CASWELL FILE

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

005094

MEMORANDUM MAY 9 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCE

SUBJECT: Triazolylalanine (THS 22112); Review of Subchronic Toxicity in Rats
EPA #: 3125-320; Record #: 154,722; Action Code: 400
Caswell #862B

TO: Henry Jacoby, PM-21
Registration Division (TS-767C)

FROM: Alan C. Katz, M.S., D.A.B.T.
Toxicologist, Review Section III
Toxicology Branch
HED (TS-769C)

Alan C Katz 4/25/86

THROUGH: William L. Burnam
Deputy Chief, Toxicology Branch
and
Theodore M. Farber, Ph.D., D.A.B.T.
Chief, Toxicology Branch

W L Burnam 4 26 86

Action Requested:

Review toxicology data; subchronic toxicity to rats.

Discussion:

The Toxicology Branch has conducted preliminary reviews of the 3-month rat feeding study with triazolylalanine (THS 2212). Results of these reviews were reported in memoranda to H. Jacoby from M. Copley (11/28/84, Doc.#004101) and A. Katz (2/28/85, Doc.#004276; and 9/10/85), copies of which are attached.

The completed DER for this study, as well as the Data Review Record Sheet and up-dated "One-liners", are also attached. The Discussion section of the DER describes numerous deficiencies in the report which should be brought to the attention of the registrant.

Conclusions:

The 3-month feeding study in rats with triazolylalanine is marginally acceptable as CORE Minimum data. No significant toxic effects were found at dietary concentrations up to and including 5,000 ppm. At 20,000 ppm (the highest dose tested), triazolylalanine caused a slight reduction of body weight gain in males but not in female Thus, for this study, the NOEL = 5000 ppm and the LEL = 20,000 ppm.

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DATA EVALUATION REPORT

A. Compound:

2-amino-3-(1,2,4-triazolyl-1-yl)-propionic acid; triazolylalanine

B. Compound Number:

THS 2212

C. Study Report Citation:

Title: "Triazolylalanine (THS 2212): Study for Subchronic Toxicity to Rats (Three-month feeding study)"

Laboratory: Bayer AG Institute of Toxicology
Wuppertal-Elberfeld

Report Number: 86476

Record Number: 154722

Caswell Number: 862B

Date: 2/24/84

EPA Accession Number: 258416

Submitted to EPA by: Mobay Chemical Corporation
Kansas City, MO 64120

Authors: Dr. D. Maruhn
Dr. E. Bomhard

D. Reviewed By: Alan C. Katz, M.S., D.A.B.T
Toxicologist
Toxicology Branch
Hazard Evaluation Division (TS-769C)

Alan C Katz
(Signature)

4/25/86
(Date)

E. Secondary Review By: William L. Burnam
Deputy Branch Chief
Toxicology Branch (TS-769C)

(Signature)

(Date)

F. Classification: CORE Minimum

G. Conclusion:

Dietary administration of triazolylalanine to male and female rats for three months at concentrations of 1250 or 5000 ppm elicited no significant toxicologic effects. Triazolylalanine at 20,000 ppm caused a slight reduction of body weight gain in males, but not in females.

H. Materials:

Test compound: THS 2212, Batch No. TLB 1207 (6th delivery); Purity: 97.5% (a.i.)
Test animals: SPF rats, strain Bor:WISW (SPF CPB)
Supplier/breeder: Winkelmann, Borchen
At initiation: 5-6 weeks of age; males: 71 g; females: 72 g.

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H. Materials (Cont'd):

The basal diet consisted of powdered feed (Altromin 1321), from Altromin Gmbh, Lage.

I. Methods:

The animals were acclimated to the laboratory for 6 days prior to initiation of treatment. They were individually housed in Makrolon cages (type II) on "dust-free wood granulate." The animal room was maintained at 23 ± 2°C and 55 ± 10% relative humidity, with a 12-hour light/dark cycle.

