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

MAY 8 1987 ~~MAY 6 1987~~

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Triazole Residues in Plants; TILT® on Pecans and Small Grains

FROM: Alan Katz Toxicologist
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Hazard Evaluation Division (TS-769C) ACK 5/6/87

THRU: Marcia vanGemert, Ph.D.
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and

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TO: Lois Rossi, PM #21
Fungicide-Herbicide Branch
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and

Residue Chemistry Branch
Hazard Evaluation Division (TS-769C)

RCB has deferred to TOX in connection with PP#4F3074 on the question of the toxicological significance of residues containing the triazole moiety. TOX has evaluated the available acute and subchronic toxicity data, as well as metabolism/pharmacokinetics, reproductive, teratogenicity, and mutagenicity studies conducted with triazole alanine, the major plant metabolite of TILT®. Overall, triazole alanine exhibits a low potential for toxicity in mammals (see attached one-liners). RCB has concluded (memorandum, A. Smith to L. Rossi and Tox Branch, 12/31/86) that background levels of naturally occurring triazole-containing components in plants "appear at high and variable levels, and such levels can mask the contribution of triazoles due to treatment with propiconazole (TILT)."

Based primarily on the data base indicating relatively low toxicity of triazole alanine, and RCB's advisory that triazole compounds occur naturally in plants (e.g., peanuts, pecans, cereal grains) at high levels relative to any contribution attributable to the application of propiconazole, TOX Branch has determined that there is at this time no compelling toxicological basis for requiring additional metabolism studies or analytical methodologies specific for the triazole moieties contributed by propiconazole.

TOX Chem No: 002A Triazolyl alanine — File Last Updated 4/14/87 — Current Date

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD50, LC50, PIS, NOEL, LEL	TOX Category	OPP Guide/ Doc. No.
90-Day feeding - rat; Bayer AG Institute for Toxicology; #T9015049; 9/13/83 & 2/24/84	Triazolyl alanine Batch #TLB-1207	252425 258416	Levels tested in BOR:WISW (SPF-CPB) strain- 0, 1250, 5000, & 20,000 ppm NOEL = 5,000 ppm LEL = 20,000 pppm (slight reduction in male body weight gain)		Supplementary 004101 004276 Minimum 005094 005352 005841
Mutagenic - Ames; Bayer AG Institute for Toxicology; #T-1006005 & T-900372; 1/5/83	THS 2212 Batch # E238099	256058	Negative for mutagenic effects up to 12,500 ug/plate with and without (S-9) activation.		Acceptable 004562 Acceptable 004469
13-Week feeding - dog; Bayer Ag Institute for Toxicology; #T-7-015-713 March 26, 1984 & 4/28/86	THS 2212 97.5% ai Batch # TLB 1207	256058	Levels tested beagle dogs - 0, 3200, 8000, and 20,000 ppm. NOEL = 8000 ppm LEL = 20,000 ppm(reduced body wt gain)		Supplementary 004469 Minimum 005841
Mutagenic-Cell transformation in vitro (BHK) Huntingdon; #ICI394A/ 81153; CTL/C/1085 5/15/81	R152056 (Triazolyl alanine)	072208 252132	Levels tested:0.5, 1, 2, 4, 8 mg/ml without S9; and 1,2,4,8,16 mg/ml with S9. Positive, with and without activation.		Acceptable 004562 Acceptable 004766
Dissimilation chemicals metabolite or impurity or contaminant or salt or photodegradent or etc			Caswell # 862AA #323 EE (CGA-64250)		
Acute oral LD50- dog; Institute fuer Toxikologie, FRG; Report #82663; 10/14/82.	THS 2212 (Triazolylalanine) 99% purity	252132	Only 2 dogs used on study; both vomited a portion of the test material within 4 hours of dosing.		Invalid 004766
Acute oral LD50- rat; Central Toxicology Laboratory, ICI Limited; #CTL/P/600; 1/18/81	R152056 (Triazolylalanine) purity unspecified	252132	LD50 > 2000 mg/kg (only level tested). No mortalities at 2000 mg/kg dose tested.	III	Supplementary 004766

Tox Chem No. 862B -Triazolyl alanine

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute oral LD_{50}-rat; Bayer AG, Institute for Toxicology; Report #82661; 10/19/82	THS 2212 (Triazolylalanine) purity unspecified ("analytically pure")	252132	LD_{50} > 5000 mg/kg. Fasted male rats showed increased urinary output the day after dosing.	IV	Minimum 004766
Acute intraperitoneal LD_{50}-rat; Bayer AG, Toxicology Institute; Report #82661; 10/19/82	THS 2212 (Triazolylalanine) purity unspecified ("analytically pure")	252132	LD_{50} > 5000 mg/kg. At 5000 mg/kg, reversible CNS effects (spastic gait, lethargy, etc.) were observed within 1 hour of dosing. The lethal dose exceeds 5000 mg/kg.		Acceptable 004766
14-Day feeding-rat; Bayer AG, Institut fur Toxikologie; Report #82662; 10/25/82	THS 2212 (Triazolylalanine ca 100% purity	252132	Range Finding. Dose levels: 0, 3000, 10,000 ppm in drinking water. No mortalities or clinical signs of toxicity in males.		Supplementary 004766
Acute oral LD_{50}-mice; Bayer AG;#82661;10/19/82	THS 2212	252132	LD_{50} > 5000 mg/kg. No toxic signs.	IV	Minimum 004766
28-Day oral - rat;Bayer AG, Institute of Toxicology; Report #11491; Study No. T6011644;1/24/83.	THS 2212 (Triazolylalanine) "analytically pure"	252132	Dose levels: by gavage in Wistar BOR:WISW SPF/Cpb strain, 0, 25, 100, 400 mg/kg. No mortalities or clinical signs of toxicity. Some changes in hematology, clinical chemistry, organ weights. NOEL > 400 mg/kg(HDT)		Supplementary 004766
One-generation reproduction-rat; Central Toxicology Laboratory. Imperial Chemical Industries PLC; Study #RR023-0/FO; Report #CTL/L/470; 9/19/83.	Triazolylalanine Batch 1-48% Batch 2-unspecified purity	252132	Pilot Study Dose levels: 0, 150, 625, 2500, 10,000 ppm. No effects at 10,000 ppm.		Supplementary 004766

