been submitted with PP #6F3431 and have been discussed in detail in DEB's memo of 12/24/87 (memo of C. Deyrup). Wheat was treated at the 5-leaf stage with either [thiophene-^{14}C] DPX-M6316 or [triazine-^{14}C] DPX-M6316. Radioactive residues in grain were reported to be less than 0.04 ppm for both studies. Studies aimed at identifying metabolites were therefore carried out using straw, which contained higher levels of activity. The following compounds were identified in wheat straw.

Compound*	^{14}C Triazine % Total Radioactive Residue	^{14}C Thiophene % Total Radioactive Residue
DPX-M6316	8.9	4.6
DPX-M6316 Acid	4.6	4.2
O-Demethyl DPX-M6316	0.9	0
Triazine Urea	5.7	-
Triazine Amine	3.3	-
O-Demethyl Triazine Amine	4.6	-
2-Ester-3-Sulfonamide	-	1.3
2-Acid-3-Sulfonamide	-	12.3

* Structures are given in Attachment 2

Including the activity found in cellulose and in sugars, about 35% of the total radioactive residue (TRR) was identified in the ^{14}C thiophene study, and about 45% was identified in the ^{14}C triazine study.

Soybean metabolism studies were submitted with PP #8G3602. These studies were reviewed in detail in DEB's memo of 5/18/88 (memo of R. Loranger). Plants at the first to third trifoliate stage were treated at rates of 16 g/ha (3.65 X rate) or 8 g/ha (1.82 X rate) with ^{14}C thiophene DPX-M6316 or ^{14}C triazine DPX-M6316. The lower dose also contained 0.25% surfactant. The following metabolic profiles emerged from these studies. The data reflect analyses of the whole plants 30 days after treatment. Mature soybeans were harvested 100 days after treatment; the maximum level of activity in the beans was 1.6 ppb.

Compound*	% Total Radioactive Residue (PPM)			
	^{14}C Triazine		^{14}C Thiophene	
	3.65 X rate No Surfactant	1.82 X rate Surfactant	3.65 X rate No Surfactant	1.82 X rate Surfactant
DPX-M6316	44 (0.030)	10 (0.018)	66 (0.061)	20 (0.026)
DPX-M6316 Acid	7 (0.005)	28 (0.050)	5 (0.005)	35 (0.045)
Triazine Amine	9 (0.006)	15 (0.027)	-	-
Amino methyltriazinol	9 (0.006)	13 (0.024)	-	-
2-Ester-3-Sulfonamide	-	-	4 (0.004)	7 (0.009)
2-Acid-3-Sulfonamide	-	-	4 (0.004)	5 (0.007)
Thiophene sulfonimide	-	-	-	5 (0.007)
%TRR Identified	69 (0.047)	66 (0.119)	79 (0.074)	72 (0.094)

* Structures are given in Attachment 2

The 0-demethyl triazine amine was not found in the soybean study, but three additional compounds were detected. These compounds are closely related to compounds which had been identified in the wheat studies. Amino methyltriazinol results from demethylation of the triazine amine, the thiophene sulfonimide arises from ring closure of the sulfonamide, and the 2-acid-3-sulfonic acid comes from hydrolysis of the corresponding sulfonamide.

The most striking aspect of the soybean study was the finding that the presence of a surfactant markedly affects the metabolic profile. In the absence of a surfactant, the parent is the major constituent, but in the presence of a surfactant, hydrolysis products predominate. Residue levels also appear to be higher when a surfactant is used.

DEB concludes that the nature of the residue is adequately understood. The residue of concern is the parent, DPX-M6316.

Animal Metabolism

The petitioner submitted a goat metabolism study in conjunction with PP #6F3431. Lactating goats were fed ^{14}C triazine DPX-M6316 or ^{14}C thiophene DPX-M6316 at a rate equivalent to 28 ppm in the diet. Including the proposed use on soybeans and the established use on wheat and barley, this rate would be equivalent to a 509 X rate in the unlikely event that the goats' total diet consisted of treated barley (80%), wheat straw (10%), and soybeans (10%).

