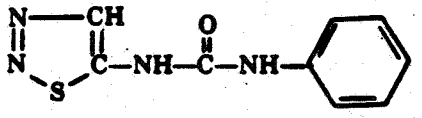
US EPA ARCHIVE DOCUMENT

2-2-93

Case No.: 4092
Chemical No(s).: 120301
CBRS Nos.: 10819, 10850, 10906
DPBarcode No.: D184052, D184501, D184983

CBRS TRANSMITTAL SHEET FOR PHASE 4 REVIEWS



Transmitted to HED on 11/13/92
Case name: Thidiazuron
Chemical name(s): N-Phenyl-N'-(1,2,3-thiadiazol-5-yl)urea
Data submitter(s): NOR-AM Chemical Company

CRM: Tom Myers/Kathryn Davis (PM-52) Phone #:308-8074

Issues/flags:

This action contains a request for a DATA WAIVER ( )
TIME EXTENSION ( )
ALTERED/DELETED USE ( )

Other: Thidiazuron has one use: as a defoliant on cotton. The registrant has committed to conduct additional studies to fulfill requirements of nature of the residue-animals, residue analytical methods- animals, storage stability, and magnitude of the residue in meat, milk, poultry and eggs. Use information was gathered from LUIS reports (9/2/92) and a product label (EPA Reg. No. 45639-89).

Branch: CBII, Reregistration Section II
Reviewed by: Felecia A. Fort W. J. Hazel, for Date: 2/2/93
Freshteh Toghrol F. Toghrol Date:

Approvals:

305-7677
Section Head: William J. Hazel, Ph.D W. J. Hazel Date: 2/2/93
Branch Chief: Edward Zager Edward Zager Date: 2/2/93
Division Approval: Penelope Fenner-Crisp, Ph.D P. A. Fenner Crisp Date: 2/2/93

cc: List D Reregistration File, RF, Circ., F.Fort, Betsy Grim (EFED), J. Smith (CCB).

Response, by Guideline

Guideline #: 171-4(a) Description: Nature of residue - plants
Is requirement applicable? (Y/N): Y
Does the summary/available information indicate that the MRID is a candidate for Phase 5 review?: Y
Data Waiver( ) Time Extension( ) Other ( )
Data Waiver/Time Extension (If applicable) Granted? (Y/N): ___
Discussion: MRID: 94246026 Summary (Cotton Plants); 94246027 Summary (Cotton By-Products); 94246028 Summary (Cotton Plants); 94246039 (Reformat).

MRID No. 94246026, 94246037. ^{14}C-labeled thidiazuron labeled at the phenyl ring was formulated as a 50% wettable powder and sprayed on cotton plants when 70 to 80% of the bolls were open at an application rate of 0.2 lb ai/A (1x). A specific activity of 1.07 mCi/mmol was reported. Samples of leaves, regrowth, stems and hulls of green bolls were collected for analysis at PHIs of 7 and 21 days. Plants harvested at the 7-day PHI contained 0.04 ppm (seeds), 2.00 ppm and 0.17 ppm (lint); 4.71 ppm and 3.83 ppm (gin trash); and 21.87 ppm and 36.89 ppm (leaves). Plants harvested at the 21-day PHI contained 0.01 ppm and <0.01 ppm (seeds); 0.27 ppm and 0.09 ppm (lint); 3.58 ppm and 1.63 ppm (gin trash); 1.21 ppm and 1.32 ppm (leaves); 0.29 and 0.56 (stem); and 0.13 (regrowth). Leaves, stems, and regrowth were extracted and only leaves and seeds (7-day PHI) were further examined to identify metabolites. In the leaves, 29% (6.31 ppm) was identified as thidiazuron, 8% was characterized as unknowns, 13% as photoproduct, and 38% as bound residue. In the seeds, 60% (0.02 ppm) was identified as thidiazuron, 6% was characterized as an unknown, 7% as a photoproduct and <12% as bound residues. Identification was accomplished by one method (TLC) and two solvent systems.

