PC Code: 120301
EPA FILE SYMBOL: 264-IEE

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

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

February 14, 2005

MEMORANDUM

Subject:	Name of Pesticide Product:	Thidiazuron Technical Cotton Defoliant
	EPA File Symbol:	264-IEE
	DP Barcode:	D312650
	Decision No.:	341003
	PC Code:	120301 Thidiazuron

From: Breann Hanson, Toxicologist B Hanson 2-14
Technical Review Branch
Registration Division (7505C)

To: Marcel Howard, RM Team 23
Herbicide Branch
Registration Division (7505C)

Applicant: Bayer CropScience
P.O. Box 12014, 2 T.W. Alexander Drive
Research Triangle Park, NC 27709

FORMULATION FROM LABEL:

Active Ingredient:			% by Wt.
120301	Thidiazuron	CAS No. 51707-55-2	99.0%
Inert Ingredients:			1.0%
		Total:	100.0%

ACTION REQUESTED:
The Product Manager requests:

> "Please review the proposed product labeling, basic CSF (dated 3/16/04), acute toxicity data for the product with EPA File No. 264-IEE."

BACKGROUND: Bayer CropScience has submitted a six pack of acute toxicity studies in support of registration for Thidiazuron Technical Cotton Defoliant, EPA File Symbol: 264-IEE. The submission included a CSF and label and blow backs of acute toxicity studies required for registration. According to the jacket for 264-IEE, studies had already been performed on the technical product and so an effort was made to uncover reviews performed on technical Thidiazuron. Old acute oral and acute inhalation toxicity studies (MRIDs 942460-07, -09) were previously reviewed in a request for tolerances memo for the A.I. (Paynter, PP#1F2527, 1H5308, 2139-REF, 30/APR/1982). The primary eye and primary dermal irritation studies (MRIDs 420996-01, -02) were previously reviewed in an HED memo (Kozumbo, HED Project No.: 2-0857, Caswell No.: 659A, 13/AUG/1992). Reviews on the remaining blowbacks could not be found, so these were reviewed by TRB. Newer acute oral, dermal and inhalation toxicity studies were submitted. The acute oral and acute dermal toxicity studies (MRIDs 461215-01, -02) were conducted at Huntingdon Life Sciences Ltd., Cambridgeshire, England . The acute inhalation toxicity study (461215-03) was conducted at Safepharm Laboratories Ltd., Derby, U.K. An old acute dermal toxicity study, which a review of could not be found, was conducted at RCC, Iringen, Switzerland. The dermal sensitization study (MRID 942460-10) was conducted at Schering AG, Germany.

RECOMMENDATIONS: The five submitted studies have been reviewed and 4 are classified as acceptable. The dermal sensitization study is unacceptable and the registrant will need to either submit this study or cite the data from a substantially similar product. The partial acute toxicity profile for Thidiazuron Technical Cotton Defoliant, EPA File Symbol: 264-IEE is:

Acute oral toxicity	III	Cited	MRID 94246007
Acute oral toxicity	III	Acceptable	MRID 46121501
Acute dermal toxicity	IV	Acceptable	MRID 46121502
Acute dermal toxicity	III	Acceptable	MRID 41426901
Acute inhalation toxicity	IV	Cited	MRID 94246009
Acute inhalation toxicity	IV	Acceptable	MRID 46121503
Primary eye irritation	IV	Cited	MRID 42099601
Primary skin irritation	IV	Cited	MRID 42099602
Dermal sensitization	--	Unacceptable	MRID 94246010

LABELING: Based on the partial toxicity profile above, the following are the precautionary and first aid statements for this product as obtained from the Label Review System. NOTE: Based on the results of an acceptable dermal sensitization study the label may need to contain the dermal sensitization precautionary statement.:

PRODUCT ID #: 000264-00822

PRODUCT NAME: Thidiazuron Technical Cotton Defoliant

PRECAUTIONARY STATEMENTS

Hazards to Humans and Domestic Animals:

SIGNAL WORD: CAUTION

Harmful if absorbed through skin or if swallowed. Avoid contact with skin, eyes or clothing. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco. Remove and wash contaminated clothing before reuse.