The levels of activity in tissues and milk are shown below.

Matrix	PPM DPX-M6316 Equivalents Triazine goat	Thiophene goat
Fat	ND	ND
Heart	ND	ND
Kidney	0.16	0.10
Liver	0.04	0.05
Muscle	0.03	ND
Milk	0.12-0.15	0.08-0.16

The petitioner identified 56.5% and 60% of the TRR in the triazine goat kidney and thiophene goat kidney, respectively. The following compounds were identified in kidney:

Thiophene sulfonimide
Triazine amine
DPX-M6316

The petitioner identified up to 90% of the TRR in triazine goat milk and up to 88% in thiophene goat milk. The following compounds were identified in milk:

DPX-M6316
DPX-M6316 acid
0-Demethyl DPX-M6316
Thiophene sulfonimide
0-Demethyl triazine amine
Triazine amine
2-Acid-3-sulfonamide

The structures for the metabolites are shown in Attachment 2.

The metabolites found in plants are also found in goats or are closely related to the goat metabolites.

DEB concludes that the nature of the residue in ruminants is adequately understood.

The maximum dietary exposure for poultry would be 0.06 ppm in poultry consuming barley and soybeans, based on the limit of determination for these commodities (0.50 x 0.02 + 0.50 x 0.05). Up to now, no detectable residues have been found on poultry feed items. Therefore poultry metabolism studies are not needed at this time. If the petitioner should propose a use which results in the occurrence of residues of concern in poultry feed items, poultry metabolism studies would be needed.

Analytical Methodology

The method described below is very similar to Method AMR-948-87, Revision 2, which was submitted with PP #6F3431. By the use of radiovalidation, this method has been shown capable of determining DPX-M6316 in weathered samples.

The analytical procedure used is Method AMR-973-87, which was submitted with PP #8G3602. The soybeans are soaked in 0.05M

sodium bicarbonate for at least two hours, the pH is adjusted to pH 3.5, methylene chloride is added, and the mixture is extracted with a Tissumizer. After centrifugation, the supernatant is filtered into a separatory funnel, and the methylene chloride extraction is repeated. The methylene chloride layer is passed through an Adsorbosil® silica solid phase column, which is then rinsed with CH_2Cl_2; the sample elutes from the column with acetonitrile. After removal of the solvent, the residue is dissolved in 3:1 hexane/isopropanol, and levels of DPX-M6316 are determined by normal phase HPLC with photoconductivity detection.

The mobile phase is n-hexane:methanol:isopropanol:acetic acid: water (750:125:125:0.9:0.1). During the course of the HPLC run, standards were interspersed with the samples so that appropriate level standards bracketed the samples.

The major difference between the method described above and Method AMR-948-87, Revision 2, is in the use of a solid phase silica column in the clean-up procedure. Method AMR-948-87 had relied upon liquid-liquid partitioning for clean-up.

The following recoveries from soybeans were reported.

	Spike level	% Recovery
PP #8G3602	0.05 ppm	80-124
	0.10 ppm	82
	0.25 ppm	132-140
PP #8F3663	0.05	84-100
	0.10	72
	0.25	80
	0.50	104

Sample chromatograms were submitted, but no standard curves were submitted.

The petitioner will need to submit standard curves to demonstrate the linearity of the detector response at the levels investigated.

Storage Stability

No storage stability data on soybeans have been submitted. Storage stability studies on wheat grain and straw were carried out in conjunction with PP #6F3431. A corn storage stability study was submitted with PP #8G3602. The results of these studies are tabulated below.

