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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: Azinphos-methyl
One-Year Dog Feeding Study (83-1b)

Project No.: 1-1701
TOX Chem No.: 374

FROM: Ray Landolt 3/31/92
Review Section I
Toxicology Branch II
Health Effects Division (H7509C)

TO: Larry Schnaubelt PM 72
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THRU: Mike Ioannou, Section Head
Review Section I
Toxicology Branch II
Health Effects Division (H7509C) M. Ioannou 3/31/92
and
Marcia van Gemert, Branch Chief
Toxicology Branch II
Health Effects Division (H7509C) Management 4/1/92

Registrant: Mobay Corporation, letter of February 22, 1991

Action Requested: Mobay has submitted a one-year dog feeding study (83-1b) for review. This study was conducted by Mobay to satisfy the data requirement of the California Department of Food and Agriculture.

Conclusion: This study is acceptable and satisfies the guideline data requirement (83-1b) for a nonrodent chronic feeding study.

Classification of data: Guideline

NOEL- 5 ppm (0.149 mg/kg/day for males and 0.157 mg/kg/day for females).

LEL - 25 ppm (0.688 mg/kg/day for males and 0.775 mg/kg/day for females) with diarrhea in males and a 35 to 43% decrease in erythrocyte cholinesterase activity in males and females at this level.

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Toxicology Profile for Azinphos-methyl

A. Toxicity Data Requirements:

The data gaps cited in the Toxicology Chapter of the Registration Standard (DER 005861) of June 4, 1986 have been fulfilled except for acute inhalation, eye and dermal irritation studies. The following toxicology data evaluation reports (DER), cite those studies that are acceptable and support the registered uses of azinphos-methyl.

Acute Testing:	Study No.	MRID/ACC.No.	DER No.
81-1 Acute Oral Toxicity	7518	255245	004622
81-2 Acute Dermal Toxicity	828383	255245	004622
81-3 Acute Inhalation Toxicity		Study requested	
81-4 Eye Irritation		Study requested	
81-5 Dermal Irritation		Study requested	
81-6 Dermal Sensitization	98565	410644-01	007300
81-7 Acute Delayed Neurotoxicity	94862	408831-01	007132
Subchronic Testing:			
82-1 90-day Feeding-Rodent Nonrodent	Execpt for the current data call-in request for neurotox/ocular effects studies, these subchronic studies are not required with acceptable rodent a and nonrodent feeding studies on file.		
Chronic Testing:			
83-1 Feeding/Carcinogenicity-Rat	99167	411199-01	008300
Two-year dog feeding	19798	00083620	007590
One-year dog feeding	100644	418048-01	This review
83-2 Carcinogenicity- Mouse	80-271-02	460091-01	008094
83-4 Teratogenicity-Rat	94987	404648-01	006760 007084
Rabbit	97406	407139-01	007659
83-4 Reproduction-Rat (two gen)	94824	403326-01	006533
(one gen)	100646	419168-01	008748
Mutagenicity Testing:			
84-2 Gene Mutation	T5573.501	403013-01	006333
Chromosomal Abberration	94575	403678-11	006621 007974
84-4 Other Genotoxic Effects	20991	255245	004622
Special Testing:			
85-1 General Metabolism	98327	408365-01	007157

85-2 Dermal Absorption - Test protocol acceptable with Toxicology review of 8/31/90

B. Toxicology Issues:

1. RfD

The current two-year dog feeding study (MRID 00083620) was initially reviewed by M.Quaife, November 20, 1969 and found acceptable. Subsequently, this study was reevaluated by G.Robinson, (DER 7590) April 10, 1986 and classified Core-Minimum. This two year dog study was conducted with four groups of four pedigree Cocker Spaniel dogs per sex fed dietary levels of 0, 5.0 ppm (low-dose) for 105 weeks, 20 ppm for 36 weeks then 50 ppm for 69 weeks (mid-dose), time weighted average of 39.2 ppm) and 50 ppm for 36 weeks, 100 ppm for 21 weeks, 150 ppm for 27 weeks and 300 ppm for the final 21 weeks (high-dose, time weighted average of 135.7 ppm).