MRID No. 94246027, 94246038. Greenhouse-grown cotton plants were sprayed with thidiazolyl-labeled (spec. act. = 3.21 uCi/mg) or phenyl-labeled thidiazuron (spec. act. = 3.88 uCi/mg.) at an application rate of 0.22 lb ai/A (1x) when more than 90% of the bolls were open. The radiolabeled cotton plants were harvested seven days after application. No radioactivity was detected in the cottonseed meats and oil. The hulls, whole seeds, gin trash and lint contained total radioactivity at 0.11 ppm, 0.05 ppm, 0.63 ppm and 0.79 ppm, respectively. Leaves and stems contained 2.96 ppm and 0.38 ppm, respectively. Of the methanol-extractable radioactivity in the leaves, (>80% of the radioactivity) 94% (thiadiazolyl-label) and 98%

(phenyl-labeled) were identified as parent by TLC. No other plant parts were analyzed.

MRID Nos. 94246028, 94246039. Phenyl-labeled thidiazuron was formulated as a 50% wettable powder and the formulation suspended in deionized water. Ten mls of the suspension was brushed on the leaves of nearly mature cotton plants in a greenhouse. The specific activity was reported as 12.6 uCi/mg. The leaves were harvested 7 days after application, washed in methanol then extracted with water and organic solvents. Of the recovered radioactivity (82.4% recovered), 96% was determined to be the parent compound and 0.2% was determined to be photoproduct. The radioactive residues were determined using thin layer chromatography and two solvents systems.

Data gap: None. The plant metabolism study appears to be adequate for Phase 5 review. The residue of concern is tentatively the parent compound, thidiazuron.

Guideline #: 171-4(b) Description: Nature of residue - animals
Is requirement applicable? (Y/N): Y
Does the summary/available information indicate that the MRID is a candidate for Phase 5 review?: N
Data Waiver( ) Time Extension( ) Other ( )
Data Waiver/Time Extension (If applicable) Granted? (Y/N): ___
Discussion: MRID: 42529002 (Cow); 42529003 (Hen)

MRID No. 42529002. [^{14}C-aniline] thidiazuron was fed to a lactating cow at a rate of 10 ppm for seven days. The animal was sacrificed within 24 hours of administration of the final dose. Radioactivity found was 0.05 ppm, 0.1 ppm, 1.5 ppm, and 1.0 ppm in fat, muscle, kidney and liver, respectively. Radioactivity reached a plateau in milk on the second day (0.2 ppm). Analysis was performed using HPLC and TLC. In liver, two unidentified components comprising 51% of the tissue radioactivity were characterized (designated G and H). Phenylurea, 4-hydroxythidiazuron, and thidiazuron constituted 13%, 4% and 2% of the total radioactivity, respectively. Partially extractable and unextractable residues comprised 3.0% and 19% of the total radioactivity, respectively. Components G, H, phenylurea, 4-hydroxy thidiazuron, thidiazuron and a polar fraction were present in kidney extracts at 18%, 11%, 15%, 6%, 3%, and 23%, respectively, of the total

radioactivity. In muscle, 58% was identified as thidiazuron, 2% as phenylurea, and 1% as 4-hydroxy thidiazuron. Components G and H comprised only 13% of the muscle radioactivity combined. In fat, Component H comprised 46% of the fat radioactivity and component G was present at 7%. Phenylurea and 4-hydroxythidiazuron were identified at 10% and 2.3%, respectively. A polar fraction constituted 11% of the fat radioactivity. Only minor amounts were nonextractable. Thidiazuron , 4-hydroxy thidiazuron, and phenylurea were identified in milk at 31%, 49%, and 3% of the milk radioactivity. Minor amounts of components G and H were characterized (≤3%).