First Aid:

If on skin:
-Take off contaminated clothing.
-Rinse skin immediately with plenty of water for 15-20 minutes.
-Call a poison control center or doctor for treatment advice.

If swallowed:
-Call a poison control center or doctor immediately for treatment advice.
-Have person sip a glass of water if able to swallow.
-Do not induce vomiting unless told to by a poison control center or doctor.
-Do not give anything to an unconscious person.

Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact 1-800-xxx-xxxx for emergency medical treatment information.

Reviewer: Breann Hanson **Date:** Feb.14, 2005
Risk Manager (EPA): Marcel Howard, RM 23

STUDY TYPE: Acute Oral Toxicity - SD rat; OPPTS 870.1100; OECD 423

TEST MATERIAL: Thidiazuron (AI: 98.7% w/w, Batch No.: CH107623-02; yellowish powder)

SYNONYMS: AE B049537

CITATION: Coleman, D.G. (2001) Rat Acute Oral Toxicity. Sponsor Study Number: Tox 20138. Unpublished study prepared by Huntingdon Life Sciences Ltd. April 5, 2001. MRID 46121501.

SPONSOR: Bayer CropScience, P.O. Box 12014, 2 T.W. Alexander Drive, Research Triangle Park, NC 27709

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 46121501), 5/sex CD strain Sprague Dawley rats (Age: 8-11 weeks, Weight: 208-229 g males, 195-202 g females; Source: Harlan U.K. Ltd., Oxon, England) were given a single oral dose of Thidiazuron (AI: 98.7% w/w, Batch No.: CH107623-02; yellowish powder) by oral gavage at a dose of 2,000 mg/kg. The test substance was formulated in 1% w/v aqueous methylcellulose. Individual animal body weights were recorded prior to test substance administration and on days 8 and 15. Clinical checks for signs of toxicity and mortality were made frequently on the initial study day and twice daily thereafter. All animals were necropsied on study day 15.

All animals survived the study period. Two female rats had weight gains of less than 10 g during the second week of the study. All remaining animals had adequate weight gains throughout the study. Signs of toxicity noted during the study included lethargy, deep respiration, hunched posture, piloerection and abnormal gait. All animals recovered from these symptoms by study 3. No gross internal findings were observed at necropsy.

Oral LD_{50} males => 2,000 mg/kg
Oral LD_{50} females => 2,000 mg/kg
Oral LD_{50} combined => 2,000 mg/kg

Based on the LD_{50} in rats, Thidiazuron is classified as EPA Toxicity Category III.

This acute oral study is classified as acceptable. It does satisfy the guideline requirement for an acute oral study (OPPTS 870.1100; OECD 423) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Dose (mg/kg)	Mortality/Number Tested		
	Males	Females	Combined
2000	0/5	0/5	0/10

A. **Mortality** - None, as noted in table.

B. Clinical observations - All animals survived the study period. Two female rats had weight gains of less than 10 g during the second week of the study. All remaining animals had adequate weight gains throughout the study. Signs of toxicity noted during the study included lethargy, deep respiration, hunched posture, piloerection and abnormal gait. All animals recovered from these symptoms by study 3.

C. Gross Necropsy - No gross internal findings were observed at necropsy.

D. Reviewer's Conclusions: Agree with study author.

Reviewer: Breann Hanson **Date:** Feb. 14, 2005
Risk Manager (EPA): Marcel Howard, RM 23

STUDY TYPE: Acute Dermal Toxicity - SD Rat; OPPTS 870.1200; OECD 402

TEST MATERIAL: Thidiazuron (AI: 98.7% w/w, Batch No.: CH107623-02; yellowish powder)

SYNONYMS: AE B049537

CITATION: Coleman, D.G. (2001) Rat Acute Dermal Toxicity. Sponsor Study number: TOX 20139. Unpublished study prepared by Huntingdon Life Sciences Ltd. April 5, 2001. MRID 46121502.