Commodity	Spike level (ppm)	Storage period (months)	% Recovery DPX-M6316
Corn grain	0.1	0	78-103
		12	86-93
		24	94-95
Corn forage	0.1	0	82-96
		12	99-119
		18	88
		24	93
Wheat straw	0.1	0	74-113
		13	76-82
		18	88-93
		24	78-89
Wheat grain	0.1	0	73-95
		12	86-92
		18	80-84
		36	74-83

The recoveries reported above were corrected for the recoveries from freshly spiked samples.

The soybean samples from field trials described in PP #8F3602 were stored from 2-14 months. Two samples were shipped at ambient temperatures but were frozen no later than 4 days after harvest. The soybean samples from field trials described in the present submission were stored from 4-5 months in a freezer.

DEB concludes that the storage stability data adequately support the residue data.

Residue Data

The residue data submitted with PP #8G3602 were collected from field trials conducted at 10 different sites (NE, TN, IN, MD, GA, SD, NC, MS, OH, and IL). The residue data submitted with the present petition were collected from field trials conducted in IL, MN, NJ, SC, VA, and WI. Altogether, these 15 states produce 61% of the nation's soybeans. The residue data reflect PHI's of 45-68 days and application rates ranging from 0.25-1.00 oz ai/A (4X-16X application rates). One trial reflected aerial application, and one trial reflected the co-application of a liquid nitrogen fertilizer. The trials that involved the use of a surfactant were located in IL, MN, NJ, SC, VA, WI, NE, TN, IN, GA, SD, NC, and MS, which produce 53% of US soybeans. These states plus the contiguous states produce 97% of the nation's soybeans. The trials in these states employed an application rate of 0.25 oz ai/A and truly represented the proposed use at a 4X rate. The label calls for the use of a surfactant, and metabolism studies indicated

surfactants affected both the metabolic profile and the residue levels.

Levels of DPX-M6316 were reported as <0.05 ppm in all samples.

Although sample chromatograms were submitted, no standard curves have been submitted so that DEB could validate the determination of the analyte. Therefore at this time DEB can make no judgment on the adequacy of the residue data.

Processing Studies

Soybeans contain about 22.4% oil; therefore the theoretical concentration factor is about 4.4X. No detectable residues were found in any of the field trials, which used rates ranging from 4X-16X. DEB would not expect residues of DPX-M6316 in the oil to exceed the proposed tolerance of 0.1 ppm, provided that the requested standard curves support the methodology used to generate the residue data.

Meat, Milk, Poultry, and Eggs

Extrapolating from the goat metabolism studies, residue levels of DPX-M6316 could be about 0.1 ppb in tissue, and up to 0.3 ppb in milk, if feed items actually contained DPX-M6316 residues at the level of detection. No detectable residues of DPX-M6316 were reported on any field samples of wheat, barley, or soybeans. The proposed use would fall under 180.6(a)(3); there is no reasonable expectation of finite residues in meat, milk, poultry, and eggs.

Other Considerations

Neither Codex, Mexico, nor Canada has established tolerances for residues of DPX-M6316 on soybeans. There will be no compatibility problem.

Attachment 1: International Residue Limit Status Sheet
Attachment 2: Structures of Metabolites

cc: PMSD/ISB, RF, Circu, Reviewer-Deyrup, PP#8F3663
RDI:J. Onley:11/4/88:R. D. Schmitt:11/4/88
TS-769:CM#2:RM810:X7484:C. Deyrup:cd:11/7/88

Attachment 1

INTERNATIONAL RESIDUE LIMIT STATUS

F. Suhre 11/5/88

CHEMICAL Sulfothifenuron DPX-M6316

CODEX NO. _____

CODEX STATUS:

☑ No Codex Proposal Step 6 or above

Residue(if Step 8): _____

Crop(s)	Limit (mg/kg)

PROPOSED U.S. TOLERANCES:

Petition No. 8F 3663

RCB Reviewer Deyrup

Residue: Me-3-[[[[(4-Methoxy-6-Me-1,3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]2-thiophene carboxylate

