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

JAN 10 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP#3F4174. Chlorethoxyfos (DPX-43898) in/on Corn. Evaluation of Analytical Method and Residue Data. (MRID #'s 412906-01 through -16, 417368-01 through -11, -13 through 19, 425592-01 through -06, -35, -36, -37, CBTS # 11060, Barcode D185835.)

FROM: Jerry B. Stokes, Chemist
Chemistry Branch I/Tolerance Support
Health Effects Division (7509C)

Jerry B. Stokes

THRU: Debra Edwards, Ph.D., Chief
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Debra Edwards
1/7/94

TO: Dennis Edwards/Rita Kumar, PM# 12
Insecticide-Rodenticide Branch
Registration Division (7505C)

and

Albin Kocialski
Chemical Coordination Branch
Health Effects Division (7509C)

E. I. du Pont de Nemours & Company requests 0.01 ppm permanent tolerances for their insecticide product Fortress 5G containing phosphorothioic acid O,O-diethyl-O-1,2,2,2-tetrachloroethyl ester (DPX-43898) as the active ingredient in/on corn grain; field corn forage, fodder, and silage; popcorn forage and fodder; sweet corn (kernel and cob with husk removed), forage, and fodder. No tolerances are proposed for corn processed commodities. No tolerances are proposed for livestock meat, fat, meat byproducts, milk, or eggs. The acceptable ANSI name is **chlorethoxyfos.**

CBTS previously commented on an EUP which was granted in 1990 (See memos of 2/10/89, G. Otakie, and 1/30/90, L. C. Cheng). Temporary tolerances, which expired on 1/16/93, were established

for chlorethoxyfos in/on field corn fodder, forage, and grain at 0.2 ppm. The proposed application rate is 1/2 that used in the EUP.

Conclusions

1a. The previous CBTS review (See memo of 2/10/89, G. Otakie) concluded that the product chemistry data of chlorethoxyfos are adequate to support an EUP request only. The product chemistry data available are adequate to support this petition only since the commercial-scale production of the TGAI has not begun.

1b. Since the proposed products are yet not in commercial production, the registrant must submit a deferral request of data submission to include the following:

i) A statement that the applicant has no facilities for producing the product in commercial quantities and does not intend to construct such facilities until the product is registered;

ii) A schedule for submitting all data required by 40 CFR 158.150 through 158.190 based upon the commercially produced material;

iii) A discussion of the formation of impurities in the commercially-produced vs. the pilot-scale, and a discussion of changes in the certified limits for the product which might result from differences between the pilot scale and commercial production processes.

2. CBTS considers the metabolism of chlorethoxyfos in corn (as a result of soil application) is adequately understood. The residue to be regulated will be determined by the HED Metabolism Committee.

3. Metabolites of chlorethoxyfos in the goat via an orally administered route include carbon dioxide, oxalic acid, serine, glycine, and lactose, with insignificant levels of undegraded parent and its oxygen analog. The metabolism in the goat is adequately understood. However, for the proposed use on corn, no tolerances are required for residues in animal commodities.

4a. The GC/EC method (AMR-1507-89) has passed a successful validation in the EPA laboratory in Beltsville, MD. An additional GC/EC method (AMR-1546-89) contained in this submission, that is very similar to the above method, i.e., only minor changes in extraction solvents and extraction volumes, has passed a successful validation from two

from two independent laboratories. Thus adequate methodology is available for analysis and enforcement of chlorethoxyfos residues. Although the EPA laboratory did not previously test the method on the oxygen analog, the petitioner has provided a method that should be capable of measuring the oxygen analog. CBTS will submit this method to the EPA laboratory for validation of the oxygen analog.

4b. Chlorethoxyfos has been tested through the FDA Multiresidue protocols A - E. Chloethoxyfos residues are recovered by Protocols C, D, and E, but not by Protocols A and B. The data will be forwarded to FDA for evaluation. The petitioner also submitted data for trichloroacetic acid, a plant and animal metabolite of chlorethoxyfos. TOX previously commented that trichloroacetic acid is not of toxicological concern and thus it will not be included in the tolerance expression, pending concurrence by the HED Metabolism Committee. Although this data for trichloroacetic acid may not be required, it will also be sent to FDA for their records.

5a. Based upon the above residue data, the proposed use on corn and the proposed tolerances are adequately supported. Residues of chlorethoxyfos and its oxygen analog in general are not expected to be detectable (<0.01 ppm, limit of quantitation for each) in corn grain, corn forage and stover as a result of the proposed use (by soil application). Likewise residues of TCA are not expected to be detectable (<0.01 ppm) in corn grain, and no greater than 0.04 ppm in corn forage and stover. However a revised Section F needs to be submitted expressed as the following:

field corn grain	0.01 ppm
field corn forage	0.01 ppm
field corn fodder	0.01 ppm
popcorn grain	0.01 ppm
popcorn fodder	0.01 ppm
sweet corn (K + CWHR)	0.01 ppm
sweet corn forage	0.01 ppm

Note: Field corn grain tolerance covers residues in sweet corn grain (dry), providing the use patterns are the same.

The need for tolerances of other residues, i.e, oxygen analog or TCA, will be determined by the HED Metabolism Committee.

5b. A confined rotational crop study was previously reviewed by EFGWB (See memo 2/21/90, E Regelman). This study was not adeqaute, and additional information was requested. The registrant also stated in his study (MRID#412906-20, AMR-1180-88) that a field rotational crop study was planned, with analytes chloroethoxyfos and trichloracetic acid (TCA). CBTS requests that the field rotation crop study be submitted for review to assess the proposed 30-day plant back and the need

for any rotational crop tolerances for chlorethoxyfos or TCA residues.