SPONSOR: Bayer CropScience, P.O. Box 12014, 2 T.W. Alexander Drive, Research Triangle Park, NC 27709

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 46121502), 5/sex of CD strain Sprague Dawley rats (Age: 8-11 weeks; Weight: 241-260 g males, 222-237 g females; Source: Harlan U.K. Ltd., Oxon, England) were dermally exposed to a single application of Thidiazuron (AI: 98.7% w/w, Batch No.: CH107623-02; yellowish powder) at 5,000 mg/kg. The test material was formulated in 1% methylcellulose and applied to the shaven dorso-lumbar area (covering 10% of the BSA) of each test animal, covered with a porous gauze and held in place with non-irritating tape, further covered with a dressing and left in place for 24 hours. Individual animal body weights were recorded prior to test substance administration and again on days 8 and 15. Clinical checks for signs of toxicity and mortality were made frequently on the initial study day and twice daily thereafter. Checks for signs of dermal irritation also occurred twice daily. Irritation was scored according to Draize. All animals were necropsied on study day 15.

All animals survived and appeared healthy throughout the study period. Two females showed weight loss at the end of the first week, persisting in one animal to study termination. Slight erythema was noted in 3/10 animals, but animals recovered from this by study day 3. Localized spots/scabbing was observed in 1 animal, resolving by study day 5. No gross internal findings were observed at necropsy.

Dermal LD_{50} Males => 5,000 mg/kg
Females => 5,000 mg/kg
Combined => 5,000 mg/kg

Based on the LD_{50} of 5,000 mg/kg, Thidiazuron is classified as EPA Toxicity Category IV.

This acute dermal study is classified acceptable. It does satisfy the guideline requirement for an acute dermal study (OPPTS 870.1200; OECD 402) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Dose (mg/kg)	Mortality/Number Tested		
	Males	Females	Combined
5000	0/5	0/5	0/10

A. Mortality - None, as noted in table.

B. Clinical observations - All animals survived and appeared healthy throughout the study period. Two females showed weight loss at the end of the first week, persisting in one animal to study termination. Slight erythema was noted in 3/10 animals, but animals recovered from this by study day 3. Localized spots/scabbing was observed in 1 animal, resolving by study day 5.

C. Gross Necropsy - No gross internal findings were observed at necropsy.

D. Reviewer's Conclusions: Agree with study author.

Reviewer: Breann Hansen **Date:** Feb. 14, 2005
Risk Manager (EPA): Marcel Howard, RM 23

STUDY TYPE: Acute Dermal Toxicity - NZW Rabbits: OPPTS 870.1200; OECD 402

TEST MATERIAL: Thidiazuron Technical (AI: 98.7% w/w, Batch No.: 7/9 82; powder)

CITATION: Ullman, L. (1984) 146 Thidiazuron: Acute dermal toxicity (LD50) study with thidiazuron technical (SN 49 537) in rabbits. Laboratory Project ID: 031140. Unpublished study prepared by RCC. May 7, 1984. MRID 41426901.

SPONSOR: Bayer CropScience, P.O. Box 12014, 2 T.W. Alexander Drive, Research Triangle Park, NC 27709

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 41426901), 3/sex of New Zealand White rabbits (Age: 15-16 weeks; Weight: 2.5-2.6 kg males, 2.6-2.8 kg females; Source: Kleintierfarm Madoerin AG, Fuellinsdorf, Switzerland) were dermally exposed to a single application of Thidiazuron Technical (AI: 98.7% w/w, Batch No.: 7/9 82; powder) at 4,000 mg/kg. The test material was formulated in 2% carboxy-methylcellulose and applied to the shaven back of each test animal, covered with an occlusive dressing, wrapped, fixed with an adhesive bandage and left in place for 24 hours. Individual animal body weights were recorded prior to test substance administration and again on days 8 and 15. Clinical checks for signs of toxicity and mortality were made frequently on the initial study day and daily thereafter. Checks for signs of dermal irritation also occurred daily. Irritation was scored according to Noaks and Sanderson. All animals were necropsied on study day 15.