Cholinesterase NOEL = 5.0 ppm (0.125 mg/kg/day)
LEL = 39.2 ppm (1.96 mg/kg/day) with decreased RBC (35%) cholinesterase activity at this level.

The existing RfD of 0.0013 mg/kg/day is based on this 2-year dog feeding study NOEL of 0.125 mg/kg/day for cholinesterase inhibition with a 10-fold uncertainty and 10-fold modifying factor.

2. Carcinogenicity

Azinphos-methyl was tentatively classified as a Group D carcinogen in the abbreviated Peer Review of May 28, 1986 (DER 007739) based on equivocal evidence of significantly elevated incidences of follicular cell thyroid and pancreatic islet cell neoplasms reported in a NCI rat study. However, azinphos-methyl was negative for carcinogenicity in a recent chronic feeding/carcinogenicity study in which Wistar rats were fed 0.25, 0.75 and 2.25 mg/kg/day for two years. In this study, an MTD was demonstrated with plasma (67%), RBC (37%), and brain (55%) cholinesterase inhibition at the 2.25 mg/kg/day level. Azinphos-methyl did not cause increased tumor incidence in CD_1 mice at dietary concentrations of 5.0, 20.0 and 40.0 ppm for two years. An MTD was demonstrated in this study with erythrocyte and brain cholinesterase inhibition at the lowest level fed.

3. Reproduction

Mobay Chemical has cited FIFRA 6(a)(2) for adverse reproductive effects at a dose in the two-generation study (15 ppm), that did not demonstrate parental toxicity (NOEL 15 ppm). Cholinesterase was not determined in this study. Subsequently, a one generation study was reviewed as an addendum to this two-generation study which demonstrated maternal cholinesterase inhibition at the reproductive NOEL (5ppm), lowest level fed.

3. Data gaps

The Toxicology Chapter of the Registration Standard (DER 005861) of June 4, 1986 identified the following studies as data gaps. These data gaps are still outstanding for azinphos-methyl.

81-3 Acute inhalation toxicity
81-4 Eye irritation
81-5 Dermal irritation

Reviewed By: Ray Landolt 3/30/92
Section I, Toxicology Branch II - H7509C
Secondary Reviewer: Mike Ioannou 3/31/92
Section I, Toxicology Branch II - H7509C

DATA EVALUATION REPORT

Study Type: One-Year Oral Toxicity- Dog (83-1b)

TOX Chem No. 374
MRID No. 418048-01
Project No. 1-1701

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

Classification: Insecticide - Cholinesterase Inhibitor

Common Name: Azinphos-methyl (E 1582)

Study No.: 100644

Date of Study: May 31,1990

Sponsor: Mobay Corporation (Bayer AG)

Testing Facility: RCC, Research and Consulting Company AG
Itingen, Switzerland

Title of Report: 52-Week Oral Toxicity (Feeding) Study with Azinphos-methyl (E 1582) in the Dog

Author: T.R.Allen, et al.

Quality Assurance: K. Schneider

Conclusion: Classification of Data - Guideline

This study satisfies the guideline data requirement (83-1b) for a nonrodent chronic oral toxicity study.

NOEL - 5 ppm (0.149 mg/kg/day for males and 0.157 mg/kg/day for females).

LEL - 25 ppm (0.688 mg/kg/day for males and 0.775 mg/kg/day for females) with diarrhea in males and a 35 to 43% decrease in male and female erythrocyte cholinesterase activity at this level.

A. Materials:

1. Test Compound - Technical azinphos-methyl, a yellow solid (flakes) of batch No.233 896 032 and a purity of 91.9%, was dissolved in acetone, mixed with micro-granulated feed for pelleting with Kliba 335 dog maintenance diet.

