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

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Azinphos-Methyl

Project No.: 9-2031
TOX Chem No.: 374

FROM: Ray Landolt 3/12/91
Review Section I
Toxicology Branch II - HFAS
Health Effects Division (H7509C)

TO: Lois Rossi, PM 74
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THRU: Mike Ioannou, Section Head J.M. Ioannou 3/12/91
Review Section I
Toxicology Branch II - HFAS
Health Effects Division (H7509C)
and
Marcia van Gemert, Branch Chief M. van Gemert 3/15/91
Toxicology Branch II - HFAS
Health Effects Division (H7509C)

Registrant: Mobay Corporation, Letter of June 1, 1989

Action Requested: Review a chronic feeding/carcinogenicity study in rats submitted in response to the Reregistration Guidance Document of September 11, 1986.

Conclusion: This study satisfies the guideline data requirement (83-1) for a chronic feeding/carcinogenicity study in rats.

Negative for carcinogenicity

A MTD was demonstrated with plasma (67%), RBC (37%), and brain (55%) cholinesterase (ChE) inhibition at the 45 ppm level.

ChE NOEL = 5 ppm (0.25 mg/kg/day)
LEL = 15 ppm (0.75 mg/kg/day) with ChE activity decreased in female plasma (19-35%), in male and female RBC (10-22%) and in female brain tissue (21%).

Systemic NOEL = 15 ppm (0.75 mg/kg/day)
LEL = 45 ppm (2.25 mg/kg/day) with alopecia, decreased b.wt. (10%) and increased relative liver weight (9%).

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Reviewed By: Ray Landolt 3/12/91
Section I, Toxicology Branch II - HFAS (H7509C)
Secondary Reviewer: Mike Ioannou 3/12/91
Section I, Toxicology Branch II - HFAS (H7509C)

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DATA EVALUATION REPORT

Study Type: Chronic Feeding/Carcinogenicity Study in Rats (83-1)

TOX Chem No. 374
MRID No. 411199-01
Project No. 9-2031

Test Material: 0,0-Dimethyl S-[(4-oxo-1,2,3-benzotriazin-3(4H)-yl) methyl]phosphorodithioate

Classification: Organic phosphate insecticide

Common Name: Azinphos-methyl (R1582)

Study No.: 99167

Date of Study: December 10, 1984

Sponsor: Mobay Corporation

Testing Facility: Bayer AG, Fachbereich Toxikologie
Federal Republic of Germany

Title of Report: Study of Chronic Toxicity and Carcinogenicity to Wistar Rats

Author: Dr. W.M. Schmidt and Dr. Chevalier

Quality Assurance: Dr. H.P. Schulz, Bayer AG, October 21, 1987

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Classification of Data - Minimum

Deficiency: Organ weights for heart, lung, ovaries, and spleen were not reported.

A. Materials

1. Test Compound - Technical azinphos-methyl of batch number 79-R-225-42 with a purity of 87.2% was used in this study. Approximately 15 percent more of the technical a.i. was used in the preparation of the nominal dietary concentrations.

2. Test Animals - Two hundred forty males weighing 73 to 89g and 240 females weighing 69 to 91g (5 to 6 week old) SPF Wistar rats were used in this study.

B. Study Design

1. Allocation of Animals - Ten rats/sex/group were used for an interim necropsy at one-year.

	One-Year		Two-Year	
Dose Levels (ppm)	Male	Female	Male	Female
Control	10	10	50	50
5	10	10	50	50
15	10	10	50	50
45	10	10	50	50

Dose levels were established from the results of a four-week range-finding study using Wistar rats (Report No. 11813, May 18, 1983). All animals were housed individually with feed and water available ad libitum. The environmental conditions were standardized with a 12-hour light/dark cycle, room temperature of 22 ± 2 °C, relative humidity approximately 50 percent and an air exchange rate of 10 times per hour.

2. Diet preparation - The test diets were mixed weekly with (Altromin® 1321 meal) a pulverized dietary ration. Peanut oil (1.0%) was added to each mix, including control, to bind the dust. The test dietary levels of 5, 15, and 45 ppm were analyzed at three month intervals and found to be within 112, 102, and 104 percent, respectively of the nominal concentration over the two-year period. The test material in the feed mixture was stable for 10 days within a tolerance range of ± 20 percent of the nominal concentration.