5/6 test animals survived, gained weight and appeared healthy throughout the study period. The one test animal that died did so on study day 12 and showed no signs of toxicity prior to death. At necropsy, the one animal that died had mucoid filled intestines, colon and rectum. No gross internal findings were observed at necropsy for the animals that survived to study termination.

Dermal LD_{50} Males => 4,000 mg/kg
Females => 4,000 mg/kg
Combined => 4,000 mg/kg

Based on the LD_{50} of 4,000 mg/kg, Thidiazuron Technical is classified as EPA Toxicity Category III.

This acute dermal study is classified as acceptable for registering this product although it does not satisfy the guideline requirement for an acute dermal study (OPPTS 870.1200; OECD 402) in the rat. In the report only 3/sex animals were treated with the test material. According to OPPTS 870.1200, at least 5/sex animals should be treated. TRB finds this study acceptable due to it producing a more restrictive acute toxicity profile.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Dose (mg/kg)	Mortality/Number Tested		
	Males	Females	Combined
4000	1/3	0/3	1/6

A. Mortality - One, as noted in table.

B. Clinical observations - 5/6 test animals survived, gained weight and appeared healthy throughout the study period. The one test animal that died did so on study day 12 and showed no signs of toxicity prior to death.

C. Gross Necropsy - At necropsy, the one animal that died had mucoid filled intestines, colon and rectum. No gross internal findings were observed at necropsy for the animals that survived to study termination.

D. Reviewer's Conclusions: Agree with study author.

E. Deficiencies: In the report only 3/sex animals were treated with the test material. According to OPPTS 870.1200, at least 5/sex animals should be treated. TRB finds this study acceptable due to it producing a more restrictive acute toxicity profile.

Reviewer: Breann Hanson Date: Feb. 14, 2005
Risk Manager (EPA): Marcel Howard, RM 23

STUDY TYPE: Acute Inhalation Toxicity - SD Rat; OPPTS 870.1300; OECD 403

TEST MATERIAL: Thidiazuron (AI: 98.7% w/w, Batch No.: CH107623-02; beige powder)

SYNONYMS: AE B049537 00 1D99 0002

CITATION: Wesson, C.M., (2001) Acute Inhalation Toxicity (Nose Only) Study in the Rat. SPL Project Number: 374/096. Unpublished study prepared by Safepharm Laboratories. March 29, 2001. MRID 46121503.

SPONSOR: Bayer CropScience, P.O. Box 12014, 2 T.W. Alexander Drive, Research Triangle Park, NC 27709

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID 46121503), 5/sex Sprague Dawley rats (Age: 8-10 weeks; Weight: 280-318 g males; 219-239 g females; Source: Charles River (UK) Ltd., Kent, England) were exposed nose-only via the inhalation route to Thidiazuron (AI: 98.7% w/w, Batch No.: CH107623-02; beige powder) for 4 hours at a gravimetrically determined concentration of 3.48 mg/L. Individual animal body weights were recorded prior to test substance administration and again on days 7 and 14. Clinical checks for signs of toxicity and mortality were made at hourly intervals during the exposure period, immediately on removal from the inhalation chamber and at 1 hour post-exposure on the initial study day. Subsequent checks for toxicity or mortality occurred once daily thereafter for the remainder of the 14-day observation period. All animals were necropsied on study day 14.

All animals survived and gained weight during the study period. Signs of toxicity noted during exposure included increased respiratory rate and wet fur in all animals and an isolated occurrence of decreased respiratory rate in one animal. Post-exposure, signs of toxicity noted included increased respiratory rate, hunched posture, piloerection, wet fur, pallor of the extremities, noisy respiration and isolated occurrences of red/brown staining around the eyes and sneezing. One-hour post-exposure improvements in the animals conditions were noted. All animals appeared asymptomatic on study day 3. At necropsy, a single instance of dark foci was noted on the lungs of one test animal. No other gross internal findings were observed at necropsy.