The test compound was mixed in the diet, and given daily for 14 weeks (May-August, 1983). Storage conditions for the technical material and the blended diet were not specified in the study report. Stability and concentration of the test substance in the diet were confirmed by analysis.

The animals were randomly assigned, by a weight-stratification design, to the following groups:

Dose Group	Dietary conc.(ppm)	Males	Females
1 (Control)	0	20	20
2 (Low)	1,250	20	20
3 (Mid)	5,000	20	20
4 (High)	20,000	20	20

Food and tap water were provided ad libitum. The animals were identified by cage marks.

The animals were observed daily. Food consumption, water consumption and body weights were recorded weekly. Clinical pathology (hematology, clinical chemistry and urinalysis) tests were conducted on specimens collected at one month and at termination from 10 randomly preselected animals/sex/group. The animals were fasted for 16 hours during urine collection. It is not clear from the text of the report (see section 4.7.1) whether the animals were fasted prior to blood collection.

Hematology

Hematocrit
Erythrocyte count
Leukocyte count
Thrombocyte count
Thromboplastin time (at termination only)
Differential leukocyte count
Mean corpuscular volume
Mean corpuscular hemoglobin
Mean corpuscular hemoglobin concentration

Clinical Chemistry

Glucose
Urea
Creatinine
Total protein
SGOT
SGPT
Alkaline phosphatase
Triglycerides
Bilirubin
Cholesterol
Sodium
Potassium
Chloride
Calcium
Phosphate

I. Methods (Cont'd):

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Urinalysis

Protein	Bilirubin
Glucose	Occult blood
Ketone	Specific gravity
Volume	Microscopic
pH	

Ophthalmoscopic examinations were performed on 10 animals/sex in the control and high dose groups.

All animals were necropsied. At termination of the study, all animals were sacrificed by exsanguination under diethyl ether anesthesia. Organs weighed at necropsy were: brain, heart, lung, liver, spleen, kidneys, adrenals, and testes. The following tissues were placed in Bouin's solution and processed for histopathologic evaluation:

Heart	Uterus	Colon
Lung	Ovaries	Rectum
Liver	Mammary tissue	Lymph nodes
Spleen	Salivary glands	Urinary bladder
Kidneys	Thyroid	Eyes
Adrenals	Pancreas	Spinal cord (3 sections)
Pituitary	Thymus	Nerve (N. ischiadicus)
Brain	Esophagus	Sternum (with marrow)
Pancreas	Stomach	Femur
Testicles	Duodenum	Skeletal muscle
Epididymides	Jejunum	Trachea
Prostate	Ileum	Aorta
Seminal vesicle	Cecum	Gross lesions

All tissues listed above were microscopically examined for all high dose and control animals and all animals which died during the study.

The numeric data were analyzed for statistical significance at the 95% and 99% limits of confidence using the Mann, Whitney U test.

J. Results:

Mean levels of consumption of the test material over 13 weeks for low, mid and high dose males were reported as 0.09, 0.37 and 1.51 g/kg/day, respectively. Consumption of test material for females was 0.10, 0.40 and 1.68 g/kg/day. Mean food consumption values for all treated groups were comparable to control values. Mean body weight gain of high dose males was slightly reduced. At week 13, the mean body weight of high dose males was approximately 9% lower than the control value; however, the mean weight of the high dose males was less than 4% lower than controls when sacrificed at termination of the study. The body weight data are summarized in Table 1.

Four females (2 in the low dose group and 2 in the mid dose group) died during the study. All of these unscheduled deaths were associated with blood collection and are not considered treatment-related. Clinical observations indicated no apparent treatment-related effect. No differences were reported

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J. Results (Cont'd):

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Table 1. Selected Body Weights, g. (Mean + std. dev.)

