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

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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
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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

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:

		number of animals	
	dose (ppm)	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)[1]

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

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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.

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