LC_{50} Males = > 3.48 mg/L
LC_{50} Females => 3.48 mg/L
LC_{50} Combined -> 3.48 mg/L

Based on the LC_{50} of 3.48 mg/L for both sexes, Thidiazuron is classified as EPA Toxicity Category IV.

This acute inhalation study is classified as acceptable. It does satisfy the guideline requirement for an acute inhalation study (OPPTS 870.1300; OECD 403) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Nominal Conc. (mg/L)	Actual Conc. (Gravimetric) (mg/L)	MMAD µm	GSD µm	Mortality/Number Tested		
				Males	Females	Combined
22.0	3.48	3.42	2.58	0/5	0/5	0/10

Test Atmosphere / Chamber Description:

Gravimetric Conc.	3.48 mg/L
Chamber Volume (L):	30
Airflow:	18 LPM
Temperature:	19-21 °C
Relative Humidity (mean):	30-55%
Time to Equilibrium:	8 minutes

Test atmosphere concentration - Samples were taken at 15 minute intervals and the concentration determined gravimetrically. Samples were withdrawn at a known rate and the volume of air sampled was measured. Dried filter samples were then used to determine the concentration.

Particle size determination - A cascade impactor was used to determine the particle size distribution of the test atmosphere. Samples were taken 3 times during exposure. Total mass of particles and the percent mass in each size range was calculated. Resulting values were converted to probits and plotted in log format.

A. Mortality - None, as noted in table.

B. Clinical observations - All animals survived and gained weight during the study period. Signs of toxicity noted during exposure included increased respiratory rate and wet fur in all animals and an isolated occurrence of decreased respiratory rate in one animal. Post-exposure, signs of toxicity noted included increased respiratory rate, hunched posture, piloerection, wet fur, pallor of the extremities, noisy respiration and isolated occurrences of red/brown staining around the eyes and sneezing. One-hour post-exposure improvements in the animals conditions were

noted. All animals appeared asymptomatic on study day 3.

C. Gross Necropsy - At necropsy, a single instance of dark foci was noted on the lungs of one test animal. No other gross internal findings were observed at necropsy.

D. Reviewer's Conclusions: Agree with study author.

Reviewer: Breann Hanson **Date:** Feb. 14, 2005
Risk Manager (EPA): Marcel Howard, RM 23

STUDY TYPE: Dermal Sensitization - Guinea Pig Winkelman; OPPTS 870.2600; OECD 406

TEST MATERIAL: Thidiazuron Technical (AI: unreported. Batch No.: unreported; appearance: unreported)

CITATION: Chow, N.L. (1975) Phase 3 Summary of MRID 00064737 (T18) Thidiazuron: Skin Sensitizing Test on Guinea Pigs. Laboratory I.D. No.: 125-75. Unpublished study prepared by NOR-AM Chemical Company. May 13, 1975. MRID 94246010.

SPONSOR: Bayer CropScience. P.O. Box 12014, 2 T.W. Alexander Drive, Research Triangle Park, NC 27709

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 94246010) with Thidiazuron Technical (AI: unreported, Batch No.: unreported; appearance: unreported), 20 male young adult Winkelman guinea pigs (Weight: 220-320 g; Source: unreported) were tested using the Buehler method. Once a day for 10 days a 1% w/v suspension of the test substance was subcutaneously injected into 10 test animals. For the first injection 0.05 mL was administered and 0.1 mL for the remaining 9 injections. 24 hours after each injection the animals were observed for dermal irritation. Fourteen days after the last induction a challenge injection of both 0.05 mL of the 1% w/v suspension and 0.05 mL of water were given to each of the test animals and to a set of 10 naive control animals. Several times over the next 24 hours the injection sites were evaluated and the animals were graded for dermal irritation. No positive control was included in this study.

Low grade reddening and swelling was noted in areas treated with both the 1% w/v suspension and water for both the test and control animals.

Based on the results of this study, Thidiazuron Technical does not have to be labeled as a dermal sensitizer.

