PMSD
1340

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

FEB 12 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Harmony® (DPX-M6316) Registration Standard
Accession Nos. 263751 and 263752 (RCB No. 1236)

FROM: Charles L. Trichilo, Ph.D., Chief
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

TO: Amy Rispin
Science Integration Staff

and

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

Attached are the Product and Residue Chemistry Chapters for the Harmony (DPX-M6316) Registration Standard, prepared in-house by C. Deyrup. This standard includes data available and reviewed up to 1/30/87.

The due date for these chapter is February 7, 1987.

As required by the Registration Standards Policy Group, the product chemistry data for end-use products are not included in this Standard. This "generic" Standard is concerned with data which are relevant to technical formulations and manufacturing-use formulations containing DPX-M6316. Also, as requested by Herb Harrison of the Registration Division, the Residue Chemistry Branch no longer addresses the physical/chemical properties of the Registration Division as manufacturers respond to the "data call-in" program.

Product Chemistry data pertaining to end-use formulations are unique to each different formulation of DPX-M6316 and as outlined in 49 FR No. 207, p 42856, October 24, 1984, must be submitted prior to reregistration and will be reviewed by the Registration Division as part of the reregistration process.

The Product Chemistry Chapter contains Appendices A, B, C, D, and E in which is listed Confidential Business Information and is to be protected. Only those copies of the Standard in RCB and those sent to Robert Taylor, the Toxicology Branch, and PMSD/ISB contain such information.

Notes to PM:

1. Although multiresidue protocols are available from NTIS, we have included a copy.

2. Residue Chemistry Branch has completed the data tables for the Residue Chemistry chapter and they are included in this package.

   If you need additional input, please advise us.

Attachment: Multiresidue protocols, I, II, III, and IV.

cc: Ann Barton, HED (cover memo only)
Judy Heckman, HED (cover memo only)
R. Coberly, TOX, HED (with CBI Attachment)
----------EAB, HED
T. Levine, SIS, HED
Emory Eldredge, ISB, PMSD (with CBI Attachment)
R. Taylor, RD (with CBI Attachment)

bcc: Subject File
Reading File
Registration Standards File (with CBI Attachment)
C. Deyrup (with CBI Attachment)
PP #6F3431 (with CBI Attachment)

TS-769c:RCB:C.Deyrup:2/5/87:JHOnley:2/5/87:RDSchmitt:2/5/87:
Rm810:CM#2:557-7484

PRODUCT CHEMISTRY

TASK 1

INTRODUCTION

FIFRA 3(c)(2) required the Agency to establish guidelines for registering pesticides in the United States. The Agency requires registrants to provide quantitative data on all added ingredients, active and inert, which are equal to or greater than 0.1% of the product by weight.

To establish the composition of products proposed for registration, the Agency requires data and information not only on the manufacturing and formulation process, but also a discussion on the formation of manufacturing impurities and other product ingredients, intentional and unintentional. Further, to assure that the composition of the product as marketed will not vary from the composition evaluated at the time of registration, applicants are required to submit a statement certifying upper and lower composition limits for the added ingredients, and upper limits for some unintentional ingredients. Guidelines Subpart B, Subdivision D (49 FR 42856) suggest specific precision limits for ingredients based on the variability of the ingredients as a function of the manufacturing process.

In addition to the data on product composition, the Agency also requires data to establish the physical and chemical properties of both the pesticide active identity and physical state of the active ingredient (e.g., melting and boiling points, ambient vapor pressure and solubility).

The Product Chemistry Data Requirements as given in 40 CFR 158.120 are listed below along with the appropriate Product Chemistry Guideline references, and the submitted product chemistry data. Corresponding to each of the Topical Discussions listed below is the Guidelines Reference No. in "Data Requirements for Pesticide Registration; Final Rule" of Oct. 24, 1984 (49 FR 42856), which explains the minimum data the Agency will need to adequately assess the product chemistry of Harmony.

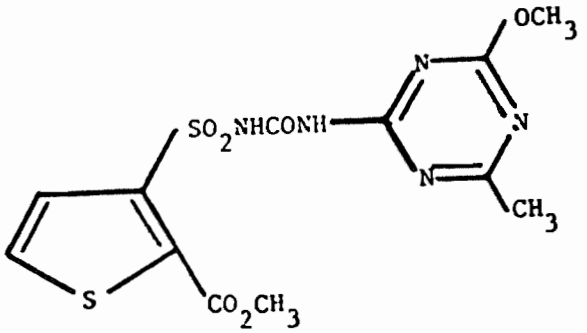
	Guidelines Reference No. of 40 CFR 158.120
Product Identity and Composition	61-(1-3)
Analysis and Certification of Product Ingredients	62-(1-3)
Physical and Chemical Characteristics	63-(2-21)

Product Chemistry Data Requirements (40 CFR 158.120)
Guideline reference:

61-1: Product Identity and Disclosure of Ingredients

The registrant is required to provide the name, nominal concentration, and certified limits of each active ingredient and the name, nominal concentration, and upper limit of each impurity. For each active ingredient the information should include the molecular, empirical, or structural formulas; the CA name, the CAS number; and the molecular weight.

Harmony (DPX-M6316) has not yet been given an ANSI name. The structure of Harmony is depicted below:



The chemical name for Harmony is methyl 3-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]-sulfonyl]-2-thiophene-carboxylate. The compound is also known as DPX-M6316 or INM-6316.

Other identifying characteristics and codes are:

Empirical Formula:	$C_{12}H_{13}N_5O_6S_2$
Molecular Weight:	387.40
CAS Registry No:	79277-27-3
Shaughnessy No:	128845
Caswell No:	573S

No additional information is required for this topic.

Information was obtained from Acc. No. 263752.

61-2: Description of the Beginning Materials and Manufacturing Process
61-3: Discussion of formation of impurities

The guidelines require that the suppliers of beginning materials be identified and that full descriptions of the beginning materials be provided. The description of the manufacturing process should in-

4

clude a discussion of each individual reaction in the process, the relative amounts of the reacting materials, the physical conditions of each step, and any purification procedures. A discussion is required to account for the presence of potential or actual impurities based upon knowledge of the composition of beginning materials, desired and side reactions of the manufacturing process, and contamination or degradation of the active material.

The data that the registrant has submitted in response to these requirements are given and discussed in the Confidential Appendix.

The following data are required for the 94% technical product:

- Details of the manufacturing process, including a description of the equipment used to produce the product, the relative amounts of beginning materials, reaction conditions, the duration of each step of the process, and purification procedures and quality control measures.

- The name and address of the manufacturer or producer, the brand name, trade name, copies of technical specs, etc., of <u>all</u> the beginning materials are needed.

- The mechanisms for formation of the impurities are not adequately discussed. A discussion of each impurity which may be present at $\geq$0.1% is required. From the chromatograms of the technical material, it appears that impurities comprising >0.1% of the technical material may not have been identified. The details of this data gap are discussed in the Confidential Appendix.

62-1: Preliminary analysis

62-2: Certification of limits

62-3: Analytical methods to verify certified limits

Five or more samples, representative of different manufactured batches, should be analyzed by appropriate methods for active ingredients and each impurity with results given for each sample. The analytical methods should be referenced to well-known, accepted procedures or a complete description should be given including validation of precision and accuracy.

A certification of upper and lower limits of the active ingredient and upper limits of each impurity is required for the technical material. A certification of the upper and lower limits of the active ingredient and each intentionally added inert is also required for the formulation. The values for the limits should be based upon a consideration of the values for the actual levels of active ingredients and impurities as shown by the analyses of the samples. An explanation is required of the procedures used to establish the certified limits.

5

The data and the analytical methodology that the registrant has submitted in response to these requirements are given and discussed in the Confidential Appendix.

The following data are required for the 94% technical:

- The petitioner will need to explain how the levels of the impurities comprising >0.1% of the technical were quantitated. If standard curves were used to quantitate the impurities, these curves will need to be submitted so that the analytical method can be validated. Sample calculations should be submitted.

- The petitioner will need to submit studies of the precision and accuracy of the method so that RCB can validate the methodology used to determine the levels of the impurities.

- The dates on which the six samples were withdrawn and analyzed should be provided.

- RCB needs to know how the upper and lower limits on the confidential statements of formula were established (e.g., a discussion of the statistical analysis).

The following data are required for Harmony™ 75 DF:

- The petitioner will need to determine the sensitivity and accuracy of the methodology used to determine the active ingredient in formulations. RCB suggests that the petitioner spike the formulation with known amounts of M6316 standard in order to determine the sensitivity and accuracy of the methodology.

- The petitioner should explain how the upper and lower limits for the active ingredient and the intentionally added inerts were established.