6. On the basis of the results from both wet and dry corn processing studies, CBTS concludes that no food/feed additive tolerances are required.

7. Based upon no chlorethoxyfos residues measured in field corn, popcorn, and sweet corn commodities (<0.01 ppm) and the results of the goat metabolism study, finite transfer of chlorethoxyfos residues is not expected to meat, fat, meat byproducts, milk, or eggs. Therefore, no tolerances on meat, fat, meat byproducts, milk, or eggs are necessary.

8. There are no CODEX, Canadian, or Mexican limits established for chlorethoxyfos. Therefore, no compatibility problem exists.

Recommendation

CBTS cannot recommended for the establishment of 0.01 ppm chlorethoxyfos tolerances in/on corn grain; field corn forage, fodder, and silage; popcorn forage and fodder; sweet corn (kernel and cob with husk removed), forage, and fodder because of conclusions 1b, 2, 5a, and 5b.

The petitioner is requested to provide the deferral request for product chemistry data reflecting commercial scale production. This deferral request must include the following:

i) A statement that the applicant has no facilities for producing the product in commercial quantities and does not intend to construct such facilities until the product is registered;

ii) A schedule for submitting all data required by 40 CFR 158.150 through 158.190 based upon the commercially produced material;

iii) A discussion of the formation of impurities in the commercially-produced vs. the pilot-scale, and a discussion of changes in the certified limits for the product which might result from differences between the pilot scale and commercial production processes.

The petitioner must submit a revised Section F to express the following tolerances:

field corn grain	0.01 ppm
field corn forage	0.01 ppm
field corn fodder	0.01 ppm
popcorn grain	0.01 ppm

popcorn fodder	0.01 ppm
sweet corn (K + CWHR)	0.01 ppm
sweet corn forage	0.01 ppm

CBTS must await the determination of the chlorethoxyfos residues to be regulated by the HED Metabolism Committee, and must review the field rotational crop study.

Detailed Considerations

Manufacture and Formulation

A previous CBTS review of chlorethoxyfos product chemistry data concluded that the data are adequate to support an EUP request only Additional product chemistry data were needed to support a Section 3 registration. CBTS also suggested that a deferral request of these data be requested by the petitioner since the proposed products were not yet in commercial production. (See memo of 2/10/89, G. Otakie).

The petitioner has submitted registrant product chemistry data, some that discusses the envisioned commercial process, and other data that were gathered from pilot-scale productions. These data are discussed here and in the Confidential Appendix.

Based upon the submission of product chemistry data to date, apparently it is the intent of the petitioner to pursue the Section 3 registration prior to full operation of a commercial production. Therefore the petitioner must submit a deferral request of data submission in accordance with the Pesticide Assessment Guidelines Subdivision D - Product Chemistry, October 1982 (see pages 42, 43, 49, 50, and 51) to include the following:

i) A statement that the applicant has no facilities for producing the product in commercial quantities and does not intend to construct such facilities until the product is registered;

ii) A schedule for submitting all data required by 40 CFR 158.150 through 158.190 based upon the commercially produced material;

iii) A discussion of the formation of impurities in the commercially-produced vs. the pilot-scale, and a discussion of changes in the certified limits for the product which might result from differences between the pilot scale and commercial production processes.

The following discussion is based upon the TGAI which has been synthesized in pilot-scale production, and the envisioned commercial process.

61-1 - Product Identity and Disclosure of Ingredients

O,O-Diethyl-O-(1,2,2,2-tetrachloroethyl)phosphorothioate is the CAS name of the active ingredient in the TGAI (technical grade active ingredient) and the EP (end product) formulation FORTRESS®5G, both produced by DuPont.

THe ANSI name is chlorethoxyfos.

Empirical Formula: $C_6H_{11}Cl_4O_3PS$

Molecular Weight: 336.0

CAS Registry No.: 54593-83-8

61-2 - Description of Beginning Materials and Manufacturing Process (MRID#417368-01)

A description of the beginning materials and manufacturing processes for the TGAI and the EP formulation FORTRESS®5G is described in the Confidential Appendix. A description and flow chart taken directly from the submission is given illustrating the manufacturing process for the TGAI. The petitioner states that the manufacturing process and starting materials for TGAI are not in production on a commercial scale, and therefore subject to change. The beginning materials and their manufacturers required for the tentative commercial process are provided, but are subject to change since the full-scale production has not yet been begun. A description of the formulation process for the manufacture of Fortress®5G is also contained in the Confidential Appendix and also may need revision for a full-scale production.

The data on the beginning materials and tentative manufacturing processes are acceptable **for this petition only.** If a Section 3 registration is established, then in order to maintain this registration the petitioner must provide the Agency the following **information on the commercial-scale production process** for the TGAI and the EP within a reasonable period after the commercial process is operating.

Beginning Materials

1. The name and address of the manufacturers or suppliers of each beginning material.

2. Copies of all available technical specifications, data sheets, and other documents by which the composition, properties, or toxicity are described.

3. All other information concerning the qualitative and quantitative composition of the beginning materials.

Manufacturing Process

1. Statements of whether the steps in the process are batch and/or continuous.

2. The amounts (e.g., weight) of the beginning materials and the order in which they are added.

3. An equipment flow chart together with a complete description of the equipment used to produce and purify the product (e.g., reaction vessels, mixers, distillation and purification equipment, etc.).