MRID No. 42529003. [^{14}C-aniline] thidiazuron was fed once daily to six hens for fourteen days at a rate of 8 ppm. Radioactivity did not plateau in eggs during this period. All tissues were first treated with protease and β-glucuronidase prior to extraction. Radioactivity found was 0.02 ppm, 0.27 ppm, 1.11 ppm, 0.66 ppm, 0.10 ppm, 0.10 ppm and 0.34 ppm in fat, gastrointestinal tract, gastro-intestinal tract contents, liver, muscle, skin and blood, respectively. In liver, two unidentified components (designated metabolites G and H) comprised the majority of the residues (75%). No thidiazuron was detected. Phenylurea and 4-hydroxy thidiazuron were detected at low levels. Two percent of the radioactivity was unextractable. The same two unidentified components (G and H) were present in muscle extracts (40%). Thidiazuron and 4-hydroxy thidiazuron accounted for 2-3% of the muscle radioactivity and phenylurea accounted for 8%. Ten percent of the radioactivity was unextractable. In fat extracts, metabolite H comprised 60% of the radioactivity. Phenylurea, thidiazuron, and 4-hydroxy thidiazuron accounted for 2 to 9% of the fat radioactivity. Nine percent of the radioactivity was unextractable. Phenylurea, thidiazuron, and component H constituted 16%, 20%, and 22% of the radioactivity in the egg, respectively. Partially extractable residues accounted for 24% of the egg radioactivity. Analysis was performed using HPLC and TLC. Metabolite H was not identified; however, it has been shown to cochromatograph with metabolite H found in cow liver.

According to the registrant, additional metabolism work including further investigations into the nature of metabolite H is being conducted and the above two studies comprise part one of the study series.

Data gap: Additional work must be performed to identify unknown

metabolites G and H which apparently compose a major part of the terminal residue in animals. Additionally, the tissues from the metabolism study should be tested using the data collection method(s) and enforcement analytical method(s).

Guideline #: 171-4(c) Description: Res. analyt. method - plant
Is requirement applicable? (Y/N): Y
Does the summary/available information indicate that the MRID is a candidate for Phase 5 review?: N
Data Waiver( ) Time Extension( ) Other ( )
Data Waiver/Time Extension (If applicable) Granted? (Y/N): ___
Discussion: MRID: 94246030 Summary (Cottonseed); 94246029 Summary (Cottonseed, Cotton Fiber); 94246040 Reformat; 41950102 (FDA MRM)

MRID No. 94246030. The registrant submitted a summary of the analytical procedure entitled "Analytical Method for Determination of Residues of Thidiazuron and Diuron in Cottonseed by Gas Chromatography with Electron Capture Detection". Cottonseed samples are extracted and hydrolyzed by alkaline reflux to the corresponding aniline. After distillation, the distillate is trapped in dilute HCl, brominated and determined as tribromoaniline (TBA) by gas chromatography with a electron capture detector (GC-ECD). The method sensitivity was shown to be 0.05 ppm. Recoveries of samples fortified at levels of 0.05 ppm to 0.20 ppm ranged from 94% to 113%. Recovery levels were corrected for apparent residues in untreated samples.

MRID No. 94246029. Another method entitled "Residue Determination of SN 49537 in Cottonseed and Cotton Fiber" was submitted by the registrant. This procedure involves hydrolyzing residues of thidiazuron in cotton seed or fiber to aniline, steam distillation and extraction into isooctane using a Bleidner Apparatus. After extraction of aniline from the organic phase into hydrochloric acid, aniline is brominated in aqueous acid solution and reextracted into toluene. Residues are determined using GC-ECD. Recoveries from cottonseed and fiber samples fortified at 0.2-4.0 ppm ranged from 62% to 113% (81% avg.); recoveries were 97-126% (113% avg.) from the respective matrices fortified at 1.0 ppm and 5.0 ppm. Low recoveries (62-69%) occurred at the 4.0 ppm fortification level. Recovery levels were corrected for apparent residues in untreated samples. The registrant states that the method is not specific for thidiazuron and interferences may occur from anthropogenic material or from biological material containing an aniline moiety. They claim that these interferences detected in control samples

were of low concentrations (up to 0.2 ppm). A limit of detection was established at 0.05 ppm.