- The petitioner will need to submit analyses of Harmony® 75 DF from regular production after the commercial manufacture of Harmony® has begun.

Physical and Chemical Characteristics: §§ 63-2 through 63-13

Note that the Residue Chemistry Branch (RCB) will no longer address the physical/chemical properties of manufacturing-use products. These will be considered later by the Registration Division as manufacturers respond to the "data call-in" program. RCB will, however, still consider physical/chemical properties of technical grades of the active ingredient.

Methods used to meet the requirements of §§ 63-2 through 63-13 shall be referenced or described in the application for registration.

63-2: Color		White
63-3: Physical State		Crystalline Solid
63-4: Odor		None
63-5: Melting Point		186°
63-7: Density		1.49 g/cc
63-8: Solubility (25°C)		
Water	(pH 4.0)	24 mg/L
	(pH 5.0)	260 mg/L
	(pH 6.0)	2400 mg/L
Acetone		11.9 mg/L
Acetonitrile		7.3 mg/L
Ethanol		0.9 mg/L
Methanol		2.6 mg/L
Hexane		<0.1 mg/L
Ethyl acetate		2.6 mg/L
Methylene chloride		27.5 mg/L
Xylenes		0.2 mg/L
63-9: Vapor Pressure		2.7×10^{-6} mm Hg/25°C
63-10: Dissociation Constant		4.0 (pKa of the acid)
63-11: Octanol/Water Partition Coefficient		0.027
63-12: pH		4.0 (slurry in water)
63-13: Stability		Stable to metals and light. Decomposes on melting. In solution, the compound is very stable in methylene chloride and ethyl acetate, moderately stable in methanol, and relatively unstable in acetone and acetonitrile. The half-life in an aqueous photolysis study is estimated to be 1 to 5 days.

The following data are required for the 94% technical material:

- The petitioner needs to specify whether the above physical/chemical characteristics describe the pure active ingredient or the technical material.
- The methods used to determine the physical and chemical characteristics of the technical material should be described or referenced.

7

- For a reversibly ionizable substrate, the octanol/water partition coefficient should be determined at pH 5.0, 7.0, and 9.0 in accordance with OTS Guidelines; CG 1400, August 1982.

- A more detailed description of the stability studies is needed; the petitioner should identify which metals were used and give the half-lives of the material in the organic solvents tested.

The data should be reported in accordance to the format and requirements of the Product Chemistry Guidelines and 40 CFR 158.120.

References (Used)

Accession Nos. 263752, 072846, 263751

8

TABLE A. DATA REQUIREMENTS FOR DPX-M6316 (HARMONY®) 94% TECHNICAL PRODUCT[a] (EPA REG NO. 352--- ; E.I. DU PONT DE NEMOURS, INC.)

Data Requirement	Composition[b]	Does EPA Have Data to Satisfy This Requirement?	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?[c]
158.120 Product Chemistry				
Product Identity and Composition:				
61-1 - Product Identity and Disclosure of Ingredients	TGAI	Yes		No
61-2 - Description of Beginning Materials and Manufacturing Process	TGAI	Partially		Yes
61-3 - Discussion of Formation of Impurities	TGAI	Partially		Yes
Analysis and Certification of Product Ingredients				
62-1 - Preliminary Analysis of Product Samples	TGAI	Partially		Yes
62-2 - Certification of Ingredient Limits	TGAI	Partially		Yes
62-3 - Analytical Methods to Verify Certified Limits	TGAI	Partially		Yes
Physical and Chemical Characteristics[d]				
63-2 - Color	TGAI	Yes		No
63-3 - Physical State	TGAI	Yes		No
63-4 - Odor	TGAI	Yes		No
63-5 - Melting Point	TGAI	Yes[e]		No
63-6 - Boiling Point	TGAI	N/A		No
63-7 - Density, Bulk Density, or Specific Gravity	TGAI	Yes		No

TABLE A. (Continued)

Data Requirement	Composition[b]	Does EPA Have Data to Satisfy This Requirement?	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?[c]
158.120 Product Chemistry (continued)				
63-8 - Solubility	TGAI or PAI	Partially[f]		Yes
63-9 - Vapor Pressure	TGAI or PAI	Yes		No
63-10 - Dissociation Constant	TGAI or PAI	Partially[f]		Yes
63-11 - Octanol/Water Partition Coefficient	PAI	Partially[g]		Yes
63-12 - pH	TGAI	Yes		No
63-13 - Stability	TGAI	Partially[f, h]		Yes
Other Requirement:				
64-1 - Submittal of samples				No

[a] The 94% technical serves as a manufacturing-use product.
[b] Composition: TGAI = technical grade of the active ingredient; PAI = pure active ingredient.
[c] Data must be submitted no later than 6-8 months from the date of this Standard.
[d] The petitioner needs to specify whether the physical and chemical characteristics refer to the TGAI or the PAI.
[e] Not applicable since the product is a solid at room temperature.
[f] The methods used to determine the physical and chemical characteristics should be described or referenced.
[g] For a reversibly ionizable substrate, the octanol/water partition coefficient should be determined at pH 5.0, 7,0, and 9.0 in accordance with OTS Guidelines; CG 1400, August, 1982.
[h] A more detailed description of the stability studies is needed; the petitioner should identify which metals were used in the stability studies and give the half-lives of the material in the organic solvents tested.

Harmony Reviews

Page _____ is not included in this copy.

Pages 11 through 22 are not included in this copy.

The material not included contains the following type of information:

X Identity of product inert ingredients

___ Identity of product impurities

X Description of the product manufacturing process

X Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

___ FIFRA registration data

___ The document is a duplicate of page(s) _____

___ The document is not responsive to the request

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

HARMONY®

RESIDUE CHEMISTRY

TASK 2

INTRODUCTION

Harmony® 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 there are, as yet, no permanent tolerances on any raw agricultural commodity. Temporary tolerances of 0.05 ppm have been established on wheat and barley grain and of 0.10 ppm on wheat and barley straw (PP #4G3138).

E.I. du Pont de Nemours and Company (Inc.) propose the establishment of a permanent tolerance for residues of DPX-M6316 in/on wheat or barley grain at 0.05 ppm.

The only formulation proposed for use is a single active ingredient formulation, Harmony 75 DF (dry flowable), which contains 75% active ingredient.

NATURE OF THE RESIDUE IN PLANTS

CONCLUSIONS:

The nature of the residue in barley and wheat grain and straw is not adequately understood. In the greenhouse study of barley and wheat (Accession No.072845), 3 residues were identified, but the contribution that these residues made to the total radioactive residue (TRR) was not given. That is, RCB can't determine from the submitted data what proportion of the TRR has been identified. This study involved the use of thiophene-labeled DPX-M6316. Also, the identities of the two metabolites identified in this study were not confirmed by an alternative method. Furthermore, although only one fraction from the greenhouse wheat study was treated with beta-glucosidase, this fraction is described in one instance as the CH_2Cl_2 fraction and in another instance as the acetone/water fraction. Also, it was not clear whether enzymatic treatment resulted in the liberation of radioactivity which could be extracted into organic solvents.

In the field treated wheat metabolism study (Accession No. 263751), which utilized thiophene and triazine-labeled DPX-M6316, the radioactive residues in mature grain were not identified.

The following data are required:

- The greenhouse wheat study identified 3 residues in 28-day samples--parent, and the metabolites 3-(amino-sulfonyl)2-thiophenecarboxylic acid and methyl 3-(amino-sulfonyl)-2-thiophenecarboxylate. However, the contribution that the metabolites made to the TRR was not given, nor was sufficient raw data submitted (i.e., dpm from the various fractions and TLC peaks) so that the proportion of the TRR which had been identified could be determined, and RCB could not calculate the amount of the metabolites. The petitioner will need to provide this information.

- At this time, RCB regards the identification of the metabolites described above as tentative, because the petitioner has not submitted data confirming the identity of these compounds by another method, such as mass spectrometry. The petitioner will need to confirm the identity of the components of the terminal residue by an alternative method.

- It is not clear from the report in Accession No. 072845 which fraction was treated with beta-glucosidase. According to p. 8, Tab D-18, "Radiochromatograms of the CH_2Cl_2 fraction from the 28-day wheat and barley extracts treated with beta-glucosidase enzyme are shown in Figure 4...Thus, CH_2Cl_2-soluble conjugates of glucose were not major metabolites of DPX-M6316 in this study." According to p. 5, Tab D-18, "Portions of the 28-day concentrated

24

acetone/water extracts were adjusted to pH 5 and incubated at 37° for about 20 hours with 10 mg of beta-glucosidase enzyme." The petitioner will need to address this discrepancy.

- In the beta-glucosidase study, the chromatograms from corresponding fractions before and after beta-glucosidase treatment were qualitatively similar, but raw data describing the amount of radioactivity extractable into organic solvents were not provided. The petitioner will need to provide this data so that RCB can determine whether enzymatic treatment liberated additional radioactive residues.