4. A complete description of the physical conditions and control parameters (e.g., temperature, pressure, humidity, mixer RPM, etc.) must be provided for each step of the process, together with a discussion of the acceptable parameter range and influence on the purity and the relative amounts and/or identity of impurities, variation of these control parameters can cause.

5. A statement of the intended chemical reactions (if any) together with a flow chart with the chemical equations for each chemical reaction occurring at each step of the process.

6. The approximate time (e.g., duration) of each step in the production process.

7. A discussion of the measures taken to assure the quality of the final product.

61-3 - Discussion of Formation of Impurities (MRID#425592-01)

Refer to the Confidential Appendix for a discussion of the formation of impurities for the TGAI.

The impurities present in the EP formulation reflect the composition of the TGAI and the intentionally added inert ingredients which are combined to produce this product. Based upon the proposed conditions, and the chemical properties of the ingredients, there is no reasonable expectation of chemical reactions occurring between any of the ingredients, or any post reactions between the a.i. and any other constituent of the product or its packaging.

The data in Confidential Appendix are sufficient to support this petition only. However, to maintain a Section 3 registration the petitioner must **comparatively discuss** the commercial-scale production process for the TGAI with the data supplied for the pilot-scale processes once the commercial process has been developed. Likewise, the petitioner must discuss if this final commercial-scale will affect any impurities in the proposed EP

formulation FORTRESS®5G. The petitioner must provide the following within a reasonable period after the commercial-scale process is operating:

1. Each impurity which may be present in the product at a level equal to or greater than 0.1 percent (1000 ppm) based on knowledge of:

   a. The composition of each beginning material and intentionally added inert ingredient;

   b. Impurities which are known to be present from other information;

   c. The substances which result from the intended reactions of the manufacturing process;

   d. Degradation or postproduction reactions of any of the product's ingredients;

   e. Contamination of the product from earlier use of the same production equipment to produce other substances or contamination from packaging materials;

   and

   f. Process control, purification, and quality control procedures used.

2. Any other impurity which was found to be present in any analysis of the commercial-scale product, but not present in the pilot-scale product.

62-1 - Preliminary Analysis (MRID#425592-02)

TGAI: chlorethoxyfos

In this submission the petitioner has supplied analyses from two pilot-scale productions, since the commercial manufacturing process for the TGAI has not begun. The petitioner states that these two samples are actually composited batches from smaller runs: sample #AG0226-139 and sample #AG0312-70-2. The first sample was produced at AG Semiworks during the period of November 1987 through January 1988. The number of batches combined to form the composited sample is not defined. The only comment is that minor variations in the processes, such as distillation techniques, were employed. The second sample was produced at the Mobile Plant Facility, August through September 1989. Three batches were composited. The composited samples were compared by GC/MS analysis, and showed similar percentages of the TGAI [a.i., 91.14%; mass balance, 98.87% (#AG0226-139); a.i., 89.56%; mass balance, 99.33% (#AG0312-70-2) and only minor differences in percentages of some impurities. No

impurity was found in one and not the other. The certified limits based on the results of teh abtch analyses are discussed in the Confidential Appendix.

The preliminary analyses of these batches contained in Confidential Appendix are acceptable for this petition only. If a Section 3 registration is established, then in order to maintain this registration, the petitioner must provide the following information within a reasonable period after the commercial-scale production has commenced:

1. Data on the size of each production run (i.e., pounds or gallons of product produced) must be provided.

2. Analysis of five samples representing five different production runs of the final commercial-scale production process for the TGAI and each impurity. If the product is produced by a batch process, each sample should be taken from a different batch of the product and if the product is produced by a continuous process, samples should be taken at intervals sufficiently spaced to provide data on any variation in product content.

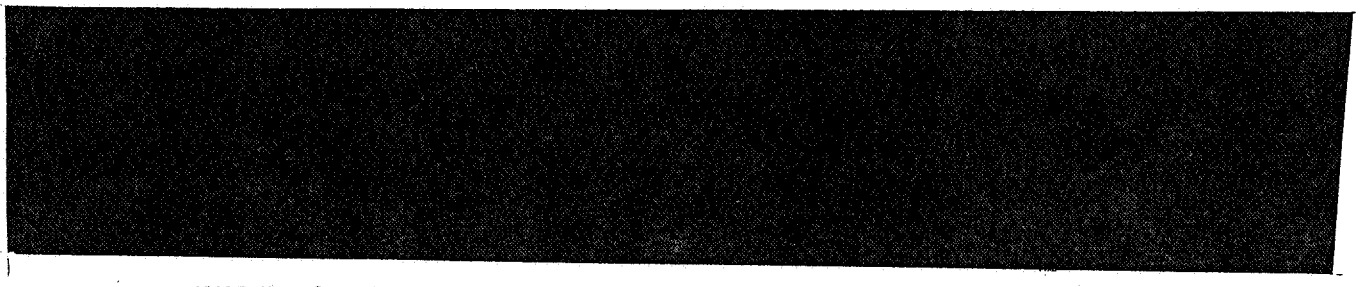
EP formulation: FORTRESS®5G

Analyses of batches of the formulation FORTRESS®5G are discussed in the Confidential Appendix.