Tox Chem No. 862B

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Two-generation reproduction-rat; Central Toxicology Laboratory, Imperial Chemical Industries PLC; RRO-255/FO and RRO255/F1; 6/21/83.	Triazolyl-alanine 97.8% purity	252132	Interim report Dose levels: 0, 500, 2000, 10,000 ppm. No effects noted in the first 3 weeks of the study.		Reserved 004766
Mutagenic-Micronucleus test-mice; Imperial Chemical Industries; Report #AC83-2413;study #TQM4; 9/14/82	R152056 (Triazolyl-alanine) purity unspecified. Batch #02199/49	252132 072208	Dose levels: 2500, 5000 mg/kg. No toxicity, chromosomal damage, or erythropoietic effects; however, animals were dosed only once and only one sex tested.		Acceptable 004562 Unacceptable 004766
Teratology-rat; Central Toxicology Lab, Imperial Chemical Industries PLC; report #CTL/P/875;10/13/83.	Triazolyl-alanine 94.8%	252132	Levels tested by gavage in Alderley Park ALpk/AP strain from day 7 to day 16 of gestation-0, 100, 300 and 1000 mg/kg. Teratogenic NOEL > 1000 mg/kg(HDT) Feto toxic NOEL = 100 mg/kg Feto toxic LEL=300 mg/kg (non-ossification of odontoid process Maternal NOEL > 1000 mg/kg(HDT)		Minimum 004766 005155
Mutagenic-DNA Damage-*E. coli*; Bayer AG, Institut fuer Toxikologie;Report #82738; 1/5/83	THS 2212 (Triazolyl-alanine) purity unspecified	252132	Dose levels: 62.5, 125, 250, 500, 1000 ug/plate. Nonactivated-no DNA damage. S9 activated-inadequate assay.	NA	Nonactivated assay: Acceptable; S9 Activated assay: Unacceptable 004766
Mutagenic-Micronucleus test-mice; Bayer AG,Institut fuer Toxikologie; Study#T4011615;Report# 11054 & 84005; 8/9/82	THS 2212 (Triazolyl-alanine)purity unspecified ("analytically pure")	252132	Weak positive response for 8000 mg/kg at 24-hr. Study unacceptable due to lack of critical data on positive and negative controls.	NA	Acceptable 004562 Unacceptable 004766 005352

Tox Chem No. 862B

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Mutagenic-Bacterial Point Mutations; Bayer kologie; Report #11388; 1/5/83.	THS 2212 (Triazolyl-purity unspecified	252132	Dose levels of 20, 100, 500, 2500, 12,500 ug/plate did not induce re- typhimurium assay. Non-activated assay not evaluated due to lack of positive control.	NA	Acceptable 004562 004469 Nonactivated assay: Unacceptable; S9 Activated assay: Acceptable 004766
Metabolism/Pharmacokinetic-rat; Bayer AG;Report #11583;2/24/83	[^{14}C] Triazolylalanine; radiochemical purity 99%	252132	Dose levels: 5 mg/kg (metabolism); 10 mg/kg (whole-body autoradiography). Rapid absorption and excretion in male rats:95 percent of administered dose was absorbed and 94.5 percent of the radioactivity measured in urine within 48 hours. None of the metabolites were identified.	NA	Acceptable 004766
Metabolism-rat;Agricultural Division CIBA-GEIGY Limited;Report #CGA 131013,82/91-92/110; 3/2/83.	[^{14}C]D-L-triazolylalanine;radiochemical purity > 99%	252132	Dose level - approx. 50 mg/kg. Almost entirely excreted within 24 hrs; primary route-urine,secondary route-feces. Metabolites: N-acetyl, and unaltered triazolylalanine in urine.	NA	Minimum 004766

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade Doc. No.
Metabolism-rat; Ciba-Geigy; Study No. 131013, Report No. 11/83; Oct. 20, 1983.	^{14}C-D,L-Triazolylalanine. Purity > 99%	252132	In 24 hours, 69-86% of the dose was excreted unchanged in the urine, 8-19% was excreted as the acetyl derivative in the urine. About 3% of the dose was excreted in the urine as unknown metabolites. The total fecal radioactivity accounted for 3% of the total dose. The fecal metabolites were similar to those found in the urine except for one that could not be identified.	NA	Acceptable 004766
Mutagenic - BALB/3T3 mouse fibroblast transformation; Ciba-Geigy; Report #840324; Sept. 12, 1984	Triazolylalanine (Purity not specified)	257997	Negative with metabolic activation; inconclusive without activation. Concentrations up to 1000 ug/ml. Repeat test requested.		Unacceptable 005155 005352