- The petitioner did not characterize the radioactive residues found in mature grain in the studies submitted with Accession No. 263751, because he claimed that the level of radioactivity was too low. However, the petitioner states that the ratio of activity between sample level and background level is 10 or more. Therefore it seems feasible to RCB that chromatograms could be informative. The petitioner should compare chromatograms from the fractions derived from the mature grain study with those from the green plants and straw after he has finished characterizing the nature of the residue in green plants and straw to determine whether the metabolic profiles in forage, straw, and grain are similar.

- Additional work on the nature of the residue in green plants and straw are needed. The petitioner will need to identify residues derived from both thiophene- and triazine-labeled DPX-M6316.

References (Used):

Accession No.'s 072845, 263751

Discussion of the data:

Greenhouse studies: wheat and barley

An interim report (Accession No. 072845) describing an investigation of the metabolism of DPX-M6316 by wheat and barley grown in greenhouses was submitted.

DPX-M6316 (thiophene-2-^{14}C, specific activity, 23.3 microCuries/mg) was dissolved in 98 ml of Surfactant WK™/acetone/water (0.2/5.0/94.9, v/v/v) and sprayed over 4 containers located in a greenhouse at a rate equivalent to 1 oz. a.i./A (2 X application rate). Plants were in the 4-leaf stage. Samples were collected at days 0, 6, 14, 21, 28, and 111. Samples from 0, 14, and 21-day foliage were washed with acetone prior to extraction with acetone-water; the other samples were not washed before acetone-water extraction. The acetone-water extracts were concentrated, acidified to pH 3,

35

and successively extracted with CH_2Cl_2 and n-butanol. The 14 and 111-day samples were not subjected to successive extraction after acetone/water extraction and acidification but were analyzed directly. The concentrated extracts and acetone washes were examined by HPLC or by TLC (visualized by exposure to X-ray film).

The extractability of radioactive residues from wheat and barley is given below.

Tissue	Day	% Total Radioactive Residue		Total DPX-M6316 equivalents (ppm)
		Acetone Wash +/or Acetone/Water	Marc	
Wheat foliage	0	94.4	5.5	2.0
	6	80.9	19.1	1.3
	14	86.2	13.8	0.66
	21	70.0	30.0	0.37
	28	80.9	19.1	0.25
wheat straw	111	47.0	53.0	0.18
Wheat grain	111	85.0	15.0	0.07
Barley foliage	0	96.4	3.6	1.7
	6	87.7	12.3	1.4
	14	72.9	27.3	0.39
	21	78.9	21.1	0.42
	28	83.2	16.8	0.31
Barley straw	111	59.0	41.0	0.19
Barley grain	111	66.8	33.2	0.08

The petitioner reported that the loss of activity with time is consistent with growth dilution.

The percent of the total radioactive residue (% TRR) which partitioned into CH_2Cl_2 or n-butanol or remained in the water is given below.

Distribution of activity from the acetone/water extract

Sample	Day	% TRR		
		CH_2Cl_2	n-Butanol	Extracted water
Wheat foliage	0	70.2	5.7	0.7
	6	43.6	27.2	10.1
	21	5.9	19.5	20.1
	28	24.6	26.3	30.1

Sample	Day	% TRR		
		CH_2Cl_2	n-Butanol	Extracted water
Barley foliage	0	72.9	2.8	1.1
	6	53.5	23.4	10.9
	21	9.0	24.2	20.4
	28	21.1	30.7	28.6

In addition to parent, compounds which migrated with methyl 3-(aminosulfonyl)-2-thiophenecarboxylate and 3-(aminosulfonyl)-2-thiophenecarboxylic acid were also detected by TLC. The contribution which these metabolites made to the TRR was not given.

The corresponding chromatograms from the wheat and barley foliage studies were similar. In the 28 day sample, the major identifiable component of the CH_2Cl_2 extract consisted of parent, whereas the major identifiable component of the n-butanol extract was 3-(aminosulfonyl)-2-thiophenecarboxylic acid. Both the n-butanol extract and the extracted aqueous phase exhibited a significant amount of activity remaining at or near the origin.

The contribution which the metabolites made to the TRR was not given; the concentration of parent in the various fractions is given below.

Sample	Day	DPX-M6316 % TRR	DPX-M6316 ppm[1]
Wheat foliage	0	75.0	1.4
	6	25.4	0.28
	14	21.2	0.12
	21	9.3	<0.01
	28	13.3	0.03
Wheat straw	111	<0.1	<0.01
Wheat grain	111	<0.1	<0.005
Barley foliage	0	83.1	1.3
Barley foliage	6	17.5	0.21
	14	8.7	0.02
	21	11.0	0.04
	28	13.1	0.03
Barley straw	111	<0.1	<0.01
Barley grain	111	<0.1	<0.005

[1] Fresh weight basis

Portions of the acetone-water extract from 28-day samples of wheat and barley were concentrated, treated with beta-glucosidase, and then extracted with dichloromethane (p. 5 and Fig. 4, Tab D-18, Accession No. 072845). According to p. 8 (Tab D-18), the methylene chloride fractions from the extracts were treated with enzyme. The radiochromatogram after enzymatic treatment was qualitatively similar to the corresponding chromatogram before treatment. The petitioner concludes, "Thus, CH_2Cl_2-soluble conjugates of glucose were not major metabolites of DPX-M6316." The major identifiable component in the extract before and after treatment was DPX-M6316. The petitioner estimates that only 3-5% of the activity around the origin was moved away from the origin by enzymatic treatment.

At the end of this interim report, the petitioner said that additional work was being conducted in order to isolate and identify other plant metabolites formed in this greenhouse study and that a wheat and barley metabolism metabolism study was being carried out in the field.

Field grown wheat

Two metabolism studies involving field treated plants were submitted with Accession No. 263751. In one study, wheat plants at the 5-leaf stage were treated with DPX-M6316 (thiophene-2-^{14}C) at a rate equivalent to 1.0 oz. a.i./A (2 X maximum proposed rate); in the other study, wheat plants at the same growth stage were treated with DPX-M6316 (triazine-2^{14}C) at the same application rate. Samples were collected on Day 0, 4, 8, 21, 28, and 63. Plants were mature on Day 63. These reports deal only with the grain. The petitioner said that analyses of the green plants and straw will be submitted later.

Thiophene labeled DPX-M6316

The frozen 0-, 4-, 8-, 21-, and 28-day plants were freeze-dried, pulverized in a Waring-Blender, weighed, and combusted. The radioactivity in plants as a function of time is given below.

	Day	DPX-M6316 equivalents; ppm (^{14}C-thiophene)
	0	5.53
	4	3.02
	8	1.86
	21	0.753
	28	0.551
(Grain)	63	0.036

A portion of the grain was pulverized, weighed, and combusted. The radioactivity of the grain corresponded to 0.036 ppm DPX-M6316.

Pulverized grain was extracted with acetone-water (80:20), which was concentrated to the aqueous, acidified to pH 4, and extracted with methylene chloride. The remaining aqueous phase was then extracted with ethyl acetate/acetonitrile (3:1). The grain which had been extracted with acetone-water still contained a significant amount of activity and was therefore soaked overnight in phosphate buffer (pH 7). The grain was filtered, dried, then extracted with 0.01 M ammonium carbonate. The grain remaining was then refluxed for 1.5 hr with 1 N HCl. The mixture was filtered, the filtrate was basified to pH 8.2, and the filtrate was concentrated to a gum. The gum was extracted for 1 hr with refluxing acetone. The distribution of activity among the various fractions is given below.

Distribution of activity derived from DPX-M6316 (^{14}C-thiophene) in wheat grain

Fraction	% TRR	DPX-M6316 equivalents (ppm)
Acetone/water		
CH_2Cl_2	4	0.001
EtOAc/CH_3CN	6	0.002
Extracted H_2O	14	0.005
Phosphate buffer	31	0.011
$(NH_4)_2CO_3$	6	0.002
HCl filtrate		
Acetone extract	0	0
Residual gum	27	0.010
Residual solids	7	0.003
	95	0.034

The petitioner reported that the total dpm in the acetone/water extract was 20700 dpm. After concentrating this phase to 59 ml, the total dpm in the extract was 11900 dpm.

The petitioner states that if 0.1 ml of the phosphate buffer, which comprised 31% of the TRR, had been injected into an HPLC, the radioactivity would have amounted to only 15 dpm over background, if all the activity were in one peak. The petitioner states that if the extract had been concentrated to 20 ml instead of 100 ml, and if 0.2 ml had been chromatographed, the activity would have been only 146 dpm over background. The petitioner states that if the radiolabeled DPX-M6316 had not been diluted with cold material, the activity would have increased only by a factor of 2. The

petitioner claims that the level of activity in any of these situations would have been too low to allow identification of radioactive residues by HPLC or TLC. Therefore no attempts were made to characterize the residues in grain.