62-2 - Certification of Limits (MRID#425592-02)

The petitioner has submitted two CSF's (EPA Form 8570-4), which include certified limits for the proposed TGAI and the EP (DuPont FORTRESS®5G). (See the Confidential Appendix). The petitioner also discussed how these certified limits were established. However, the petitioner notes that since the commercial manufacturing process is not in the production stage, the batches from such a process could be slightly different from the pilot-scale and the certified limits may be subject to change. Therefore, If a Section 3 registration is granted prior to the commercial process being placed in production, then the proposed certified limits for the TGAI and the EP must be corrected, if necessary, in order to maintain such a registration within a reasonable period after the commercial-scale production has commenced.

62-3- Analytical Methods to Verify Certified Limits



QUALITY CONTROL PROCEDURE INFORMATION IS NOT INCLUDED

[redacted]

63 - Physical and Chemical Characteristics (MRID#417368-02)

Summarized below are the physicochemical properties of the technical grade or pure form of chlorethoxyfos as furnished by the petitioner. (MRID#417368-02). Also included are data for the EP formulation, FORTRESS®5G

Guidelines Reference No. (40 CFR 158.120)	Description
63-2 - Color	TGAI: Light brown to dark brown EP: Brown
63-3 - Physical State	TGAI: Liquid EP: Solid
63-4 - Odor	TGAI: Strong, objectionable odor characteristic of sulfur-containing compounds EP: Typical of organophosphorus compounds
63-5 - Boiling Point	TGAI: 105 to 115 C at 0.8 mm Hg
63-7 - Density	TGAI: 1.41 g/mL at 20 C EP: 42 to 45 lb/ft^3
63-8 - Solubility	PAI: 2.09 ppm in water at 25 C PAI: At least 20 g per 100 mL at 20 C in: acetone, acetonitrile, dichloromethane, ethyl acetate, hexane, methanol, or xylene
63-9 - Vapor Pressure	PAI: 1.7×10^{-3} mm Hg at 25 C
63-10 - Dissociation Constant	N/A, the structure of chlorethoxyfos does not

	allow for any significant acid or base characteristics
63-11 - Octanol/Water Partition Coefficient	PAI: 3.9×10^{-4} at 25 C
63-12 - pH	TGAI: 3.52 EP: 5.38 (1% dispersion in water)
63-13 - Stability	TGAI: Stable at 55 C for 2 weeks; Stable at 55 C for 2 weeks in presence of 316 stainless steel or 504 ppm Fe_2O_3. Stable for at least 18 1/2 months at room temperature.
63-14 - Oxidizing or Reducing Action	EP: Does not contain oxidizing or reducing agents
63-15 - Flammability	EP: Flashpoint over 230 F
63-16 - Explodability	EP: Not explosive
63-17 - Storage Stability	EP: Stable
63-18 - Viscosity	TGAI: 9.0 centipoise at 25 C EP: Does not apply
63-19 - Miscibility	EP: Does not apply
63-20 - Corrosion Characteristics	EP: Not corrosive, to packaging material
63-21 - Dielectric Breakdown Voltage	EP: This material is not a liquid and is not intended for use in and around electrical equipment

For the purposes of this petition only, the above physical and chemical characteristics on the TGAI and the PAI are adequate. However, if a Section 3 registration is established , then to maintain this registration the petitioner must provide acceptable data on the physical and chemical characteristics for the TGAI

prepared with the commercial-scale process (with the exception of data on the PAI for 63-8 - Solubility, 63-9 - Vapor Pressure, 63-10 - Dissociation Constant, and 63-I1 - Octanol/Water Partition Coefficient). These data must be provided within a reasonable period after the commercial-scale production has commenced.

64-1 - Submittal of Samples

If not alredy completed, the petitioner must submit samples of the TGAI (200 g) and PAI (5 g) along with the analytical method for the a.i. to the following address:

Active Ingredients Program
Attn: Head, Analytical Chemistry Section
Analytical Chemistry Branch
Benefits and Economic Analysis Division
Office of Pesticide Programs
Environmental Protection Agency
Building 306, BARC East
Beltsville, MD 20705

Proposed Use

Chlorethoxyfos is a soil insecticide that is applied at planting time into the planting furrow or as a 6-8 inch band over the planting row at the rate of 0.32 oz a.i./1000 feet of row (.27 to 0.35 lb a.i./A based upon row spacing of 40 to 30 inches respectively). Rotate to corn at anytime. All other crops may be planted 30 days after application. No PHI is proposed.

Nature of the Residue in Corn (MRID # 412906-01)

No additional data have been submitted in this petition. Previously, a 14C-chlorethoxyfos corn metabolism study was reviewed by CBTS. Carbon-14 labeled at the trichloro carbon of chlorethoxyfos with a specific activity of 4 mCi/mg (8770 dpm/ug) was used; the radiochemical purity was ca 99%.

Corn plants were treated at 2.4 lb ai/A or approximately 10 times the proposed field rate in order to obtain sufficient quantities of degradation products for characterization and identification. Plants were sampled 30, 60, 119 and 151 days after treatment. The day 119 corn plants represent mid dough stage. The day 151 harvest represents plants at maturity for grain harvest. The plant tissue analyzed consisted of leaves from day 30 and day 60 and all aerial parts of the plant except grain from the day 119 and day 151 samples.

Distribution of Extractable Radioactivity in Corn Grain and Foliage

Days	Sample	Extractable (% of TTR)
30	leaves	92.8
60	leaves	87.5
119	grain	99.9
	aerial plant minus grain	89.2
151	grain	94.2
	aerial plant minus grain	87.1

Radioactivity in plant tissues and grain was analyzed and/or confirmed by GC, TLC, HPLC and/or GC/MS. The major components identified included trichloroacetic acid (TCA), D-glucose, and oxalate; neither the parent compound nor the oxygen analog was detected in any fraction.