2. Test Animals - Sixteen male and 16 female, 4 to 4.5 month old, pure-bred Beagle dogs weighing between 5.4 and 8.5 Kg were used in this study. The animals were dewormed and vaccinated against distemper, leptospirosis, contagious hepatitis, rabies, bordetella, parainfluenza and parvovirosis.

B. Study Design:

1. Allocation of Animals

Group	Dose Levels (ppm)	No.Male	No.Female
1	Control	4	4
2	5.0	4	4
3	25.0	4	4
4	125.0	4	4

All animals were housed individually with temperature(20°C), relative humidity(40-70%), and air changes(20/hr.) controlled to provide a uniform environment. A 12-hour light/dark cycle was provided "with at least 8 hours music during the light period". The music selection was not reported, however this should not detract from the quality of this study. Water was available ad libitum.

2. Statistics - The significance of intergroup differences in body weights, hematology, clinical chemistry and organ weights were determined. The Dunnett-Test, based on a pooled variance estimate. was applied for comparison of the treated and the control groups for each sex.

C. Methods and Results:

1. Observations - Individual observations were recorded twice daily for signs of toxicity and changes in behavior.

a. Gross - An increased incidence of mucoid diarrhea accompained by occasional emesis was observed for males and females at the 125 ppm level as compared to the controls. Males at the 25 ppm level exhibited an increased incidence of mucoid diarrhea and occasional emesis, being more severe than observed for males at the 125 ppm level.

b. Mortality - None in the control or test groups.

c. Diet - Each dog received a daily diet of 300g of a dry repelleted Kliba 335 dog maintenance diet at ten AM. At one PM the ration was withdrawn, weighed and the food consumed was recorded.

i. Food consumption- Group mean food consumption was comparable between the control and test levels for male and female dogs.

ii. Stability- Dietary levels were prepared every two weeks and stored refrigerated at -20°C in paper bags. Stability of the test material was determined initially, then at 7, 14, 21, 30 days and then at five months. Azinphos-methyl is stable in the dog maintenance diet over a period of 15 days at -20°C and for 24-hours at room temperature.

Test material intake - The following table, from this report, summarizes the dietary intake of azinphos-methyl.

	Mean Dietary Intake				
Group	Dietary level (ppm)		Male (mg/kg/day)		Female (mg/kg/day)
2	5.0		0.149		0.157
		4.62*		4.94*	
3	25.0		0.688		0.775
		5.59*		5.59*	
4	125.0		3.844		4.333

* IGR - Inter Group Ratio, the test material intake between successive groups.

	Mean Dietary Concentrations		
Group	Nominal(ppm)	Mean(%)of Nominal	St.Dev.(%)of Nominal
2	5.0	95.7	4.5
3	25.0	94.0	1.8
4	125.0	95.1	2.0

c. Diet(con't)

iii. Homogeneity of the dietary levels fed was analyzed initially and then at three month intervals for the duration of the study.

Homogeneity of the dietary levels ranged from -5% to 4.0% of the mean concentration.

d. Body weight - All animals were weighed weekly.

Males at the 125 ppm level exhibited a slight decrease in body weight gain (6.3%) as compared to the controls (15.2%) over the 53 week period. The following table, from this report, summarizes the percent increase in mean body weight gain as compared to the pretest values.

	Dietary Levels (ppm)			
	Control	5.0	25.0	125.0
Males	15.2	14.5	17.6	6.3
Females	19.6	16.1	14.7	15.2

e. Hearing test - All animals were tested for hearing impairment initially then during weeks 13, 26 and 52.

No effect on hearing impairment was reported.

f Ophthalmoscopy examinations were performed on each animal initially then during weeks 13, 26, and 52.

No treatment related findings were observed.