This study is classified as **unacceptable**. It does not satisfy the guideline requirement for a primary dermal sensitization study (OPPTS 870.2600; OECD 406) in the Guinea pig. The reported information does not meet current GLP standards. No certification of the test substance is submitted, so it is not clear as to what was actually tested (A.I.%) and no information on batch/lot number or the test substance appearance is provided. The source of the animals is not reported. Results are not reported in a way for this reviewer to accept the laboratory's conclusion. There are no individual or group scores for dermal irritation during the induction or challenge phases reported. Also, it is not clearly stated that the control animals were treated with the test substance at challenge. No historical positive control study was submitted. This is required to ensure the testing facilities ability in recognizing/performing a dermal sensitization

study. No Quality Assurance statement was provided with the study. Also, The GLP and Data Confidentiality statements submitted were signed in 1990. 15 years after the test was performed.

COMPLIANCE: Signed and dated GLP, and Data Confidentiality statements were provided.

I. PROCEDURE

A. Induction - Once a day for 10 days a 1% w/v suspension of the test substance was subcutaneously injected into 10 test animals. For the first injection 0.05 mL was administered and 0.1 mL for the remaining 9 injections. 24 hours after each injection the animals were observed for dermal irritation.

B. Challenge - Fourteen days after the last induction a challenge injection of both 0.05 mL of the 1% w/v suspension and 0.05 mL of water were given to each of the test animals and to a set of 10 naive control animals. Several times over the next 24 hours the injection sites were evaluated and the animals were graded for dermal irritation. No positive control was included in this study.

C. Naive Controls - A set of 10 naive control guinea pigs were treated in the same manner as the test animals except they were treated with the suspension fluid only.

II. RESULTS and DISCUSSION:

A. Reactions and duration - Low grade reddening and swelling was noted in areas treated with both the 1% w/v suspension and water for both the test and control animals.

B. Positive control - No positive control study was included in this study.

C. Reviewer's Conclusions: Disagree with study author.

D. Deficiencies: The reported information does not meet current GLP standards. No certification of the test substance is submitted, so it is not clear as to what was actually tested (A.I.%) and no information on batch/lot number or the test substance appearance is provided. The source of the animals is not reported. Results are not reported in a way for this reviewer to accept the laboratory's conclusion. There are no individual or group scores for dermal irritation during the induction or challenge phases reported. Also, it is not clearly stated that the control animals were treated with the test substance at challenge. No historical positive control study was submitted. This is required to ensure the testing facilities ability in recognizing/performing a dermal sensitization study. No Quality Assurance statement was provided with the study. Also, The GLP and Data Confidentiality statements submitted were signed in 1990, 15 years after the test was performed.

1. DP BARCODE: D
2. PC CODE:
3. CURRENT DATE: 14/FEB/2005
4. TEST MATERIAL:
[a] Thidiazuron (AI: 98.7% w/w. Batch No.: CH107623-02; yellowish powder)
[b] Thidiazuron Technical (AI: 98.7% w/w, Batch No.: 7/9 82; powder)
[c] Thidiazuron (AI: 98.7% w/w, Batch No.: CH107623-02; beige powder)
[d] Thidiazuron Technical (AI: unreported, Batch No.: unreported; appearance: unreported)

Study/Species/Lab Study # /Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat [a] Huntingdon Life Sciences Ltd. TOX 20138/04-05-2001	46121501	LD_{50} =>2,000 mg/kg (males, females combined)	III	A
Acute dermal toxicity/rat [a] Huntingdon Life Sciences Ltd. TOX 20139/04-05-2001	46121502	LD_{50} => 5,000 mg/kg (males, females combined)	IV	A
Acute dermal toxicity/rabbit [b] RCC 031140/05-07-1984	41426901	LD_{50} -> 4,000 mg/kg (males, females combined)	III	A
Acute inhalation toxicity/rat [c] SafePharm Laboratories TOX 20142/03-29-2001	46121503	LD_{50} => 3.48 mg/L (males, females combined)	IV	A
Dermal sensitization/guinea pig [d] Schering AG 125/75 09-06-1975	94246010	Is not a dermal sensitizer	–	U

Core Grade Key: A =Acceptable, S = Supplementary, U = Unacceptable, W = Waived