Radioactivity in Corn Plant Tissues and Corn Grain					
Days	Sample	PPM	%TCA	Glucose	Oxalate
30	leaves	0.71	84	NA	NA
60	leaves	1.6	78.7	NA	NA
119	grain	0.33	14.2	74	NA
	aerial plant minus grain	1.08	51.6	3.3	17.8
151	grain	0.32	4.5	73.4	NA
	aerial plant minus grain	0.65	19.9	12.4	12.4

NA: not analyzed or not available

The registrant postulated that chlorethoxyfos is being converted to diethyl thiophosphate and trichloroacetate in the soil. TCA is being taken up by the plant and metabolized to oxalate and carbon dioxide. The carbon dioxide is being reincorporated into starch/ glucose.

In a 1988 meeting with du Pont pertaining to an EUP request for chlorethoxyfos, TOX indicated that they were not concerned with TCA at this time (See memo of conference, 9/21/88, R Loranger). The

HED Metabolism Committee will be asked to concur on this conclusion.

For the purpose of this tolerance petition, we consider the metabolism of chlorethoxyfos in corn (as a result of soil application) to be adequately understood. The residue to be regulated will be determined by the HED Metabolism Committee.

CBTS had commented previously "For full registration, additional supporting data such as spectra for the identification of glucose and analysis procedure and results for oxalate may need to be submitted. Furthermore, additional metabolism studies may be necessary should a different mode of application (e.g. foliar) be desired in the future." (See memo of 1/30/90, L. Cheng). Based upon the additional data and petition comments, CBTS does not need the additional data for glucose and oxalate. However, any future applications which may involve direct plant applications will require additional metabolism data.

Nature of the Residue in Animals (MRID#'s 412906-02, 417368-04)

No additional data are submitted. The petitioner has submitted additional comments to support the previous goat metabolism. (MRID# 417368-04)

CBTS had stated for the EUP,

> "In summary, metabolites of DPX-43898 in the goat via orally administered route include carbon dioxide, oxalic acid, serine, glycine, and lactose with insignificant levels of undegraded parent and its oxygen analog.
>
> DEB concludes that for the purpose of this temporary tolerance petition the metabolism of DPX-43898 in the goat is adequately understood, and the residue to be regulated is the parent compound.
>
> For full registration, a higher accountability level of the administered dose (>70%) in the goat study and additional supporting raw data may be required. Furthermore, since the major component found in corn grain, forage and fodder was TCA (and very little parent), a study using TCA may be necessary depending on the Toxicology Branch's assessment of TCA." (See memo of 1/30/90, L. Cheng).

In the previous study (MRID# 412906-02) three 49-50 Kg lactating goats were employed. One goat was dosed at 0.5 ppm carbon-14 chlorethoxyfos (labeled at the trichloro carbon; specific activity of 58.4 uCi/mg; radiochemical purity of 98-99%) for 5 consecutive days while another one was dosed at 10 ppm for 3 consecutive days for metabolite characterization purposes. One animal was used as an untreated control.

The dose was administered after the morning milking. Two milk samples were collected each day. All goats were sacrificed 24 hours after the last dose. All samples (liver, kidney, muscle, fat, milk, urine and feces) were frozen immediately and shipped to the analytical laboratories.

Radioactive carbon dioxide was collected for one day from the 10 ppm dose only. The dosing material was found to be stable under the study conditions. Unused capsules containing the active ingredient had 96.5-99.3% radiochemical purity.

Distribution of extractable activity in various tissues, milk, etc.

Distribution of Extractable 14C Activity in Tissue, Milk, and Body Fluids				
Matrix	Low Dose		High Dose	
	ppm	% total	ppm	% total
liver	0.184	3.9	3,83	5.7
kidney	0.051	0.2	0.776	0.2
muscle	0.01	2.6	0.165	3.6
fat	≤0.002		0.02	0.3
urine		21.7		19.2
feces		10.7		13.2
CO_2				15 (day 1)
Total		39.1		57.2

Tissues were extracted with aqueous methanol, centrifuged, and filtered. Both the filtrate and the residue were further extracted with either ether or hexane under acidic or neutral conditions (if applicable). Hydrolysis under enzymatic conditions were performed on insoluble residues or precipitated pellets.

In milk the 0.5 ppm dose gave 0.012 to 0.054 ppm (6.7% of total dose), while the 10.0 ppm dose gave 0.17 to 0.81 ppm (5.5% of total dose). Fractionation of milk samples resulted in 3 fractions: milk fat (4.5% of total activity in milk), milk supernatant (56.5%) and milk proteins (39%). The fat fraction was not further analyzed. The major fraction (supernatant) was analyzed by HPLC to show 3 significant components (M1, 46.2%; M2, 5.1%; and M3, 2.2%). M1 had the same retention time as lactose, and upon beta-galactosidase treatment resulted in a component that had the same retention time of galactose and glucose (not resolved under the HPLC conditions). Parent was not found in milk supernatant fraction. The protein fraction after TFA precipitation and derivatization with

phenylisothiocyanate (PITC) yielded HPLC retention times same as those of serine PITC (13.9%) and glycine PITC (8.2%) derivatives. The remaining activity was not further characterized.

Insignificant amounts (<0.1% of tissue total or <0.01 ppm parent equivalent) of the parent or its oxygen analog were detected in tissues. Components identified in various tissues (liver, kidney, and muscle) showed incorporation of the TCA in the serine and glycine in a variety of percentages ranging from 0.3 to 38. The remaining amounts of radioactivity (1.5 to 17%) consisted of possibly 4 other components, but were not readily available for identification.