2. Clinical Findings - Blood was collected for hematolgy and clinical chemistry determinations prior to treatment then during weeks 13, 26 and 52. Blood was withdrawn from fasted animals prior to feeding the test material.

a. Hematological parameters examined: The checked (*) parameters are recommended by Subdivision F testing guidelines of November 1989.

* Leukocyte count	Methemoglobin
* Erythrocyte count	Mean corpuscular hemoglobin
* Hemoglobin	Mean corpuscular concentration
* Hematocrit	Mean corpuscular volume
Reticulocyte count	Red cell morphology
* Platelet count	Prothrombin time
* Defferential count	Partial prothrombin time
Nucleated erythrocyte count	Heinz bodies

No treatment related effects were reported at the dietary levels fed.

b. Clinical chemistry parameters examined: The checked (*) parameters are recommended by Subdivision F testing guidelines of November 1989.

* Alkaline phosphatase	* Urea	* Calcium
* Aspartate aminotransferase	Triglycerides	* Phorphorus
Alanine aminotransferase	* Glucose	* Sodium
* Lactate dehydrogenase	* Creatinine	* Potassium
Gamma-glutamyl transferase	* Bilirubin	* Chloride
Ornithine carbamyl transferase	Lipids	* Protein, total
Triiodothyronine	* Cholesterol	* Albumin
Thyroxine	* Creatinine kinase	Protein electrophoresis

At the 125 ppm level, male albumin and A/G values were significantly ($p<0.05$) reduced by 13 and 20% respectively, during week 13. A 7 to 17% decrease in the albumin and A/G values were observed during the 26 and 52-week intervals of the study.

c. Cholinesterase (ChE) activity -Blood was collected for cholinesterase determinations prior to treatment then during weeks 4, 13, 26, and 52. Blood was collected one hour after food was withdrawn. ChE values were determined using a Technicon AutoAnalyzer II Continuous-flow system. The following table summarizes the percent inhibition of ChE activity for the dietary levels fed as compared to the control values.

Males	Plasma				Erothrocyte				Brain
Interval(week)	4	13	26	52	4	13	26	52	52
Dose(ppm)									
5.0	11	13	14	11	0	8	8	0	0
25.0	12	15	12	12	22	40**	32	27	10
125.0	37	53**	58**	53**	66**	87**	88**	86**	27**

Females	Plasma				Erothrocyte				Brain
Interval(week)	4	13	26	52	4	13	26	52	52
Dose(ppm)									
5.0	0	0	0	12	11	16	21	15	0
25.0	14	17	32	30	20	43**	37**	35*	1.0
125..0	52*	58**	57**	53**	86**	92**	91**	86**	20*

* Statistically significant - ($p<0.05$)
** Statistically significant - ($p<0.01$)

At the 25 ppm level a significant ($p<0.01$) decrease in erythrocyte ChE activity was reported for males during week 13 by 40% and for females during weeks 13, 26 and 52 by 43, 37 and 35%, respectively. A significant ($p<0.01$) decrease in male and female plasma (52 to 58%), erythrocyte (66 to 91%) and brain (20 to 27%) ChE activity was reported at the 125 ppm level during the experimental period as compared to the control values.

d. Cytochrome P-450, N-demethylase and O-demethylase activity were determined from liver tissue collected during necropsy at the termination of the study.

At the 125 ppm level cytochrome P-450 activity was significantly ($p<0.05$) increased for males by 39% accompanied by a 15% increase observed for females at this level.

An increase in N-demethylase activity was observed in males and females at the 125 ppm level by 34 and 30%, respectively.

e. Urinalysis - Urine was collected by catheterization prior to treatment then during weeks 4, 13, 26, and 52. The following parameters were examined. The checked (*) parmeters are recommended by Subdivision F guidelines of November, 1989.

* Appearance	* Protein	* Blood
Color	* Bilirubin	* Urobilinogen
* Specific gravity	* Glucose	* Sediment(microscopic)
pH	* Ketones	* Volume (was not reported)

No treatment related changes were reported in the parameters examined for either males or females at the dietary levels fed.