Dietary conc.(ppm)	Week 0	4	8	13
Males				
0	71 ± 4	189 ± 13	256 ± 24	315 ± 23
1250	72 ± 4	189 ± 15	269 ± 24	312 ± 25
5000	71 ± 4	187 ± 12	270 ± 21	309 ± 29
20,000	71 ± 5	171** ± 14	243** ± 20	288** ± 25
Females				
0	71 ± 7	133 ± 8	170 ± 13	189 ± 11
1250	73 ± 5	133 ± 9	171 ± 11	188 ± 11
5000	72 ± 5	137 ± 12	176 ± 14	193 ± 15
20,000	72 ± 5	136 ± 9	171 ± 12	186 ± 13

**p<0.01

between groups with respect to appearance or behavior; however, individual daily clinical observations were not presented in the study report. No treatment-related ocular effects were found in any of the animals examined.

The study report states that "the treated rats in the 1250 to 20,000 ppm dose groups did not differ toxicologically significantly from the controls, either in erythrocyte, leucocyte and thrombocyte counts, or in haemoglobin level and mean corpuscular volume." However, this reviewer notes that total leucocyte levels were slightly lower than those of controls at 1 month and at termination in mid and high dose males and at termination in high dose females. These data are presented in the following table:

Table 2. Mean Leucocyte Counts (x 10^9/l?)[% difference from control mean]

Dietary conc. (ppm)	1 Month Males	1 Month Females	3 Months Males	3 Months Females
0	8.6	8.4	10.1	9.6
1,250	7.5 [13]	7.8 [7]	9.6 [5]	8.2[15]
5,000	7.0** [19]	7.8 [7]	8.4** [17]	8.3[14]
20,000	7.1** [17]	7.7 [8]	8.3* [18]	7.2** [25]

*p<0.05
**p<0.01

No other hematologic changes are considered remarkable.

No significant treatment-related blood chemistry changes were found, with the possible exception of reduced triglyceride levels in females. Triglyceride data are summarized in Table 3.

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J. Results (Cont'd):

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Table 3. Triglyceride Levels (mmol/l)

3 Months

Dietary conc.(ppm)	Males	Females
0	1.22	1.30
1,250	1.03	1.24
5,000	1.11	0.77**
20,000	0.72**	0.85**

**p<0.01

No additional evidence was found to indicate any alteration in liver function.

Urinalysis results revealed no apparent treatment-related effects.

Evaluation of gross necropsy observations did not indicate any alterations related to treatment. In high dose males, mean absolute and relative (i.e., organ:body weight) heart weights were slightly reduced and relative kidney weights were slightly increased compared to control values. These data are presented in the following table:

Table 4. Selected Organ Weights

Absolute Weights

	Males			Females		
Dietary conc.(ppm)	Body(g)	Heart (mg)	Kidneys (mg)	Body(g)	Heart(mg)	Kidneys(mg)
0	304	904	1844	184	652	1228
1,250	298	869	1895	186	630	1239
5,000	305	885	1863	190	632	1261
20,000	293	817*	1902	187	644	1295

Relative Weights (mg organ weight/100 g body weight)

	Males		Females	
Dietary conc.(ppm)	Heart	Kidneys	Heart	Kidneys
0	298	611	354	669
1,250	294	642	339	667
5,000	290	614	335*	667
20,000	280*	652*	346	695

*p<0.05

There was no histomorphologic evidence of any alteration related to treatment with triazolylalanine.

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K. Discussion:

At a dietary concentration of 20,000 ppm, body weight gain of males was slightly reduced. The reductions in total leucocytes and serum triglyceride levels, while considered to be treatment-related, are of minimal clinical significance. In the absence of any related histologic changes, the slightly reduced heart weights and increased kidney weights among high dose males are of questionable relationship to treatment and are not regarded as significant, per se.

The U-test used to analyze the hematology, blood chemistry, body weight, food consumption, and organ weight data is a non-parametric test. No justification is presented in the report for the use of non-parametric rather than parametric tests of these numeric data. Application of ANOVA would have been more appropriate.