Activities in urine were identified to include serine, glycine (both confirmed by HPLC and TLC cochromatography with the respective PITC derivative), oxalic acid (confirmed by HPLC cochromatography with its dimethyl derivative), and glycine conjugates of benzoic acid and phenylacetic acid; and in feces appeared to consist of predominantly bile pigments and <0.7% TCA. Mass spectra of hippuric acid methyl ester and phenaceturic acid methyl ester were submitted. Spectra for other derivatives (e.g. PITC of serine and glycine) were not submitted.

In this submission, the petitioner has stated that the following:

"The metabolism of DPX-43898 in the goat was extensive. No significant residues of parent or its oxon analog were found. Essentially all metabolites detected were the result of reincorporation of radioactivity into natural products. The major metabolite was carbon dioxide. It is likely that the amount of labeled carbon dioxide evolved was significantly underestimated for two reasons. First, measurement of evolution of labeled carbon dioxide was conducted for only the first day, and a significant amount of labeled CO_2 was still being expired 24 hours after the first dose. It is expected that a significant amount of the first dose would also have been expired on the second and the third day after dosing, based on a similar situation observed in the rat metabolism study. In this study male and female rats were given a single dose of 14C-DPX-43898 and expired CO_2 was monitored for 7 days after dosing. Carbon dioxide was a significant metabolite averaging 10-11% of the total dose. Of this amount, only 50-60% of the radioactivity was expired within the first 24 hours. The remainder was expired 2-7 days after dosing.

If one assumes that evolution of radiolabeled carbon dioxide in the goat follows a similar pattern as to the rat, then a significant

amount of the first dose would have been accounted for if CO_2 collection had continued and recovered radioactivity would have been greater than 70%.

Metabolism of DPX-43898 was more extensive in the goat than in the rat (i.e., essentially all of DPX-43898 was converted to carbon dioxide and biosynthetic intermediates like glycine and serine that get incorporated into proteins, etc., and take longer to clear from the animal than chlorinated metabolites that represented well over half of the administered dose in the rat). It is therefore likely that an even higher percentage of the first day's dose would have been evolved as 14C-carbon dioxide from the goat during the second and third days compared to the evolution of 14C-carbon dioxide on the second and third days in the rat.

The second reason for the underestimation of evolved 14C-carbon dioxide is that collection of carbon dioxide was done at selected times for only three-minute intervals and only dealt with elimination via nose and mouth. Ruminants are well-known to eruct (belch) considerable amounts of carbon dioxide and methane normally. It is likely that under stress conditions used (gas mask for three-minute collection intervals), the animal did not eruct thereby significantly lowering the estimate of radiolabel in carbon dioxide. In addition, rectal elimination of gases was not measured. Du Pont believes that complete recovery of radioactivity from a goat evolving major quantities of labeled carbon dioxide is impractical and not warranted.

In other goat metabolism studies conducted for Du Pont by the same contract laboratory, where carbon dioxide was not a significant product, material balances of 97 and 98% were obtained, demonstrating that the experimental design of the in-life phase of the study was adequate. For these reasons, Du Pont believes that an adequate recovery of radioactivity was obtained and that the metabolism of DPX-43898 in the goat is extensive and sufficiently understood for regulatory purposes." (Du Pont Report No. AMR-962-87)

CBTS has reviewed the metabolism again, and has determined that the petitioner conclusions are adequate. Therefore, CBTS now considers the goat metabolism study sufficient to support the proposed Section 3 registration. No additional ruminant metabolism data is needed.

Analytical Method (MRID # 412906-03)

In the previous CBTS review for the EUP, several methods were discussed. One residue method for determining chlorethoxyfos and its oxygen analog was a capillary GC method equipped with a mass spectrometric detector with a limit of quantitation of 0.01 ppm. (Du Pont Study No. AMR-1195-88). A capillary GC/EC method (AMR-1253-88, MRID# 412906-14) was described for the analysis of TCA with a limit of quantitation of 0.01 ppm. A capillary GC/EC analytical procedure for the determination of chlorethoxyfos in fish tissues is also described with a limit of quantitation of 0.02 ppm. (AMR-1441-89, MRID# 412906-07). Two similar GC/EC methods

for determining residues of chlorethoxyfos and its oxygen analog in soil, and in sediment and top soil, with limits of quantitation of 0.01 and 0.02 ppm were also submitted. (AMR-1194-88, MRID# 412906-03, and AMR-1409-89, MRID# 412906-06, respectively).

CBTS had requested the Analytical Chemistry Branch, BEAD, in Beltsville, MD to evaluate the petitioner's Method #AMR-1507-89 on corn grain, forage, and fodder at fortification levels of 0.02 and 0.05 ppm. (See memo of 2/14/90, L. Cheng). This method involved a extraction procedure similar to the GC/MSD method (AMR-1195-88). However instead of a charcoal column cleanup, disposable Si column were eluted with ethyl acetate: hexane mixtures. The eluting fractions were analyzed on GC equipped with an electron capture detection. The method can be used to determine both chlorethoxyfos and its oxon analog. A successful validation was completed with good recoveries for both fortification levels of chlorethoxyfos only: corn grain, 78-93%; corn forage, 86-97%; corn fodder, 73-85%. (The oxon analog was not run since it would not be included in the tolerance expression.) There were no major or minor modifications to the method. CBTS concluded that the GC/EC method (#AMR-1507-89) was suitable for residue analysis and enforcement of chlorethoxyfos. (See memo of 9/14/90, L. Cheng). The limit of quantitation is 0.01 ppm. Although the EPA laboratory did not test the method on the oxygen analog, the petitioner has provided a method that should be capable of measuring the oxygen analog. CBTS will submit this method to the EPA laboratory for validation of the oxygen analog.