MRID No. 41950102. Thidiazuron were subjected to the Multiresidue Method of analysis in PAM I, Protocol C. Thidiazuron is not a N-methyl carbamate nor an acid or phenol and cottonseed (only registered use) is a fatty crop; therefore, Protocols A, B, and D were not required. Testing through Protocol C was not successful so further testing was suspended.

Data gap: The above methods are not adequate for data collection or enforcement because of the nonspecificity of the method, i.e. it will detect any aniline-containing moiety. The registrant must submit data collection and regulatory analytical method(s) for the determination of thidiazuron and its metabolites in/on plant matrices. If new metabolites (which require regulation) are found in future plant metabolism studies, if deemed necessary, then analytical method(s) must be developed for them as well. Any regulatory methods submitted will require an independent method validation as described in PR Notice 88-5 (July 15, 1988).

Guideline #: 171-4(d) Description: Res. anal. method - animals
Is requirement applicable? (Y/N): Y
Does the summary/available information indicate that the MRID is a candidate for Phase 5 review?: N
Data Waiver( ) Time Extension( ) Other ( )
Data Waiver/Time Extension (If applicable) Granted? (Y/N): ___
Discussion: No data was submitted to fulfill this requirement; however, the registrant has committed to do this study.

Data gap: The registrant must submit data collection and regulatory analytical method(s) for the determination of thidiazuron [and its metabolites] in/on animal matrices. If new metabolites (which require regulation) are found in the animal metabolism studies, then analytical method(s) must be developed for them as well. Any regulatory methods submitted will require an independent method validation as described in PR Notice 88-5 (July 15, 1988).

DUE 10/93

Guideline #: 171-4(e) Description: Storage stability
Is requirement applicable? (Y/N): Y
Does the summary/available information indicate that the MRID is a candidate for Phase 5 review?: N
Data Waiver( ) Time Extension( ) Other ( )
Data Waiver/Time Extension (If applicable) Granted? (Y/N): ___
Discussion: No storage stability data were submitted by the registrant in spite of the fact that samples were stored for up to 5 months at ambient temperatures and then frozen for up to 11 months.

Data gap: Storage stability studies must be conducted on cotton seed and cotton processed products for which a field trial and/or processing study has been (or will be) conducted, as well as representative livestock commodities. If the feeding/grazing restriction is removed from labels, forage storage stability data will also be required. Use of field-weathered samples is strongly recommended. Storage conditions must reflect the storage conditions of the treated samples (from the field trial and processing studies) with respect to temperature, length of storage, containers, lighting, etc. If there are any metabolites and/or degradates included in the tolerance expressions, then they must be tested as well. The chosen intervals must allow for unforeseen delays in sample storage.

DUE 5/94

Guideline #: 171-4(f) Description: Mag. res. - potable water
Is requirement applicable? (Y/N): N
Does the summary/available information indicate that the MRID is a candidate for Phase 5 review?: N/A
Data Waiver( ) Time Extension( ) Other ( )
Data Waiver/Time Extension (If applicable) Granted? (Y/N): ___
Discussion: N/A

Data gap: N/A

Guideline #: 171-4(g) Description: Magnitude residue - fish
Is requirement applicable? (Y/N): N
Does the summary/available information indicate that the MRID is a candidate for Phase 5 review?: N/A
Data Waiver( ) Time Extension( ) Other ( )
Data Waiver/Time Extension (If applicable) Granted? (Y/N): ___
Discussion: N/A