3. Statistics - Individual body weight, water intake, clinical laboratory parameters and organ weights were subjected to the following calculations (per this study report).

"Arithmetic group means, standard deviations(s), and upper and lower confidence limits at the confidence level 1 - alpha = 95 percent and 1 - alpha = 99 percent. The data

for the test populations were compared with the control population by means of the significance test (U-test) of H.B. Mann and D.R. Whitney (Ann. Math. Stat., 18:50 (1974)) and F. Wilcoxon (Biometrics, 1:80 (1945)) at the significance level alpha = 5 percent and alpha = 1 percent (two-tailed).

In the case of remarkable differences in frequency, incidence data (mortality, clinical signs, etc.) were processed using the exact test of Fisher (Statistical Methods for Research Workers, Oliver & Boyd, Edinbourgh, 1925) at the significance level alpha = 5 percent and alpha = 1 percent (two-tailed)."

C. Methods and Results

1. Observations - All animals were observed twice daily for signs of toxicity and mortality. A detailed examination of individual animals was performed weekly.

   a. Gross - An increased incidence of alopecia was observed for animals fed the 45 ppm level occurring in males (15/60 vs. 8/60 for controls) and significantly ($p < 0.01$) in females (49/59 vs. 18/60 for controls) during weeks 8 through the termination of the study.

   b. Palpable masses - No treatment-related incidence or time of occurrence was observed between the test and control groups.

   c. Ophthalmology examinations were performed at 12 months on all control and test animals scheduled for the interim sacrifice and at 24 months on 10 animals per sex from the control and 45 ppm dose groups.

      No treatment-related findings were observed between the test and control group.

   d. Mortality - The number of animals surviving 104 weeks of dietary exposure to 5, 15, and 45 ppm of azinphos-methyl was comparable to the control survival rate for the same period.

Cumulative Mortality over the 104-Week Period

Dose Level (ppm)	Males		Females	
	Number	Percent	Number	Percent
Control	9	18	11	22
5	7	14	10	20
15	6	12	13	26
45	7	14	13	26

e. Body weights were determined initially, weekly through week 13, then at two-week intervals for the duration of the study.

Body weight gain was significantly ($p < 0.01$) decreased at the 45 ppm level for females by 5 percent during the first year and significantly ($p < 0.01$) for males by 10 percent over the two-year period as compared to the controls.

f. Food consumption was determined weekly.

Food consumption between the controls and test males was comparable over the two-year period; however, an approximate 12 percent increase in food intake was reported for females fed the 45 ppm level during the later 26 weeks of the study.

g. Dietary Intake of Azinphos-methyl over 104 Weeks

	Male		Female	
Dose Level (ppm)	mg/kg/day	Total mg/kg	mg/kg/day	Total mg/kg
5	0.25	182	0.31	227
15	0.75	544	0.96	696
45	2.33	1693	3.11	2262

h. Water intake was determined for all groups during weeks 32, 41, 51, 61, 71, 82, 91, and 101 of the study.

Mean daily water intake for females fed the 45 ppm level was significantly ($p<0.05$) increased by 13-18% during the later 19 weeks of the study.

2. Clinical Findings - Blood was collected for hematolgy and clinical chemistry determinations at 3, 6, 12, 18, and 24 months from 10 animals per sex per group.

a. Hematological parameters examined

Leukocyte differential count
Erythrocyte count and morphology
Hemoglobin
Hematocrit
Thrombocyte count
Leukocyte count
Mean corpuscular hemoglobin
Mean corpuscular concentration
Mean corpuscular volume

Thrombocyte values were significantly ($p < 0.05$) elevated for females fed the 45 ppm level, as compared to the control values by 20 to 25 percent during the last 12 months of the study. However, these values were reported to be within the normal range of variation.

b. Clinical chemistry parameters examined

Alkaline phosphatase	Urea
Aspartate aminotransferase	Triglycerides
Alanine aminotransferase	Phosphate (inorganic)
Glucose	Calcium
Bilirubin	Potassium
Creatinine	Sodium
Total protein	Chloride