Triazine labeled DPX-M6316

The frozen 0-, 4-, 8-, 21-, and 28-day plants were thawed, weighed, oven-dried (80°C, 48 hr), and combusted. The procedure differed from the previous experiment in that the plants were oven-dried instead of freeze-dried. The radioactivity observed in plants as a function of time is given below.

	Day	DPX-M6316 equivalents (ppm)[1]
	0	4.32-5.00
	4	2.54-3.17
	8	0.95-1.67
	28	0.117-1.672
(Grain)	63	0.013-0.023

[1]Fresh weight basis

The petitioner points out that the kinetics for the triazine labeled study are similar to those of the thiophene labeled study; the half-life was about 4 days in both studies.

The pulverized wheat grain was extracted with acetone/water (80:20). The extract was concentrated to one-tenth of the original volume, acidified to pH 4, and extracted with methylene chloride (3 times). The acidified extract was then extracted 3 times with ethyl acetate/acetonitrile (3:1).

The distribution of radioactivity in the various fractions is given below.

Fraction	% TRR	DPX-M6316 equivalents (ppm)
Acetone/water		
CH_2Cl_2	8	0.001
EtOAc/CH_3CN	6	0.001
Extracted H_2O	37	0.004
Residual solids	64	0.007
	116	0.014

The radioactive residues in the various fractions from this study were not characterized because of the low levels of activity.

30

NATURE OF THE RESIDUE IN ANIMALS

Conclusions

No animal metabolism studies have been submitted because the petitioner has proposed a label prohibiting the use of treated crop for forage or hay and prohibiting the use of treated straw for the feeding or bedding of livestock. RCB does not consider the restriction on straw to be practical.

The nature of the residue in grain, wheat straw, and forage are not yet adequately understood. If residues of especial toxicological concern are identified in wheat and barley grain and/or significant levels of residues of toxicological concern are found in wheat straw from the proposed use on wheat, poultry and ruminant metabolism studies may be required. If the plant metabolism studies result in the identification of a metabolite that is not found in livestock, then additional livestock metabolism studies involving dosing with this metabolite may be required.

RESIDUE ANALYTICAL METHODS

Conclusions

The submitted methodology (Accession No. 263751) determines only DPX-M6216 per se. A copy of the proposed enforcement method was sent to EPA's Analytical Chemistry Section (ACS, COB, BUD) for evaluation.

ACS has reported to RCB on difficulties encountered in attempting to carry out a method trial of E.I. du Pont de Nemours & Co.'s Method No. AMR-235-84, revised 1/30/85 (PP #6F3431, memo of W.R. Bontoyan, 10/31/86).

The problems associated with this method were:

1. The method was unclear as written;

2. Probably the method would require a chemist of considerable experience in order to obtain reproducible results; and

3. After examining the submitted chromatograms, the Analytical Chemistry Section believes that the method is marginal and perhaps unacceptable for regulatory or monitoring analyses of wheat straw.

RCB concludes that the proposed enforcement methodology for residues of DPX-M6316 on wheat and barley grain and straw is not adequate as submitted. However, the methodology is considered adequate for the generation of residue data on grain.

The following data are required:

- The petitioner will need to submit revised enforcement methodology; this methodology will need to undergo a method trial.

- The Residue Chemistry Data Requirements in 40 CFR 158.125 (b)(15) require that regulated pesticide residues be subjected to one or more of the multiresidue procedures published in an Addendum to Pesticide Assessment Guidelines Subdivision O: Residue Chemistry Data Requirements for Analytical Methods in 40 CFR Part 158.125, Multiresidue Protocols. To our knowledge, such testing has not been conducted on DPX-M6316. Therefore, the following data will be required: Residues of DPX-M6316 in/on crop samples must be subjected to analysis by multiresidue protocols. Protocols for Methods I, II, III, and IV are available from National Technical Information Service under Order No. PB 86 203734/AS.

30

The following data may also be required:

- Additional methodology may have to be developed if other residues of toxicological concern (besides DPX-M6316) are found in the terminal residues of straw.
- Analytical methodology suitable for the determination of residues of concern in animal commodities may be needed, if a significant dietary burden from toxic residues on straw is imposed upon livestock.

References (Used):

Accession No. 263751

Discussion of the data-Accession No. 263751

The proposed enforcement analytical methodology for the determination of DPX-M6316 in wheat or barley grain and straw is described in Document No. AMR-235-84, revised 1-30-85.

Wheat Grain-Extraction

Residues were extracted from wheat grain with ethyl acetate using a Tekmar Tissumizer®. The sample was centrifuged at 2500 rpm for 10 minutes. The supernatant was decanted into a separatory funnel, and the residue was re-extracted and centrifuged. The extracts were combined in the separatory funnel.

The ethyl acetate extract was extracted 3 times with 0.1 M sodium carbonate. The pH of the combined aqueous extracts was adjusted to pH 3.5 with 1.0 N HCl which was added dropwise to avoid decomposition of DPX-M6316 from over-acidification. The acidified aqueous layer was extracted with methylene chloride, which was drained into a second separatory funnel, and then drained into a flask. The intermediate separation is necessary in order to obtain a better separation of the organic from the aqueous layer. The aqueous layer was extracted twice more with methylene chloride.

Wheat Straw, Barley Grain, Barley Straw-Extraction

Residues were extracted from wheat straw, barley grain, and barley straw with 0.1 M sodium bicarbonate using a Tekmar Tissumizer®. The sample was then centrifuged for 10 minutes at 2500 rpm. The supernatant was filtered through a glass wool plug and collected in a beaker. The glass wool plug was not used for barley grain. The extraction and centrifugation were repeated twice more. All extracts were combined in the beaker.

The aqueous extract was acidified to pH 3.5 with 1.0 N HCl, which was added dropwise to prevent decomposition of the parent compound from over-acidification. The aqueous extract was extracted 3 times with methylene chloride; the combined extracts were collected in a beaker and then decanted into a flask.

Wheat Grain and Straw; Barley Grain and Straw-Quantification

The methylene chloride extracts obtained above were concentrated to 4-5 ml, transferred to a centrifuge tube, and evaporated to dryness under a stream of N_2 on an N-EVAP at room temperature. The samples were then dissolved in cyclohexane/isopropanol (3:1), with dilution to a final volume of 5 ml. The extracts were passed through a Millipore filter before analysis by HPLC. In order to achieve the maximum sensitivity of the photoconductivity detector used for this analysis, the flow of the mobile phase through the analytical and reference loops must be balanced within 2% with a metering valve (Nupro Model SS-25A-TFE). The mobile phase was a mixture of cyclohexane, methanol, and isopropanol (6:1:1) which contained about 0.1% acetic acid.

The column used was a Du Pont Zorbax® SIL (25 cm x 4.6 mm) maintained at 35°C. Recoveries from wheat and barley grain and straw are tabulated below.

Sample	Fortification level (ppb)	# of Recoveries	Recovery range (%)
Wheat grain	20	16	71-98
Wheat straw	50	12	68-112
Barley grain	20	6	87-105
Barley straw	50	6	67-95

Representative chromatograms of control and fortified samples of wheat and barley grain and straw were submitted.

Analytical Methodology--Accession No. 072845

Residue data on wheat and barley grain and straw were submitted with Accession No. 072845; the residue data on grain were re-submitted with Accession No. 0263751.

The methodology for the determination of residues of DPX-M6316 differed from that described above for wheat straw, barley grain, and barley straw in the extraction procedure. Residues were extracted from these commodities with ethyl acetate/acetic acid (75:0.5, v:v) instead of with aqueous sodium bicarbonate. The work-up of these extracts then followed the work-up of the ethyl acetate extract obtained from the extraction of wheat in the procedure described above.

The recoveries of DPX-M6316 from wheat and barley straw and barley grain are given below.

Sample	Fortification level (ppb)	# of Recoveries	Recovery range (%)
Wheat straw	50	11	47-100
Barley grain	20	4	75-100
Barley straw	50	1	80

The submitted methodology determines only DPX-M6316 per se.

STORAGE STABILITY DATA

Conclusions

The available data indicate that residues of DPX-M6316 on wheat and barley grain are stable under freezer storage conditions for at least 18 months.

The grain and straw samples from 18 field trials described in Accession No. 072845 were either stored or shipped unfrozen or under unspecified conditions by the field trial cooperators. The time from sampling to analysis was not given for any of the samples. Furthermore, the storage conditions of the samples after arrival at the analytical laboratory were not described. Therefore, the submitted storage stability data do not support much of the field residue data submitted with Accession No. 072845.