The statement in section 4.2 of the report: "The animals were identified by cage marks", suggests that this was the only method of animal identification. A more reliable means of identification should have been used to prevent possible mix-ups such as may occur when an animal is removed from its cage and inadvertently returned to the wrong cage, or when animals are transferred to clean cages.

Two males in the mid dose group showed the greatest degree of growth retardation or reduced body weight gain from week 6 through week 13. Animal #84 gained a mere 26 grams during this 7-week period, and Animal #100 showed only a 12-gram gain for the same period -- principally because of a remarkable 81-gram loss during week 12-13. Neither of these cases is cited in the text or in the clinical observations section of the Addendum. Additional concerns regarding the quality of clinical evaluations are aroused by such vague observations as (Addendum): "Abnormality on tooth" (1 mid and 2 high dose males; 1 high dose female) and "Unspecific signs of illness" (2 high dose males), with no further explanation given. Also questionable is a 78-gram increase in the body weight of Animal #19 (control male) during week 13. The mean weight gain for this group during this period was 12 grams; excluding the data for Animal #19 during this period would result in a group mean weight increase of 9 grams. Parenthetically, it is tempting to speculate that, considering the inadequate means of identification, animals #100 and #19 may have inadvertently been switched near termination of the study.

The study report submission should have included a copy of the protocol, as well as a description and explanation of all deviations which occurred during the study, if applicable. With respect to the Quality Control statement for this report, the scope of each of the checks/inspections cited were not specified.

The text of the report states that "(t)en animals per sex and group were ophthalmologically examined before the start and at the end of the study." However, results were reported only for 10 animals/sex in the control and high dose groups only.

A table summarizing gross observations at necropsy was not provided in the study report. Tabulation of these data, summarized by sex and dose, is required under FIFRA Subdivision F Guidelines, §82-1(h)(3)(i). However, the individual observations were carefully reviewed by the Toxicology Branch, and no treatment-related effects were found.

K. Discussion (Cont'd):

In-life clinical observations were not presented in accordance with FIFRA Guidelines. The test report summary should include individual animal data regarding the time of observation of each abnormal sign and its subsequent course, in accordance with §82-1(h)(3)(iii)(B).

As noted in a previous memorandum (A. Katz to H. Jacoby, 9/10/85), homogeneity of the test substance in the blended diet was not established.

Despite the deficiencies noted above, this study appears to be scientifically valid on an overall basis and is considered marginally acceptable as a CORE Minimum study.

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

005094

SEP 10 1985

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Triazolylalanine (THS 2212); Diet Analysis for Subchronic Feeding Study in Rats

EPA Reg. #: 3125-320; Record #: 155160
Accession #: 258662
Caswell #: 862 B
Data Submitted By: Mobay Chemical Corporation
(Mobay Report No. 86476)

TO: Henry M. Jacoby
Product Manager (21)
Registration Division (TS-767)

FROM: Alan C. Katz, M.S., D.A.B.T. 9/3/85
Toxicology Branch
Hazard Evaluation Division (TS-769C)

THRU: Robert P. Zendzian, Ph.D. 9/9/85 9/10/85
Acting Head, Review Section IV

Action Requested:

Review captioned data (Mobay Report No. 86476: "Summary of Diet Analysis Results"; dated April 15, 1985). This data was not included in the original submission of data pertaining to a 90-day rat feeding study with triazolylalanine, and was requested by the Toxicology Branch (see attached memo, ACK to HMJ, 2/8/85).

Discussion:

Homogenicity results require additional clarification. The data presented were generated in association with Study Number T8015 796; however, the subchronic rat study under primary review is identified as Study No. T9015 049. In order to evaluate the relevance of these data, it must be demonstrated that the methods and materials used in both studies were identical with respect to diet preparation. Also, it is not stated whether the 3 samples tested at each of the 2 concentrations were taken from the same batch of blended feed. Further, we note that 2 values are presented for each sample tested; it is not clear whether these individual values represent determinations on "replicate" portions from each sample, or duplicate determinations on the same sample. The registrant should address the issues of sensitivity of the method used, and the reasons for any apparent intra-sample variability. Methods used in diet preparation and sampling should be more fully explained.