No dose-related changes were reported in the clinical chemistry parameters examined.

c. Cholinesterase (ChE) activity in plasma and erythrocytes was determined at 1, 3, 6, 12, 18, and 24 months and in brain at 12 and 24 months on 10 animals per sex per group. Cholinesterase activity was determined by the Ellmann method.

i. Plasma ChE activity was significantly ($p < 0.01$) decreased at the 45 ppm level in males (38 to 49%) and in females (54 to 67%), as compared to the control values, over the 24 month period. A significant ($p < 0.01$) decrease in plasma ChE activity, as compared to the controls, was reported for females (19 to 35%) fed the 15 ppm level over the 24 month period.

ii. Erythrocyte ChE activity was significantly ($p < 0.01$) decreased at the 45 ppm level in males (20 to 37%) and in females (23 to 31%), as compared to the control values, over the 24 month period. A significant ($p < 0.01$) decrease in erythrocyte ChE activity, as compared to the control values, was reported for males (10 to 22%) and for females (12 to 20%) fed the 15 ppm level over the 24 month period. At the 5 ppm level, a significant ($p < 0.01$) decrease in erythrocyte ChE activity was reported for males by 12 percent at the termination (24 months) of the study.

iii. Brain ChE activity was significantly ($p < 0.01$) decreased, as compared to controls, at the 45 ppm level during the 12 month interval for females by 50 percent and at the termination of the study for males and females by 32 to 55 percent, respectively. A significant decrease ($p < 0.01$) in brain ChE activity was reported at the 15 ppm level for females by 21 percent at the termination of the study.

Summary of Significant ($p < 0.01$) Cholinesterase Activity Inhibition*

Dose (ppm)	Plasma (%) Male	Plasma (%) Female	Erythrocyte (%) Male	Erythrocyte (%) Female	Brain (%) Male	Brain (%) Female
5	—	—	12	—	—	—
15	—	19-35	10-22	12-20	—	21
45	38-49	54-67	20-37	23-31	32	50-55

*As compared to the control values over the 24 month period.

d. Urinalysis - Urine was collected from 10 rats/group at intervals of 6, 12, 18, and 24 months. The animals were fasted overnight (16hr.) during urine collection. The following parameters were examined.

Bilirubin	Protein
Urobilinogen	Blood
Ketones	pH
Glucose	Sediment (microscopic)
Volume	Specific gravity

No treatment related changes were reported in the urinalysis parameters examined for either male or female rats.

3. Terminal Observations - All animals that died during the study or sacrificed at the 12 month (10/sex/group) and 24 month interval were subjected to gross necropsy. Animals assigned to the interim necropsy and surviving rats at the 24 month interval were anesthetized and sacrificed by exsanguination. The following tissues were collected for histopathological examination and the (X) checked organs were weighed.

X	Adrenals		Ileum		Salivary gland
	Aorta		Jejunum		Sciatic nerve
	Bone marrow	X	Kidney		Seminal vesicles
X	Brain	X	Liver		Spleen
	Cecum		Lungs		Sternum
	Colon		Lymph (mesenteric and cervical) nodes		Stomach
	Duodenum			X	Testes
	Epididymides		Musculature		Thymus
	Esophagus		Ovaries		Thyroid
	Eyes		Pancreas		Trachea
	Femur		Pituitary		Urinary bladder
	Heart		Prostate		Uterus
			Rectum		

Organ weights for heart, lung, overies, and spleen were not recorded.

a. Gross pathology - No gross pathological findings were reported in the male or female rats related to the dosage levels tested.

b. Organ weights - At the 45 ppm level female relative liver weight was significantly ($p < 0.01$) increased at the termination of the study by 9%.

Male relative brain weight, at the 45 ppm level was significantly ($p < 0.01$) increased at the 12 and 24 month interval by 11 and 7 percent, respectively.

c. Histopathological examination

i. Nonneoplastic changes - No nonneoplastic histopathological findings were reported relative to the dosage levels fed to male and female rats for two years.

ii. Neoplastic changes - No neoplastic histopathological findings were reported relative to the dosage levels fed to male and female rats for two years.

Conclusion: This study satisfies the guideline data requirement (83-1) for a chronic feeding/carcinogenicity study in rats.

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