Data gap: N/A

Guideline #: 171-4(h) Description: Mag. res. - irrigated crop
Is requirement applicable? (Y/N): N
Does the summary/available information indicate that the MRID is a candidate for Phase 5 review?: N/A
Data Waiver( ) Time Extension( ) Other ( )
Data Waiver/Time Extension (If applicable) Granted? (Y/N): ___
Discussion: N/A

Data gap: N/A

Guideline #: 171-4(i) Description: Mag. res. - food handling
Is requirement applicable? (Y/N): N
Does the summary/available information indicate that the MRID is a candidate for Phase 5 review?: N/A
Data Waiver( ) Time Extension( ) Other ( )
Data Waiver/Time Extension (If applicable) Granted? (Y/N): ___
Discussion: N/A

Data gap: N/A

Guideline #: 171-4(j) Description: Mag. meat/milk/poultry/eggs
Is requirement applicable? (Y/N): Y
Does the summary/available information indicate that the MRID is a candidate for Phase 5 review?: N
Data Waiver( ) Time Extension( ) Other ( )
Data Waiver/Time Extension (If applicable) Granted? (Y/N): ___
Discussion: No data were submitted; however, the registrant has committed to generate new studies.

DUE 5/94.

Data gap: Thidiazuron must be fed (1X, 3X, and 10X the maximum anticipated dietary intake) to dairy cattle, poultry, and/or other livestock, as applicable. Livestock are to be treated for a minimum of 28 days or until residues plateau in the milk or eggs, whichever is longer. Following oral treatment, test animals should be sacrificed within 24 hours of the final dose. Feeding levels should be determined based on the latest crop residue data generated or to be generated. When determining the feeding levels the registrant should consider the maximum crop residue levels possible and the dietary burden based on Table II Subdivision O - Residue Chemistry Guidelines.

Guideline #: 171-4(k/l) Description: Cotton field trials/process
Is requirement applicable? (Y/N): Y
Does the summary/available information indicate that the MRID is a candidate for Phase 5 review?: N
Data Waiver( ) Time Extension( ) Other ( )
Data Waiver/Time Extension (If applicable) Granted? (Y/N): ___
Discussion: MRID: 94246031 Summary (Cotton Seed); 94246041 Reformat; 94246033 (Cotton Processed Commodities); 94246042 Reformat

MRID Nos. 94246031, 94246041. One application of the 50% wettable powder at rates of 0.1 to 0.5 lbs ai/A was applied by ground and air to cotton plants. The label appears to allow two applications on mature cotton plants (each at 0.3 lb ai/A) with a limit of 0.6 lbs ai/A/season and a PHI of 5 days. PHIs of 0 to 43 days were used. Thirty eight trials were conducted in 7 states (GA, MS, SC, AZ, TX, CA and FL). These states comprise 72% of the cotton production in the United States (Ag. Stat, 1990). Residues in control cottonseed samples ranged from 0.01 ppm to 0.118 ppm. Residues (not corrected for apparent residues in control samples) in treated cottonseed samples ranged from <0.02 ppm to 0.437 ppm (reflects 0-day PHI and 0.5 lbs ai/A). Analytical method "Residue Determination of SN 49537 in Cottonseed and Cotton Fiber" (MRID No. 94246029) was the method used for data collection and has been deemed unacceptable.

MRID Nos. 94246033, 94246042. One application of thidiazuron was applied by ground equipment at 0.2 to 0.5 lbs a.i./A and harvested at PHIs of 0 to 38 days. Additionally samples of cottonseed were spiked with thidiazuron at a level of 2.7 ppm. In spiked samples, the net average residues found were 2.6 ppm, 1.4 ppm, 4.4 ppm, 0.63 ppm, 0.07 ppm, and <0.05 ppm in cottonseed, meal,

hulls, soapstock, crude oil, and refined oil respectively. These results were summarized and assumed to be corrected for checks; however, this information was not reported. Residues in processed products from field weathered samples ranged from 0.004 to 1.672 ppm from an application at 0.25 lbs ai/A and 0.007 to 2.062 ppm from an application at 0.5 lbs ai/A. Residues in control samples ranged from 0.009 to 4.316 ppm. Residues detected in the control samples were higher than residues in most treated samples in its corresponding field trial. The registrant claims that residues in most processed products were not detectable since they subtracted the residues found in control samples from the residues found in the treated samples. The method used is not acceptable (see Guideline 171-4(c)).