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Conclusions:

The data presented are considered adequate to establish purity of the test substance (97.5%) as well as stability and concentration in the diet for this study. Homogenicity data could not be evaluated, and is therefore considered unacceptable. The Toxicology Branch, however, does not find this deficiency alone to be sufficient cause to consider this particular study invalid, and will complete its evaluation based on the merits of other data provided.

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

004276

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: TILT Fungicide; Petition Nos. 4F3007 (Pecans), 4E3026 (Bananas), 4F3074 (Rice, Wheat, Barley, Rye), 4G3075 (Rice, Wheat, Barley, Rye); Caswell No. 323EE.

TO: Henry Jacoby
Product Manager #21
Registration Division (TS-767C)

THRU: Christine F. Chaisson, Ph.D. C F Chaisson 2/1/85
Head, Review Section IV
Toxicology Branch
Hazard Evaluation Division (TS-769C)

FROM: Alan C. Katz, M.S., D.A.B.T. Alan C Katz 2/8/85
Toxicology Branch
Hazard Evaluation Division (TS-769C)

The Toxicology Branch has conducted a preliminary review of the 90-day rat feeding study with triazole alanine (THS 2212; Bayer AG Institute of Toxicology, Wuppertal-Elberfeld, Report no. 12397; EPA Accession Nos. 072207, and 073114), including the histopathological data which was submitted to this Agency by CIBA-GEIGY Corporation on November 29, 1984. The following deficiencies have been noted:

1) Except for the histopathology section, the final report is not signed by responsible personnel and does not contain a Quality Assurance statement by the sponsor or contractor.

2) Clinical observations are not presented for individual animals or summarized according to sex/dose group.

3) Results of ophthalmological examinations are not presented.

4) Sufficient data to establish purity of the test substance and homogeneity, stability and concentration in the diet are not presented.

The sponsor must address the deficiencies cited above in order for the Toxicology Branch to complete its evaluation of this study.

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

004101

005094

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg. No. 3125-320. Review of the intermediate study titled "Triazolylalanine (THS 2212) Subchronic Toxicity Investigations in Rats", Mobay Report No. 86110, 9/13/83.
Tox. Chem. No. 862B
Accession No. 252425.

TO: Henry Jacoby, PM #21
Registration Division (TS-767C)

FROM: Marion P. Copley, D.V.M. Marion P. Copley 11/26/84
Toxicology Branch
Hazard Evaluation Division (TS-769C)

THRU: Edwin R. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769C)
Budd 11/26/84

Mobay Chemical Corporation has submitted this intermediate data as part of a prior document titled "Properties and Safety Assessment of Triazolyl Alanine" (sent December 19, 1983, accession No. 252132). The current study is a 90 day oral feeding rat study using triazolyl alanine, a crop metabolite of Bayleton® and other triazole containing compounds. Conclusions for this study are deferred until receipt and analysis of the histopathology in the final report.

COPLEY, Disc.2, Doc.3, Triazolyl alanine, #862B, 5/10/84||11/26/84

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STUDY TYPE: 90 Day Oral Feeding Study in Rats, Intermediate Report Without Histopathology

ACCESSION NUMBER: 252425 TOX. CHEM. NO.: 862B

STUDY NUMBER: Mobay Report No. 86110
Bayer AG Institute for Toxicology No. T9015049

SPONSOR: Mobay Chemical Corporation

TESTING FACILITY: Bayer AG Institute for Toxicology, Germany

AUTHORS: D.Maruhn, E.Bomhard

REPORT ISSUED: September 13, 1983

TEST MATERIAL: Triazolyl alanine (THS 2212), 97.5% a.i.; a metabolite of various triazole-containing pesticides in crops. Batch TLB 1207.