RCB concludes that the residue data from the following field trials described in Accession No. 263751 are not supported by the storage stability data:

Site	Commodity	Storage conditions
Grandin, ND	Wheat	Room temperature, 3 weeks, then frozen
Buhl, ID	Barley	Room temperature, 6 weeks, then frozen
Lamont, ND	Barley	Room temperature, 2 weeks, then frozen
Garfield, WA	Barley	Room temperature, 4 weeks, then frozen
Redfield, SD	Barley	No information available

The residue data are not supported by the storage stability study because the storage stability study was conducted under freezer storage conditions. In order to validate the field residue data, the storage stability study should reflect the conditions under which the samples were actually stored.

The additional information will be required:

- In order to support the wheat and barley residue data on grain and straw, the petitioner will need to provide more information on storage conditions. The storage stability data indicate that there is no significant deterioration of DPX-M6316 residues on grain after periods of up to 18 months in a freezer. Generally, in order for the residue data to be

considered valid, the samples from the field trials should be stored under the same conditions as are used in the storage stability study, although extenuating circumstances such as PHI's which are long relative to the period of time that the sample was left unfrozen and the nature of the crop (water content) may be taken into consideration. RCB needs to know how long the samples were stored frozen before analysis. The storage period extends from harvest to analysis. If samples were not immediately frozen, the petitioner will need to inform RCB when these samples were frozen so that RCB can determine if the residue data are valid and/or submit appropriate storage stability data.

- Storage stability on straw will be needed to validate the residue data on straw samples (Accession No. 072845). These samples were either stored and shipped unfrozen or under unspecified conditions. The straw storage stability study should reflect the conditions under which the straw samples were stored. If additional residue data are generated on straw, appropriate storage stability data will be needed.

The following information may be required:

- If additional residues of concern are identified in the metabolism studies, storage stability data on these compounds may be required.

References (Used):

Accession No.'s 072845, 263751

Discussion of the Data:

The petitioner has submitted the results of a study investigating the stability of residues of DPX-M6316 on wheat grain stored in a freezer. Samples were spiked at a level of 100 ppb. The recoveries as a function of time are given below.

Storage period (months)	% Recovery DPX-M6316
0	81-95
1	110-115
3	94-98
6	91-93
12	86-92
18	80-84

The above recoveries have been corrected for the recoveries from fresh fortifications (average recovery, 105%).

MAGNITUDE OF THE RESIDUE IN PLANTS

The nature of the residue in plants is not yet adequately understood. If additional residues of toxicological concern are identified at some future date, residue data on these compounds will also be required. Also, the crop group conclusions stated below represent the minimum residue chemistry data base acceptable for purposes of establishing a group tolerance. Should the registrant elect to propose a crop group tolerance, complete considerations must be given to all data requirements stated in the 40 CFR 180.34.

Cereal Grains Group

A group tolerance is not appropriate at this time for the following reasons:

- Adequate residue data is not available for representative crops of this group (corn-fresh sweet corn and dried field corn, rice, sorghum, and wheat)
- The metabolism of DPX-M6316 in plants is not adequately understood.

Barley:

Tolerance:

A tolerance of 0.05 ppm DPX-M6316 is proposed on barley grain. No tolerance has been proposed for barley forage and straw.

Use Directions and Limitations:

(1) Type of Applications: Foliar application--aerial application, in at least 3 gallons spray volume per acre; ground application, in at least 5 gallons spray volume per acre. Tank mixes with Hoelon, Avenge, or other suitable registered herbicides are permitted, unless the use directions for the other herbicides conflict with the use directions of DPX-M6316.

(2) Dosage: Up to 2/3 ounce of Harmony® per acre (0.5 oz a.i./A). The addition of a nonionic surfactant of at least 80% active ingredient strength at 0.25% vol/vol is recommended (except for the low desert valleys of Imperial and Riverside counties of CA or in AZ or if liquid-nitrogen fertilizer solutions are used as spray carriers).

(3) Application Schedule: after 2-leaf stage but before the boot stage. A minimum PHI of 36 days is implied by these use directions. Broadleaf weeds should be less than 4 inches tall or wide, and wild garlic plants should be 6 to 12 inches tall with 4 to 6 inches of new growth.

(4) Geographical Restrictions: None for the active ingredient; see"Dosage" above for the restrictions which apply to the addition of a surfactant.

(5) Formulations: 75% dry flowable

(6) Limitations: There is a restriction against grazing or feeding forage or hay from treated areas to livestock. There is also a restriction against feeding treated straw to livestock or using treated straw for bedding of livestock.

Wheat or barley underseeded with another crop are not to be treated with DPX-M6316.

Conclusions

1). The petitioner will need to specify that only one application per season is permitted in a revised Section B/label.

2). The label should stipulate that only EPA-approved surfactants be used.

3). In this particular case, which involves treatment in the interval between the 2-leaf stage but before boot stage, RCB concludes that the foraging restriction is practical. The proposed use would permit grazing for 4-6 weeks, after which the cattle would have to be removed anyway. The crop could then be treated with Harmony™ in the time interval remaining before boot stage (Dr. A.E. Foster, University of North Dakota, Dr. T. Peeper, Oklahoma State University).

4). According to Professors Foster and Peeper, barley straw, unlike wheat straw is rarely used for feed/bedding. Barley straw is brittle, and beards tend to stick to the straw and can cause itchiness in the animals. Therefore RCB concludes that the restriction against using barley straw for feed or bedding is practical, and barley straw is under the grower's control.

5). RCB concludes that residue levels resulting from aerial treatment of barley are essentially the same as from ground equipment application.

6). Residue data from 4 barley field trials were submitted with Accession No. 072845. The submitted storage stability data do not support the residue data because the samples were either stored and shipped unfrozen or under unspecified conditions. Residue data from 10 barley trials were submitted with Accession No. 263751. RCB concludes that the storage stability data support the residue data from 6 of these trials [conducted in ND, CA (3), MT, and OR; treatment rates, 0.5-1.25 oz. a.i./A; PHI's, 45-108 days].

7). RCB concludes that the field residue data on barley, supported by storage stability data, satisfy the geographical distribution needed for barley grain. The states in which trials were conducted, plus the contiguous states, produce about 85% of the nation's barley. However, these residue data on barley reflect PHI's of 49-108 days, whereas the proposed use implies a possible PHI of 36 days. Therefore, residue data on barley (or wheat) reflecting a 36 day PHI are needed.

8). Since the nature of the residue is not yet adequately understood, RCB is unable to determine the appropriateness of the proposed tolerance on barley. Should other residues of toxicological concern besides parent be identified, residue data reflecting analyses for these residues may also be required.

9). At this time RCB will not require a processing study. Radioactive residues in mature wheat grain 63 days after a 2 X application rate ranged from 0.013 to 0.038 ppm. However, after the nature of the residue in grain has been adequately delineated, processing studies may be required on grain treated at exaggerated rates.

References (Used):

Accession No's 072845, 263751

Discussion of the Residue Data for Barley:

Accession No. 072845

Residue data from 4 field trials (CO, ID, OR, and ND) were submitted with Accession No. 072845. The data reflect a single application at a rate of 0.25-2.0 oz.a.i./A (proposed maximum rate, 0.5 oz. a.i./A). PHI's of 46-112 days were observed. The proposed use permits application up to boot stage, which can occur 36 days before harvest. Application was with ground equipment.

Residue levels of DPX-M6316 were reported to be <0.02 ppm on all grain samples. Two samples of straw were analyzed. After treatment with DPX-M6316 at rates of 0.5 and 1.0 oz. a.i./A, DPX-M6313 levels in straw 108 days after application were reported to be <0.05 ppm .

All the samples in this study were either stored and shipped unfrozen or under unspecified conditions.

40

Accession No. 263751

Additional residue data reflecting ground equipment (6 trials) and aerial application (4 trials) to barley in field trials conducted in ID, WA, SD, OR, ND, CA, and MT were submitted with Accession No. 263751.

Barley samples from Lamont, ID, Buhl, ID, and Garfield, WA, were stored 2 weeks to 1.5 months at room temperature by the field trial cooperators. No information was available on the storage conditions for the Redfield, SD, trial. The samples from the other 6 trials, all of which utilized surfactant and were conducted in OR, ND, CA, and MT, were either stored frozen from harvest until analysis or stored at room temperature for a week or less before being frozen. These states plus the contiguous states produce about 85% of the nation's barley. Judging from the dates on the cover letters describing these trials, the samples were stored a maximum of 18 months before analysis. Four trials were conducted with aerial application and two trials were conducted with ground equipment applications.