In this submission, the petitioner has provided Method #AMR-1546-89 (MRID#417368-08), in addition to validation of this method for parent chlorethoxyfos from two independent laboratories [MRID#417368-09, AMR-1625-90 (corn grain, green forage, and dry fodder/stover, conducted by McKenzie Laboratories, Phoenix, AZ), and MRID#417368-10, AMR-1732-90 (corn dry fodder/stover, conducted by Minnesota Valley Testing Laboratories, New Ulm, MN]. CBTS has reviewed this method and has found it to be very similar to AMR-1507-89, except for some minor solvent changes, and solvent elution volumes. The independent laboratory made only several, very minor changes in the method.

This method is also adequate for enforcement of chlorethoxyfos residues in corn. However, since AMR-1507-89 passed the EPA validation, this method will be forwarded to FDA for inclusion into PAM II.

The petitioner has submitted data in support of multiresidue analyses according to the FDA multiresidue methodology. Chlorethoxyfos has been tested through the FDA Multiresidue protocols A - E (MRID#417368-14). Chloethoxyfos residues are recovered by Protocols C, D, and E, but not by Protocols A and B. The data will be forwarded to FDA for evaluation. The petitioner also submitted data for trichloroacetic acid, a plant an animal metabolite of chlorethoxyfos. TOX previously commented that trichloroacetic acid is not of toxicological concern and thus it

will not be included in the tolerance expression, pending concurrence by the HED Metabolism Committee. Although this data for trichloroacetic acid may not be requirement, it will also be sent to FDA for their records.

Storage stability

The petitioner had previous submitted storage stability studies for the parent, chlorethoxyfos, its oxygen analog, and trichloroacetic acid in corn grain, corn green forage, and mature fodder. Samples were initially spiked with 0.1 ppm chlorethoxyfos and stored under freezer conditions (-20 C) for 24 months. Recoveries from corn grain ranged 63-100%; forage, 83-130; and fodder, 70-145%. (MRID#425592-35)

Samples were initially spiked with 0.1 ppm IN-34158 (oxygen analog of chlorethoxyfos) and stored under freezer conditions (-20 C) for 24 months. Recoveries from corn grain ranged 68-91%; forage, 67-129%; and fodder, 65-126%. (MRID#425592-36)

Samples were initially spiked with 0.1 ppm trichloroacetic acid and stored under freezer conditions (-20 C) for 24 months. Recoveries from corn grain ranged 64-86%; forage, 68-109%; and fodder, 70-95%. (MRID#425592-37)

Additional data have been submitted in this petition.

The storage stability data is adequate to support the proposed use on corn.

Residue Data

Residue trials (25 field experiments) were conducted at sites located in the major corn-growing regions of the US (MRID#417368-15). Rates equivalent to 1x, 2x, and 4x the proposed field use rates were used. Plants were harvested at the middough stage to simulate harvest for forage or ensilage (PHI's of 73-125 days) and at maturity (PHI's of 103-161 days). Samples of forage, mature grain, and stover were analyzed for the parent and its oxygen analog by capillary GC/MSD method AMR-1195-88 and for TCA by capillary GC/EC method AMR-1253-88. Samples were stored frozen (-3 to -10 C) up to 450 days prior to analysis.

Non-detectable residues of chlorethoxyfos (<0.01 ppm) and its oxygen analog (<0.01 ppm) were found in all samples from all the 25 field trials. A majority of the samples showed <0.01 ppm TCA. Samples with higher values did not exceed 0.06 ppm except in one site in ND where TCA reached 0.3 ppm in grain (2x and 4x rates), and 0.38 and 0.55 ppm in stover (4X rate). All controls had <0.01 ppm of all three chemicals. Samples were fortified with chlorethoxyfos (74 samples total) and its oxygen analog (74 samples total) at 0.01, 0.02, and 0.04 ppm and TCA (147 samples total) at 0.01, 0.02, 0.04, 0.10, and 0.20 ppm. Recoveries ranged from 71-

124%, ave. 94% (chlorethoxyfos), 68-147%, ave. 95% (oxygen analog), and 65-115, ave 82% (TCA).

There is no expectation of chlorethoxyfos residues (<0.01 ppm) in field corn and popcorn forage, mature grain, or stover for the proposed use. Likewise, there is not expectation of the chlorethoxyfos oxygen analog residue <0.01 ppm in field corn and popcorn forage, mature grain, or stover for at the proposed use. TCA residues are not expected to exceed 0.04 ppm in the middough stage forage and stover, and 0.01 ppm in mature grain from the proposed use.

Additional data are submitted for sweet corn.

Residue trials (10 field experiments) were conducted at sites located in the major sweet corn-growing regions of the US (MRID#417368-18). Rates equivalent to 1x, 2x, and 4x the proposed field use rates were used. Plants were harvested at the fresh market stage and were separated into ears and stover. Ears were separated into grain and cannery waste (cobs plus husks) prior to analysis. PHI's ranged from 61 to 100 days. Samples of grain, stover, and husks plus cobs were analyzed for the parent and its oxygen analog by capillary GC/MSD method AMR-1195-88 and for TCA by capillary GC/EC method AMR-1253-88. Samples were stored frozen (-3 to -10 C) less than one year prior to analysis.