SYNONYM: °2-amino-3-(1,2,4-triazol-1-yl)-propanoic acid

MATERIALS and METHODS: Five-6 week old male and female BOR:WISW(SPF CPB) rats (weighing 67-76 gm) were acclimated for 6 days. They were assigned to light and heavy groups then randomly distributed to the following treatment groups:

	dose (ppm)	number of animals male	female
control	0	20	20
low dose (LDT)	1250	20	20
mid dose (MDT)	5000	20	20
high dose (HDT)	20000	20	20

Animals were individually housed in an environmentally controlled room. They received water ad libitum and fresh pulverized food with test substance once a week. Although the rats had individual numbers, they were only identified by cage markers.

General Observations: During the 3 month test period, body weight, food consumption and water consumption were recorded weekly. All rats were observed twice daily on weekdays and once daily on weekends and holidays for clinical signs. Pupillary reflexes, eye adnexa, conjunctiva, anterior chamber and retina of each eye were evaluated in ten animals/sex in the control and HDT groups at the start and the end of the study.

Laboratory Studies: Tests were done on the same 10 randomly picked animals of each sex in each group at 1 and 3 months after treatment was initiated. The animals were fasted for 16 hr during urine collection. Blood was collected from the caudal vein and the orbital vein plexus. The parameters examined were as follows: Hematology - Erythrocyte, leukocyte and thrombocyte number, hemoglobin, hematocrit, mean cell volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), differential blood cell count and thromboplastin time. Clinical Chemistry Alkaline phosphatase (ALP), glutamate-oxaloacetate-transaminase (GOT), glutamate-pyruvic-transaminase (GPT), bilirubin, cholesterol, total protein, glucose, urea, creatinine, triglycerides, calcium, potassium, sodium,

inorganic phosphate and chloride. Urinalysis - volume, specific gravity, pH, glucose, protein, bilirubin, urobilinogen, ketone and the presence of blood were determined. Appearance was also noted and the sediment examined microscopically.
Pathology: Animals that died during the study were necropsied, examined macroscopically, and tissues (listed below) were fixed in Bouin's solution. At 3 months all surviving animals were narcotized with diethyl ether, exsanguinated and necropsied. After macroscopic examination, the following tissues were removed to Bouin's fixative for histopathology: aorta, eyes, duodenum, jejunum, ileum, cecum, colon, rectum, femur, *brain, bladder, *heart, *testes, hypophysis, salivary glands, *liver, *lungs, lymph nodes, stomach, mammary glands, *spleen, epididymides, *adrenals, *kidneys, esophagus, *ovaries, pancreas, prostate, spinal cord, seminal vesicles, thyroid, skeletal muscle, ischial nerve, sternum/bone marrow, thymus, trachea, uterus and visible lesions.
All tissues from animals that died during the study and control and high dose rats were examined microscopically. Only the liver, lungs and kidneys and lesions were examined histologically in the 1250 and 5000 ppm groups.
Statistics: Arithmetic means, standard deviations and upper and lower limits of the confidence range (1-a = 95% and 99%) were calculated. The U-test of Mann, Whitney and Wilcox was used to compare treatment values to the control values (a = 5%, 1%).

RESULTS:
Mortality: Two females each at 1250 and 5000 ppm died due to either anesthesia or hypovolemia during routine blood collection.
General Observations: There was no treatment related body weight change in the females or in the low and mid dose males. High dose males gained weight slightly slower from week 3 and weighed about 8% less than controls by termination (a=1%):

Male Body Weights (gm)

week	0	4	8	13
0 ppm	71	189	256	315
1250 ppm	72	189	269	312
5000 ppm	71	187	270	309
20000 ppm	71	171	243	288

There was no treatment related change in food or water consumption for either males or females. Average daily intake of test compound was similar for males and females:

Test compound intake (gm/kg/day)