Residue levels of DPX-M6316 from these trials ranged from <0.02 to <0.05 ppm. The residue data reflect PHI's of 45-108 days and application rates of 0.33-1.25 oz a.i./A (up to a 2.5 X application rate).

Residue levels of DPX-M6316 from all the trials submitted with Accession No. 263751 (reflecting treatment rates of 0.33 to 1.5 oz. a.i./A, and PHI's of 45 to 108 days) were reported to be <0.02 to <0.05 ppm.

Wheat

Tolerance:

A tolerance of 0.05 ppm DPX-M6316 is proposed on wheat grain. No tolerance has been proposed for wheat forage and straw.

Use Directions and Limitations:

(1) Type of Applications: Foliar application--aerial application, in at least 3 gallons spray volume per acre; ground application, in at least 5 gallons spray volume per acre. Tank mixes with Hoelon, Avenge, or other suitable registered herbicides are permitted, unless the use directions for the other herbicides conflict with the use directions of DPX-M6316.

(2) Dosage: Up to 2/3 ounce of Harmony® per acre (0.5 oz a.i./A). The addition of a nonionic surfactant of at least 80% active ingredient strength at 0.25% vol/vol is recommended (except for the low desert valleys of Imperial and Riverside counties of CA or in AZ or if liquid-nitrogen fertilizer solutions are used as spray carriers.

(3) Application Schedule: after 2-leaf stage but before the boot stage. A minimum PHI of 36 days is implied by these use directions. Broadleaf weeds should be less than 4 inches tall or wide, and wild garlic plants should be 6 to 12 inches tall with 4 to 6 inches of new growth.

(4) Geographical Restrictions: None for the active ingredient; see"Dosage" above for the restrictions which apply to the addition of a surfactant.

(5) Formulations: 75% dry flowable

(6) Limitations: There is a restriction against grazing or feeding forage or hay from treated areas to livestock. There is also a restriction against feeding treated straw to livestock or using treated straw for bedding of livestock.

Wheat or barley underseeded with another crop are not to be treated with DPX-M6316.

Conclusions

1). The petitioner will need to specify that only one application per season is permitted in a revised Section B/label.

2). The label should stipulate that only EPA-approved surfactants be used.

3). Wheat is commonly foraged by cattle. (Dr. A.M. Decker, Professor of Forage Crops, University of Maryland, Dr. D.J. Schingoethe, Professor of Dairy Nutrition, South Dakota State University). The proposed use would permit grazing for 4-6 weeks, after which the cattle would have to be removed anyway, in order to avoid damage to the seed head. The crop could then be treated with Harmony® in the time interval remaining before boot stage (Dr. Decker; Dr. E. Krencer, Oklahoma State University). Therefore, in this particular case, which involves treatment in the interval between the 2-leaf stage but before boot stage, RCB concludes that the foraging restriction is practical.

4). Although the current Pesticide Assessment Guidelines, Subdivision O, list wheat straw as being under grower control, this statement is an error, which will be corrected in the forthcoming Pesticide Assessment Guidelines.

It appears that about 35% of the respondents in the straw usage survey submitted by the petitioner either sold straw, used their own straw for feed and/or bedding, or did both. Dr. D.J. Schingoethe, Professor of Dairy Nutrition, South Dakota State University, said that the use of straw for bedding is so common, that it would not be realistic to

expect farmers to obey this restriction. The farmers would have to dispose of treated straw and then buy straw from someone else. Both Dr. Schingoethe and Dr. Decker (Professor Forage Crops, University of Maryland) said that cattle bedded in straw would eat some of the bedding and therefore nutritionists conducting experiments do not bed cattle in straw for this reason. The amount of straw consumed by the cattle would depend upon the quality of the hay in their diet, the amount of fiber in their diet, and the quality of the straw. Dr. Decker said that in times of drought more straw would be sold; during a severe drought such as this year's drought in MD, farmers might sell treated straw, despite a label restriction against using treated straw for feed or bedding. Considering the size of the US wheat crop and the factors discussed above, RCB concludes that a label prohibiting the use of treated straw for feed or bedding is not practical.

Since the label restriction against using straw for bedding or feed is not considered practical, the petitioner will need to submit a revised Section B/label which does not contain this restriction. The petitioner will also need to submit a revised Section F which contains an appropriate tolerance for residues of DPX-M6316 on wheat straw.

5). RCB concludes that residue levels resulting from aerial treatment of wheat are essentially the same as from ground equipment application.

6). RCB needs to know how long the wheat grain and straw samples described in Accession No. 072845 were stored before analysis. The storage period extends from harvest to analysis. If samples were not immediately frozen after sampling, the petitioner will need to inform RCB when these samples were frozen so that RCB can determine if the residue data are valid and/or submit appropriate storage stability data.

7). Residue data from 5 wheat trials were submitted with Accession No. 263751. RCB concludes that the storage stability data support the residue data in the wheat trials from WA, ID, CA, and CO (3 trials on winter wheat and one on spring wheat; treatment rates, 0.5-1.5 oz. a.i./A; PHI's, 62-99 days). Since most of the wheat grain and straw residue data cannot be validated at this time, RCB will need additional wheat residue data (on grain and straw) from states in the Midwest (e.g., KS, IL, MN), Southeast (e.g., FL, GA), Southwest (e.g., OK, TX), and Northeast (e.g., NY, NJ, DE), if the petitioner can't support the previously submitted wheat residue data. Additional residue data from the West would also be needed. Although the residue data from WA, ID, CA, and CO were judged to be valid, only one trial (WA) was conducted on spring wheat and straw. Some of the required residue data should reflect the shortest practical PHI (about 36 days).

43

8). Since the nature of the residue is not yet adequately understood, RCB is unable to determine the appropriateness of the proposed tolerance on wheat. Should other residues of toxicological concern besides parent be identified, residue data reflecting analyses for these residues may also be required.

9). At this time RCB will not require a processing study. Radioactive residues in mature wheat grain 63 days after a 2 X application rate ranged from 0.013 to 0.038 ppm. However, after the nature of the residue in grain has been adequately delineated, processing studies may be required on grain treated at exaggerated rates.

References (used):

Accession No.'s 072845, 263751

Discussion of Residue Data for Wheat:

Accession No. 072845

Residue data generated from 14 wheat field trials reflecting analyses for residues of DPX-M6316 were submitted with Accession No. 072845. Residue data reflecting analyses of straw samples from 9 of the field trials were also submitted. The field trials were conducted in OH, CO, DE, ND, MN, ID, OK, KS, and FL. All samples from these trials were either stored and shipped in an unfrozen condition or under unspecified conditions.

Wheat was treated with DPX-M6316 at rates ranging from 0.25-4 oz. a.i./A. PHI's of 48-118 days were observed. The proposed use permits application up to boot stage, which can occur 36 days before harvest. Application was with ground equipment.

Residue levels of DPX-M6316 were reported as <0.02 ppm in all samples of wheat grain and <0.05 ppm in all samples of wheat straw.

Accession No. 263751

Additional residue data reflecting aerial application to wheat in 5 field trials conducted in WA, ID, ND, CA, AND CO were submitted with Accession No. 263751. Two samples of wheat straw were analyzed. The field trials reflect treatment rates ranging from 0.3 to 1.5 oz. a.i./A and PHI's of 62-99 days. The maximum proposed rate is 0.5 oz. a.i./A and treatment before the boot stage, which can occur 36 days before harvest.

Of the 5 wheat trials, the samples from 4 trials (WA, ID, CA, and CO) were either stored and shipped frozen or were stored at room temperature for a week or less before being shipped to the laboratory where they were frozen. The total storage period for the samples from these trials, which involved the use of

surfactant, did not appear to exceed 11 months. The samples from ND were stored at room temperature for 3 weeks before being shipped and frozen.

Residue levels of DPX-M6316 were reported as <0.02 ppm in all the wheat grain samples.

In the WA trial, residue levels of DPX-M6316 were reported as <0.05 ppm in straw treated at rates of 0.75 and 1.0 oz. a.i./A with a PHI of 90 days.

The petitioner has provided a survey conducted by Doane Marketing Research, Inc. to support the contention that a restriction against the use of treated straw for feed or bedding is enforceable and economically feasible.

The survey was conducted because, according to the petitioner, RCB had expressed concern that the sale of straw represented such an attractive economic inducement that a significant number of growers would ignore a label restriction against selling straw. The proposed restriction against the use of treated straw for feed or bedding would also imply a prohibition against selling the straw because the buyer would not know whether the straw had been treated or not.