Data gap: The available field trial and processing data are unacceptable for several reasons: (i) a nonspecific method of analysis was used which resulted in interference from endogenous/anthropogenic sources (this was quite dramatic in processed products); (ii) no storage stability data are available to validate data reflecting preanalysis sample storage at ambient temperatures for up to 5 months followed by frozen storage for up to 11 months; (iii) none of the trials reflected two applications; and (iv) only 38 of 140 cottonseed samples had been both treated at the single maximum application rate (or greater) and harvested near the label PHI of 7 days.

Data depicting residues of thidiazuron and its regulated metabolites in/on cottonseed must be submitted. If the forage feeding restriction is deleted from labels, forage data will also be required. The 50% WP in water-soluble bags must be applied (each in separate tests) at the maximum label rate, the maximum number of applications, and the minimum PHI of 5 days using ground equipment. The tests must be conducted in GA, MS, AR, AZ, TX, CA and TN which represent the major cotton production regions. Adequate methodology must be developed for data collection and enforcement. The registrant must propose amendments to their labels clearly specifying the maximum single application rate/A, maximum seasonal rate/A, and minimum interval between the two applications; the data required herein must reflect these proposed label amendments.

A processing study must be conducted for cotton beginning with seed bearing detectable field-weathered residues of the parent and the regulated metabolites. Samples should be processed into meal, hulls, soapstock, crude oil, and refined oil to determine the residue concentration or reduction factor(s). If the cotton is treated at exaggerated rates equivalent to at least the theoretical

concentration factor due to processing and no detectable residues are found on the rac, then processing studies are not required. Note: exaggerated rates may be necessary.

ADDITIONAL COMMENTS:
The registrant is advised to consult the Subdivision O Residue Chemistry Guidelines, the Standard Evaluation Procedures, the Data Reporting Guidelines, and the Phase 3 Technical Guidance concerning conduct of residue chemistry studies. If the registrant has additional concerns they are advised to submit a protocol for CBRS review.

PRODUCT CHEMISTRY

Case No.: **4092** Case Name Thidiazuron
Chemical No(s).: **120301** Chemical Name(s): Thidiazuron
Registrant: NOR-AM Chemical Company

Guideline Number	Is requirement applicable?	Does summary or available information indicate MRID is a candidate for Phase 5 review?	Are additional data required?	MRID Number
61-1	Y	Y	N	41761101
61-2(a)	Y	Y	N	41761101
61-2(b)	Y	Y	N	41761101
62-1	Y	Y	N	41786201
62-2	Y	Y	N	41786201
62-3	Y	Y	N	41786201
63-2	Y	Y	N	41987101
63-3	Y	Y	N	41987101
63-4	Y	Y	N	41987101
63-5	Y	Y	N	41987101
63-6	N/A	N/A	N/A	N/A
63-7	Y	Y	N	41987101
63-8	Y	Y	N	41364906 41786202
63-9	Y	Y	N	94246001
63-10	Y	Y	N	41364901
63-11	Y	Y	N	41364906
63-12	Y	Y	N	41987101
63-13	Y	Y	N	41786202

Key: Y=yes; N=no; I=a decision cannot be made at this time; S=fully satisfies requirement; P=partially; N/A=not applicable; U=unsatisfactory.

Note: All submitted product chemistry data for thidiazuron (a plant growth regulator cotton defoliant) has been tentatively satisfied. However, we reserve the right to require additional data during the Phase 5 Review.