Group (ppm)	male	female
control	0	0
1250	.09	.10
5000	.37	.40
20000	1.51	1.68

There were no treatment related differences in appearance, behavior, activity or coat condition for males or females in any treatment group. There was also no indication by the registrant of eye damage due to treatment.
Laboratory Studies: Hematology - Although the registrant reported no treatment related, biologically significant changes, several parameters showed potentially treatment related trends. Leukocyte counts (although within normal limits) were significantly decreased in HDT and MDT males at both 1 and 3 months as well as HDT females at 3 months. Absolute neutrophil counts showed a small but dose related decrease in males at 1 month but at 3 months the absolute neutrophil

*these tissues were weighed

count had a dose related increase. Lymphocytes were increased in mid and high dose males at 1 month but decreased in the same groups at 3 months. Thrombocytes were also significantly depressed in the HDT males and females at 1 month. All other parameters appeared to be unchanged by treatment. Clinical chemistry - Triglycerides were depressed in high dose males and mid and high dose females at both 1 and 3 months. All other clinical chemistries were within normal ranges, not statistically significant or not biologically relevant. Urinalysis - There were no treatment related changes in the parameters tested. Pathology: There were no macroscopic or organ weight (absolute and relative) changes clearly related to treatment in either males or females. Absolute and relative kidney weights, however, tended to be increased in high dosage level males and females. Histopathology results were not included in this report (they will be sent by the registrant later).

DISCUSSION: The 4 early female deaths were not compound related as they occurred only in the low and mid doses and were related to blood collecting procedures. A slight decrease in HDT male body weight was the only pertinent change or toxic sign. Although the hematology trends mentioned in the results may be treatment related, they were within the normal range and did not deviate greatly from control values. Decreased triglycerides in HDT males and MDT and HDT females may also be compound related but the biological relevance in the absence of histopathology can not be determined at this point. All other laboratory test results were within normal ranges. There were no pretest data which made it hard to distinguish between small treatment related effects and intergroup variation.

CONCLUSIONS: Deferred until receipt and evaluation of the histopathology report.

CLASSIFICATION: Core-supplementary until the histopathology has been evaluated.

Marion P. Copley, D.V.M. MPC 11/26/89
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769C)

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Tox Chem No. 862B -Triazolyl alanine | File Last Updated 4/26/86 | Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ 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
Mutagenic - Ames; Bayer AG Institute for Toxicology; #T-1006005 and T-900372; January 5, 1983	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	THS 2212 97.5% ai Batch # TLB 1207	256058	Levels tested beagle dogs - 0, 3200, 8000, and 20,000 ppm. NOEL = cannot be established until the additional requested data is evaluated.		Supplementary 004469
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 LD_{50}-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 LD_{50}-rat; Central Toxicology Laboratory, ICI Limited; #CTL/P/600; 1/18/81	R152056 (Triazolylalanine) purity unspecified	252132	LD_{50} > 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

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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;9/14/82.	R152056 (Triazolyl-alanine) purity unspecified.	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
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; Report #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

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Mutagenic-Bacterial Point Mutations; Bayer kologie; Report #11388; 1/5/83.	THS 2212 (Triazolyl- purity unspe- cified	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/Pharmacokine- tic-rat; Bayer AG;Report #11583;2/24/83	[^{14}C] Tri- azolylalanine; radiochemical purity 99%	252132	Dose levels: 5 mg/kg (metabolism); 10 mg/kg (whole-body autoradiogra- phy). Rapid absorption and excre- tion in male rats:95 percent of ad- ministered dose was absorbed and 94.5 percent of the radioactivity measured in urine within 48 hours. None of the metabolites were identi- fied.	NA	Acceptable 004766
Metabolism-rat;Agricul- tural Division CIBA- GEIGY Limited;Report #CGA 131013,82/91-92/ 110; 3/2/83.	[^{14}C]D-L- triazolyl- alanine;radio- chemical puri- ty > 99%	252132	Dose level - approx. 50 mg/kg. Al- most entirely excreted within 24 hrs; primary route-urine,secondary route-feces. Metabolites: N-acetyl, and unaltered triazolylalanine in urine.	NA	Minimum 004766

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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