The survey was conducted in CA, the Red River Valley region (ND, SD, and MN), and the "areas of wild garlic infestation in the Midwest and South." There were 200 respondents from each region. Minimum acreage requirements were 150 acres in the Red River Valley, 100 acres in CA, and 50 acres in the Garlic region. The restrictions were chosen so that the respondents for each region were representative of about 80% of all the wheat and barley grown. Some of the findings of this survey are:

1. About 21% of the farmers have sold straw sometime in the last five years. About 31% of the CA farmers, 18% of the garlic area farmers, and 7% of the Red River Valley farmers have sold straw sometime in the last 5 years. About 13% of the respondents sold straw in 1985; of those farmers who had sold straw sometime in the last five years (but not in 1985), 72% had sold straw for 3 or 4 of the last 5 years.

2. Up to 15.9% of the straw from any year may come into contact with livestock, either from use on the farm on which the crop was grown or through the sale of straw. Of the 600 respondents, 165 reported using the straw for feed or bedding, and 78 reported selling the straw.

3. Although 13% of the farmers sold straw in 1985, only 7% of the 1985 straw crop was actually sold.

4. The farmers that do sell straw would probably sell more

straw if they could find more buyers and if the price of straw increased.

5. Straw sales account for about 6% of the wheat and barley income for those farmers who do sell straw.

MAGNITUDE OF THE RESIDUE IN MEAT, MILK, POULTRY, AND EGGS

Tolerances

No tolerances have been proposed for animal commodities.

Conclusions

The following commodities may be consumed by livestock.

Commodity	% in Diet			
	Beef cattle	Dairy cattle	Broilers	Layers
Wheat straw	10	10	--	--
Barley grain	80	50	50	50
Wheat grain	50	50	70	50

RCB has concluded that the restrictions against foraging wheat and barley and using barley straw for feed and bedding are practical but that a wheat straw use restriction is not practical.

At this time RCB is unable to determine whether ruminant and poultry feeding studies and tolerances for meat, milk, poultry, and eggs are needed. After the nature of the residue has been delineated in straw and grain, and valid residue data on wheat straw and wheat and barley grain for all residues of concern have been submitted, RCB will consider the question of secondary residues arising in meat, milk, poultry, and eggs from the proposed use on wheat and barley.

References (Used):

Harris Feed Guide; Pesticide Assessment Guidelines, Subdivision O: Residue Chemistry

TOLERANCE REASSESSMENT SUMMARY

The nature of the residue in plants is not adequately understood. If additional metabolism studies identify residues other than parent which need to be regulated, then adequate analytical methodology may have to be developed, appropriate residue data will need to be generated, and the proposed tolerances on wheat and barley may need to be revised.

The proposed enforcement method did not pass the method trial. An adequate enforcement method will be needed to determine residues of DPX-M6316 in plants. Because of a lack of information on the conditions under which samples were stored, the residue data on wheat grain are not adequate to support the proposed tolerance.

Moreover, none of the residue data on wheat and barley grain reflected the minimum practical PHI of about 36 days.

Once the nature of the residue in wheat and barley is more adequately understood, processing studies on wheat or barley treated at exaggerated rates may be required.

The residue data on wheat and barley are not adequate to permit RCB to estimate the impact upon livestock from residues arising from the proposed uses.

GENERIC DATA REQUIREMENTS FOR HARMONY™

Data Requirement		Test Substance[1]/	Does EPA Have Data?	Bibliographic Citation (Accession No.)	Must Additional Data Be Submitted?	Time Frame for Submission[2]/
158.125 Residue Chemistry						
171-2.	Chemical Identity[3]/					
171-3.	Directions for Use		(See Index)			
171-4.	Nature of the Residue (Metabolism) -Plants	PAIRA	Partially	072845 263751	Yes[4]/	12 Months
	-Livestock	Paira & Metabolites	No		Reserved[5]/	
171-4.	Residue Analytical Methods -Plant and Animal Residues	TGAI & Metabolites	Partially	072845 263751	Yes[6]/	6 Months
171-4.	Storage Stability Data	TEP & Metabolites	Partially	072845 263751	Yes[7]/	6 Months
171-4.	Magnitude of the Residue -Crop Field Trials					
	-Cereal Grains Group[8]/	TEP	Partially	072845 263751	No	

(continued, footnotes follow.)

GENERIC DATA REQUIREMENTS FOR HARMONY™ (Continued)

Data Requirement	Test Substance[1]/	Does EPA Have Data?	Bibliographic Citation (Accession No.)	Must Additional Data Be Submitted?	Time Frame for Submission[2]/
171-4. Magnitude of the Residue -Crop Field Trials					
o Barley	TEP	Partially	072845 263751	Yes[9]/	18 Months
o Wheat		Partially	078245 263751	Yes[10]/	18 Months
-Meat/Milk/ Poultry/Eggs		No		Reserved[11]/	

1/ Test Substance: TGAI = Technical grade of the active ingredient; PAIRA = Pure active ingredient, radiolabeled; TEP = Typical end-use product

2/ Data must be submitted within the indicated time frame, based on the date of this Guidance Document

3/ Refer to Product Chemistry Data Requirement Tables.

4/ The greenhouse wheat study identified 3 residues in 28-day samples--parent, and the metabolites 3-(aminosulfonyl)2-thiophenecarboxylic acid and methyl 3-(aminosulfonyl)-2-thiophenecarboxylate. However, the contribution that the metabolites made to the TRR was not given, nor was sufficient raw data submitted (i.e., dpm from the various fractions and TLC peaks) so that the proportion of the TRR which had been identified could be determined, and RCB could not calculate the amount of the metabolites. The petitioner will need to provide this information.

At this time, RCB regards the identification of the metabolites described above as tentative, because the petitioner has not submitted data confirming the identity of these compounds by another method, such as mass spectrometry. The petitioner will need to confirm the identity of the components of the terminal residue by an alternative method.

It is not clear from the report in Accession No. 072845 which fraction was treated with beta-glucosidase. According to p. 8, Tab D-18, "Radiochromatograms of the $\underline{CH_2Cl_2}$ fraction from the 28-day wheat and barley extracts treated with beta-glucosidase enzyme are shown in Figure 4...Thus, $\underline{CH_2Cl_2\text{-soluble}}$ conjugates of glucose were not major metabolites of DPX-M6316 in this study." According to p. 5, Tab D-18, "Portions of the 28-day concentrated acetone/water extracts were adjusted to pH 5 and incubated at 37° for about 20 hours with 10 mg of beta-glucosidase enzyme." The petitioner will need to address this discrepancy.

In the beta-glucosidase study, the chromatograms from corresponding fractions before and after beta-glucosidase treatment were qualitatively similar, but raw data describing the amount of radioactivity extractable into organic solvents were not provided. The petitioner will need to provide this data so that RCB can determine whether enzymatic treatment liberated additional radioactive residues.

The petitioner did not characterize the radioactive residues found in mature grain in the studies submitted with Accession No. 263751, because he claimed that the level of radioactivity was too

low. However, the petitioner states that the ratio of activity between sample level and background level is 10 or more. Therefore it seems feasible to RCB that chromatograms could be informative. The petitioner should compare chromatograms from the fractions derived from the mature grain study with those from the green plants and straw after he has finished characterizing the nature of the residue in green plants and straw to determine whether the metabolic profiles in forage, straw, and grain are similar.

Additional work on the nature of the residue in green plants and straw are needed. The petitioner will need to identify residues derived from both thiophene- and triazine-labeled DPX-M6316.

5/ No animal metabolism studies have been submitted because the petitioner has proposed a label prohibiting the use of treated crop for forage or hay and prohibiting the use of treated straw for the feeding or bedding of livestock. RCB does not consider the restriction on straw to be practical.

The nature of the residue in grain, wheat straw, and forage are not yet adequately understood. If residues of especial toxicological concern are identified in wheat and barley grain and/or significant levels of residues of toxicological concern are found in wheat straw from the proposed use on wheat, poultry and ruminant metabolism studies may be required. If the plant metabolism studies result in the identification of a metabolite that is not found in livestock, additional livestock metabolism studies involving dosing with this metabolite may also be required.

6/ EPA's Analytical Chemistry Section (ACS, COB, BUD) has reported to RCB on difficulties encountered in attempting to carry out a method trial of E.I. du Pont de Nemours & Co.'s Method No. AMR-235-84, revised 1/30/85 (PP #6F3431, memo of W.R. Bontoyan, 10/31/86). RCB concludes that the proposed enforcement methodology for residues of DPX-M6316 on wheat and barley grain and straw is not adequate as submitted. However, the methodology is considered adequate for the generation of residue data on grain.

The petitioner will need to submit revised enforcement methodology; this methodology will need to undergo a method trial.