Crop(s)	Limit (mg/kg)
Soybeans	0.1 ppm

CANADIAN LIMITS:

☑ No Canadian limit

Residue: _____

Crop(s)	Limit (mg/kg)

MEXICAN LIMITS:

☑ No Mexican limit

Residue: _____

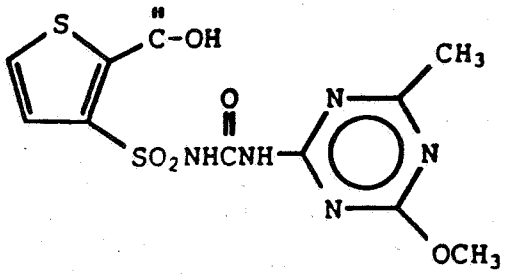
Crop(s)	Limit (mg/kg)

NOTES:

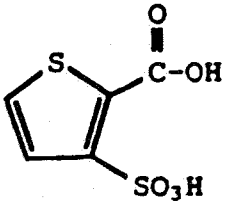
10

Form revised 1986

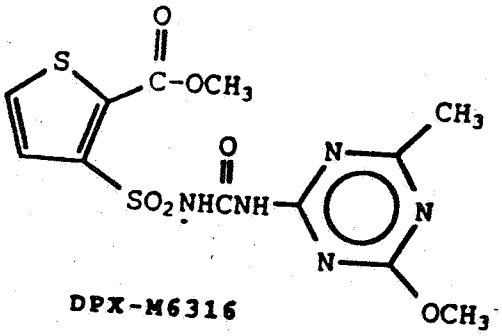
Attachment 2
to
PP#8F3663 (DEB #4297)



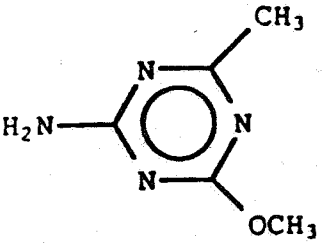
DPX-M6316 ACID



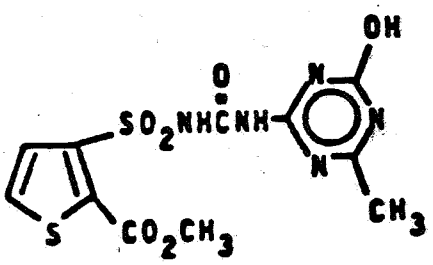
2-ACID-3-SULFONIC ACID



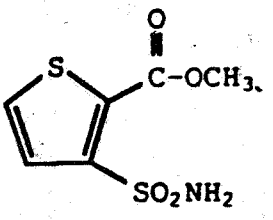
DPX-M6316



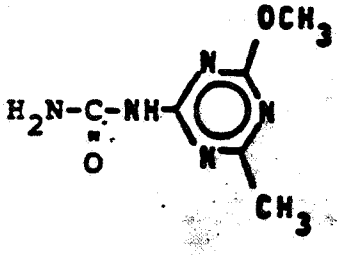
TRIAZINE AMINE



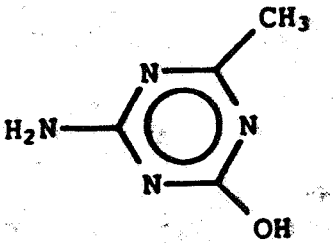
O-demethyl M6316



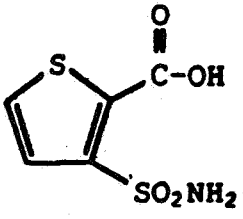
2-ESTER-3-SULFONAMIDE



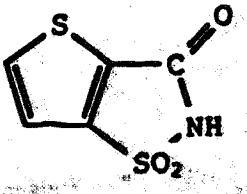
triazine urea



amino methyltriazinol



2-ACID-3-
SULFONAMIDE



Thiophene
Sulfonimide