Non-detectable residues of chlorethoxyfos (<0.01 ppm) and its oxygen analog (<0.01 ppm) were found in all samples except one (0.01 ppm , 2x rate) including the stover and the cannery waste from all 10 field trials. TCA residues were <0.01 ppm in all samples of grain and cannery waste except one (0.01 ppm, 2x rate). Stover samples ranged from <0.01 to 0.06 ppm. All controls had <0.01 ppm of all three chemicals. Samples were fortified with chlorethoxyfos (74 samples total) and its oxygen analog (74 samples total) at 0.01, 0.02, and 0.04 ppm and TCA (147 samples total) at 0.01, 0.02, 0.04, 0.10, and 0.20 ppm. Recoveries ranged from 71-124%, ave. 94% (chlorethoxyfos), 68-147%, ave. 95% (oxygen analog), and 65-115, ave 82% (TCA).

There is no expectation of chlorethoxyfos residue (<0.01 ppm) in field corn and popcorn forage, mature grain, or stover for the proposed use. Likewise, there is no expectation of the chlorethoxyfos oxygen analog residue (<0.01 ppm) in field corn and popcorn forage, mature grain, or stover for at the proposed use. TCA residues are not expected to exceed 0.04 ppm in the middough stage forage and stover, and 0.01 ppm in mature grain.
Seven studies were also conducted to determine residues of chlorethoxyfos, its oxygen analog, and TCA in corn plants over time in field corn (IA, IL, KS, NC, and OH) and popcorn (IN) (MRID#417368-16). The planting at KS did not grow due to drought conditions. Test plots at planting were treated 2x and 4x the proposed field use rates of chlorethoxyfos at all site except IN

(1x and 2x). Samples of corn were collected at seven stages of crop development. Residue analysis showed <0.01 ppm parent and <0.01 ppm oxygen analog in whole plants (as well as grain and stover) throughout. TCA was found at the early to mid stages of plant growth at 0.01-0.57 ppm and <0.01-0.03 ppm in mature grain and stover.

Based upon the above residue data, the proposed use on corn and the proposed tolerances are adequately supported.

Dry Milling Study (MRID#412906-16)

Corn grain harvested from plants that were treated with 20x the proposed use rate was used in a processing study. Samples were stored at ambient temperature before processing. The study was conducted at the Food Protein Research and Development Center, Texas A & M University. According to the protocol, corn kernels were cleaned and air dried to 15% moisture. Water was then added (up to 22%), cracked, dried and cooled. Following screening and aspiration, the kernels were separated into grits, germs and hulls. The germs were pressed to yield crude oil and presscake. Samples of meal and flour were also collected for residue analysis.

Residue analysis showed <0.01 ppm parent and <0.01 ppm its oxygen analog on all samples of grain, meal, grits, flour, and crude oil; 0.02 ppm TCA in grain, meal, grits and flour, and <0.01 ppm TCA in crude and refined oil. The proposed tolerance of 0.01 ppm on corn grain will adequately cover any finite residues that might be in processed commodities from the dry milling process.

Wet Milling Study (MRID#417368-19)

Corn grain harvested from plants that were treated with 20x the proposed use rate was used in a processing study. Samples were stored at ambient temperature before processing. The study was conducted at the Food Protein Research and Development Center, Texas A & M University. According to the protocol, corn kernels were cleaned and air dried to 15% moisture. The grain is treated with sulfurous acid water up to 48 hours. The steeped corn (45% moisture) is ground in a disc mill. The kernels were separated into germs, hulls, endosperm, and pieces of bound germ. The germs were pressed to yield crude oil and presscake. Samples of grain, starch, and oil [expeller (crude); solvent-extracted (crude); and, oil (refined)] were also collected for residue analysis.

Residue analysis showed <0.01 ppm parent and <0.01 ppm its oxygen analog on all samples of grain, starch, and all oils. TCA also showed residues <0.01 ppm in all processed commodities except the solvent-extracted oil (0.04 ppm). The proposed tolerance of 0.01 ppm on corn grain will adequately cover any finite residues that might be in processed commodities from the wet milling process.

Meat, Milk, Poultry and Eggs

Corn grain, forage and fodder may be fed to livestock animals. Since residues of chlorethoxyfos were not detected (<0.01 ppm) in corn grain, forage, and fodder, and the goat metabolism study showed extensive conversion of chlorethoxyfos to CO_2 and natural products, CBTS concludes that for the purpose of this petition no tolerances for meat, milk, poultry, and eggs are required.

Rotational Crops

A confined rotational crop study was previously reviewed by EFGWB (See memo 2/21/90, E Regelman). This study was not adeqaute, and additional information was requested. The registrant also stated in his study (MRID#412906-20, AMR-1180-88) that a field rotation crop study was planned, with analytes chlorethoxyfos and trichloracetic acid (TCA). CBTS requests that the field rotation crop study be submitted for review to assess the proposed 30 plant back and the need for any rotation crop tolerances for chlorethoxyfos residues.

Other considerations:

There are no CODEX, Canadian, or Mexican limits established for chlorethoxyfos. Therefore, no compatibility problem exists.

Attachment: Confidential Appendix

cc with Attachment: PP#3F4174; J. Stokes (CBTS); chlorethoxyfos S. F.; R.F.
cc without Attachment: Circu.
RDI: PErrico:12/07/93:RLoranger:1/4/94
7509C:CBTS:JStokes:js:Rm 803:CM#2:305-7561:1/6/94

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