The Residue Chemistry Data Requirements in 40 CFR 158.125 (b)(15) require that regulated pesticide residues be subjected to one or more of the multiresidue procedures published in an Addendum to Pesticide Assessment Guidelines Subdivision O: Residue Chemistry Data Requirements for Analytical Methods in 40 CFR Part 158.125, Multiresidue Protocols. To our knowledge, such testing has not been conducted on DPX-M6316. Therefore, the following data will be required: Residues of DPX-M6316 in/on crop samples must be subjected to analysis by multiresidue protocols. Protocols for Methods I, II, III, and IV are available from National Technical Information Service under Order No. PB

86 203734/AS.

Additional methodology may have to be developed if other residues of toxicological concern (besides DPX-M6316) are found in the terminal residues of straw.

Analytical methodology suitable for the determination of residues of concern in animal commodities may be needed, if a significant dietary burden from toxic residues on straw is imposed upon livestock.

7/ In order to support the wheat and barley residue data on grain and straw, the petitioner will need to provide more information on storage conditions. The storage stability data indicate that there is no significant deterioration of DPX-M6316 residues on grain after periods of up to 18 months in a freezer. Generally, in order for the residue data to be considered valid, the samples from the field trials should be stored under the same conditions as are used in the storage stability study, although extenuating circumstances such as PHI's which are long relative to the period of time that the sample was left unfrozen and the nature of the crop (water content) may be taken into consideration. RCB needs to know how long the samples were stored frozen before analysis. The storage period extends from harvest to analysis. If samples were not immediately frozen, the petitioner will need to inform RCB when these samples were frozen so that RCB can determine if the residue data are valid and/or submit appropriate storage stability data.

Storage stability on straw will be needed to validate the residue data on straw samples (Accession No. 072845). These samples were either stored and shipped unfrozen or under unspecified conditions. The straw storage stability study should reflect the conditions under which the straw samples were stored. If additional residue data are generated on straw, appropriate storage stability data will be needed.

If additional residues of concern are identified in the metabolism studies, storage stability data on these compounds may be required.

8/ Adequate residue data is not available for representative crops of this group (corn-fresh sweet corn and dried field corn, rice, sorghum, and wheat). The metabolism of DPX-M6316 in plants is not adequately understood.

9/ The petitioner will need to specify that only one application per season is permitted on barley in a revised Section B/label.

The label should stipulate that only EPA-approved surfactants be used.

In this particular case, which involves treatment in the interval between the 2-leaf stage but before boot stage, RCB concludes that the foraging restriction is practical. The proposed use would permit grazing for 4-6 weeks, after which the cattle would have to be removed anyway. The crop could then be treated with Harmony™ in the time interval remaining before boot stage (Dr. A.E. Foster, University of North Dakota, Dr. T. Peeper, Oklahoma State University).

Barley straw, unlike wheat straw is rarely used for feed/bedding. Barley straw is brittle, and beards tend to stick to the straw and can cause itchiness in the animals. Therefore RCB concludes that the restriction against using barley straw for feed or bedding is practical, and barley straw is under the grower's control.

RCB concludes that residue levels resulting from aerial treatment of barley are essentially the same as from ground equipment application.

Residue data from 4 barley field trials were submitted with Accession No. 072845. The submitted storage stability data do not support the residue data because the samples were either stored and shipped unfrozen or under unspecified conditions. Residue data from 10 barley trials were submitted with Accession No. 263751. RCB concludes that the storage stability data support the residue data from 6 of these trials [conducted in ND, CA (3), MT, and OR; treatment rates, 0.5-1.25 oz. a.i./A; PHI's, 45-108 days].

RCB concludes that the field residue data on barley, supported by storage stability data, satisfy the geographical distribution needed for barley grain. The states in which trials were conducted, plus the contiguous states, produce about 85% of the nation's barley. However, these residue data on barley reflect PHI's of 49-108 days, whereas the proposed use implies a possible PHI of 36 days. Therefore, residue data on barley (or wheat) reflecting a 36 day PHI are needed. Since the nature of the residue is not yet adequately understood, RCB is unable to determine the appropriateness of the proposed tolerance on barley. Should other residues of toxicological concern besides parent be identified, residue data reflecting analyses for these residues may also be required.

At this time RCB will not require a processing study. Radioactive residues in mature wheat grain 63 days after a 2 X application rate ranged from 0.013 to 0.038 ppm. However, after the nature of the residue in grain has been adequately delineated, processing studies may be required on grain treated at exaggerated rates.

10/ The petitioner will need to specify that only one application per season is permitted on wheat in a revised Section B/label.

The label should stipulate that only EPA-approved surfactants be used.

Wheat is commonly foraged by cattle. (Dr. A.M. Decker, Professor of Forage Crops, University of Maryland, Dr. D.J. Schingoethe, Professor of Dairy Nutrition, South Dakota State University). The proposed use would permit grazing for 4-6 weeks, after which the cattle would have to be removed anyway, in order to avoid damage to the seed head. The crop could then be treated with Harmony® in the time interval remaining before boot stage (Dr. Decker; Dr. E. Krencer, Oklahoma State University). Therefore, in this particular case, which involves treatment in the interval between the 2-leaf stage but before boot stage, RCB concludes that the foraging restriction is practical.

Although the current Pesticide Assessment Guidelines, Subdivision O, list wheat straw as being under grower control, this statement is an error, which will be corrected in the forthcoming Pesticide Assessment Guidelines.

It appears that about 35% of the respondents in the straw usage survey submitted by the petitioner either sold straw, used their own straw for feed and/or bedding, or did both. Dr. D.J. Schingoethe, Professor of Dairy Nutrition, South Dakota State University, said that the use of straw for bedding is so common, that it would not be realistic to expect farmers to obey this restriction. The farmers would have to dispose of treated straw and then buy straw from someone else. Both Dr. Schingoethe and Dr. Decker (Professor Forage Crops, University of Maryland) said that cattle bedded in straw would eat some of the bedding and therefore nutritionists conducting experiments do not bed cattle in straw for this reason. The amount of straw consumed by the cattle would depend upon the quality of the hay in their diet, the amount of fiber in their diet, and the quality of the straw. Dr. Decker said that in times of drought more straw would be sold; during a severe drought such as this year's drought in MD, farmers might sell treated straw, despite a label restriction against using treated straw for feed or bedding. Considering the size of the US wheat crop and the factors discussed above, RCB concludes that a label prohibiting the use of treated straw for feed or bedding is not practical.

Since the label restriction against using straw for bedding or feed is not considered practical, the petitioner will need to submit a revised Section B/label which does not contain this restriction. The petitioner will also need to submit a revised Section F which contains an appropriate tolerance for residues of DPX-M6316 on wheat straw.

RCB concludes that residue levels resulting from aerial treatment of wheat are essentially the same as from ground equipment application.

RCB needs to know how long the wheat grain and straw samples described in Accession No. 072845 were stored before analysis. The storage period extends from harvest to analysis. If samples were not immediately frozen after sampling, the petitioner will need to inform RCB when these samples were frozen so that RCB can determine if the residue data are valid and/or submit appropriate storage stability data.

Residue data from 5 wheat trials were submitted with Accession No. 263751. RCB concludes that the storage stability data support the residue data in the wheat trials from WA, ID, CA, and CO (3 trials on winter wheat and one on spring wheat; treatment rates, 0.5-1.5 oz. a.i./A; PHI's, 62-99 days). Since most of the wheat grain and straw residue data cannot be validated at this time, RCB will need additional wheat residue data (on grain and straw) from states in the Midwest (e.g., KS, IL, MN), Southeast (e.g., FL, GA), Southwest (e.g., OK, TX), and Northeast (e.g., NY, NJ, DE), if the petitioner can't support the previously submitted wheat residue data. Additional residue data from the West would also be needed. Although the residue data from WA, ID, CA, and CO were judged to be valid, only one trial (WA) was conducted on spring wheat and straw. Some of the required residue data should reflect the shortest practical PHI (about 36 days).

34

Since the nature of the residue is not yet adequately understood, RCB is unable to determine the appropriateness of the proposed tolerance on wheat. Should other residues of toxicological concern besides parent be identified, residue data reflecting analyses for these residues may also be required.

At this time RCB will not require a processing study. Radioactive residues in mature wheat grain 63 days after a 2 X application rate ranged from 0.013 to 0.038 ppm. However, after the nature of the residue in grain has been adequately delineated, processing studies may be required on grain treated at exaggerated rates.

11/ RCB has concluded that the restrictions against foraging wheat and barley and using barley straw for feed and bedding are practical but that a wheat straw use restriction is not practical. At this time RCB is unable to determine whether ruminant and poultry feeding studies and tolerances for meat, milk, poultry, and eggs are needed. After the nature of the residue has been delineated in straw and grain, and valid residue data on wheat straw and wheat and barley grain for all residues of concern have been submitted, RCB will consider the question of secondary residues arising in meat, milk, poultry, and eggs from the proposed use on wheat and barley.