3. Terminal Observations - On the completion of the experimental period, all animals were anesthetized and then killed by exanguination. The following tissues were collected for histopathological examination and the checked (x) organs were weighed. The checked (*) parameters were recommended by Subdivision F guidelines of November, 1989.

*	X	Adrenals	*		Ileum			Sciatic nerve
		Aorta			Jejunum	*		Skeletal muscle
*		Bone marrow	*	X	Kidney	*		Skin
*	X	Brain	*	X	Liver	*		Spinal cord- cervical
*		Caecum	*	X	Lungs			thoracic and lumbar
*		Colon	*		Lymph-mesenteric and	*	X	Spleen
*		Duodenum			retropharyngeal	*		Stomach
*		Epididymis	*		Mammary gland	*	X	Testes
*		Esophagus	*	X	Ovaries	*		Thymus
*		Eye and optic nerve	*	X	Pancreas	*	X	Thyroid and
		Femur	*		Pituitary			parathyroid
		Gallblader		X	Prostate			Tongue
*	X	Heart	*		Rectum	*		Trachea
		Bone, femur	*		Salivary gland	*		Urinary bladder
						*		Uterus

a. Organ weights - Terminal body weights were reduced at the 125 ppm level as compared to the controls for male and females by 12 and 16%, respectively. No dose related changes in absolute or relative organ weights were reported for females at the dosage levels tested. Male kidney to brain weight ratios were significantly ($p<0.05$) reduced at the 125 ppm level by 17%. Male spleen organ weight changes are summarized in following table with the percent decrease in ( ) as compared to the respective control values.

	Dietary Levels (ppm)			
Male Spleen Weight	0	5.0	25.0	125.0
Absolute (g)	68.6	48.0(30)	30.5(55)	24.4(64)
Relative to body weight	0.63	0.47(25)	0.29(54)*	0.26(59)*
Relative to brain weight	81.0	55.2(32)	34.4(58)*	29.6(63)*

* Statistically significant ($p<0.05$)

b. Macroscopic findings - The spleen of 4/4 male controls was reported to appear congested. This would account for the increased absolute spleen weights recorded for the control males. The study author atttibutes this finding as "an artifact resulting from the administration of barbiturate". The incidence of congested spleen occurred in males at the 5.0 ppm (2/4), 25 ppm (0/4) and 125 ppm (1/4) level and in females at the control (1/4), 5.0 ppm (1/4), 25.0 ppm (1/4) and 125 ppm (0/4) level. No other gross pathological findings were reported.

c. Histopathological examination - Congestion of the spleen observed during gross necropsy was confirmed upon microscopic examination. No histopathological findings were reported.

Conclusion: This study satisfies the guideline data requirement (83-1b) for a nonrodent chronic feeding study.

Classification of Data - Guideline

The toxicity of azinphos-methyl, when fed to Begale dogs at 5, 25 and 125 ppm for 7-days per week for 52 weeks, was evident by a significant decrease in male and female plasma (52 to 58%), erythrocyte (66 to 92%) and brain (20 to 27%) cholinesterase activity at the 125 ppm level. Other significant clinical chemistry findings at the high dose level were reported for males with a 39% increase in cytochrome P-450 activity. Serum albumin and A/G values were significantly reduced by 13 and 20%, respectively for males at the 125 ppm level during the 13th week of the study. Gross observations at the high dose level include mucoid diarrhea and occasional emesis reported for male and females at this level. At the 25 ppm level males exhibited diarrhea accompanied by a 35 to 43% decrease in male and female erythrocyte cholinesterase activity.

NOEL = 5.0 ppm (0.125 mg/kg/day)
LEL = 25.0 ppm (0.625 mg/kg/day) with diarrhea in males and a 35 to 43% decrease in erythrocyte cholinseterase activity in males and females at this level.