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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: Asana Insecticide 1.9 EC (24.0% ai),
EPA File Symbol 201-URI; and
Technical Asana Insecticide (75.0% ai)
EPA File Symbol 201-URO
Submission of a 1-Year Dog Feeding Study

Tox. Chem. No. 77A

FROM: William B. Greear, M.P.H. William B. Greear 3/3/87
Section VII, Toxicology Branch
Hazard Evaluation Division (TS-769C)

TO: Adam Heyward, PMT 15
Insecticide-Rodenticide Branch
Registration Division (TS-767C)

THRU: Albin B. Kocialski, Ph.D., Supervisory Pharmacologist
Section VII, Toxicology Branch
Hazard Evaluation Division (TS-769C) ABK 3/12/87

and

Theodore M. Farber, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Under a cover letter dated October 3, 1986, E.L. Hobson, Shell Oil Company, submitted the results of a 1-year feeding study in dogs entitled "One Year Oral Study in Dogs with MO 70616 Technical," Record No. WRC RIR-467. The study has been evaluated and the no-observable-effect level (NOEL) was determined to be 200 ppm (the highest dose tested). The

study has been classified as Core-Supplementary. The study may receive a higher classification provided the following data/information are submitted:

1. Data on the stability of MO 70616 in the diet for all dose levels at ambient temperatures for at least 18 weeks.

2. Clarification of whether all animals were fed diets up to 18 weeks after mixing with MO 70616 throughout the study.

3. The results of the probe study that was used to select the dose levels used in the 1-year study.

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Reviewed by: Y.M. Ioannou
Section VII, Toxicology Branch (TS-769C)
Secondary Reviewer: A.B. Kocialski
Section VII, Toxicology Branch (TS-769C)

DATA EVALUATION REPORT

Study Type: Chronic Toxicity

Tox. Chem. No.: 77A

Accession Number: 265247

Test Material: MO 70616

Synonyms: Pydrin®

Study Number: 6160-103

Sponsor: Shell Development Company
Houston, TX

Testing Facility: Hazleton Laboratories America, Inc.
Madison, WI

Title of Report: One-Year Oral Study in Dogs with MO 70616
Technical

Authors: S.R.W. Petse and B.C. Dickie

Report Issued: August 21, 1986

Conclusions:

MO 70616 does not produce any toxic effects when fed to male and female dogs at 25, 50, 100, or 200 ppm for 1 year. The LEL and NOEL were higher than 200 ppm, the HDT.

Classification: Core-Supplementary

Materials:

The test material (MO 70616), a thick brown liquid, with a reported chemical purity of 98.7% (lot #2-3-0-0) was used in this study. Male and female young adult beagle dogs (obtained from Marshall Research Animals, North Rose, New York) approximately 7 months old and weighing between 6.3 and 9.2 kg were used as test animals. All animals were given a complete physical examination during the 2-week acclimation period to the laboratory conditions. The dogs were identified by a permanent numbered ear tag and housed individually in metal cages which were kept in air-conditioned rooms (separate room for each sex) with a minimum of 10 air changes/hour, a temperature of 21 °C ± 2, a relative humidity of 50% ± 20% and a 12-hour light/12-hour dark cycle. Each animal was provided, for a 4-hour period daily, with Certified Canine Diet #5007. Water was available ad libitum.

Study Design:

Animals (30 males and 30 females) were stratified by weight and randomly assigned to the following five test groups:

Test Group	Dose (ppm)	Number of Animals/Group Male	Female
1. Control	0	6	6
2. MO 70616	25	6	6
3. MO 70616	50	6	6
4. MO 70616	100	6	6
5. MO 70616	200	6	6

The diets with the appropriate test article concentrations (25, 50, 100, or 200 ppm) were prepared by dissolving MO 70616 in acetone and mixing the resulting solution with the diet (dog chow). Fresh test diets were prepared every few weeks (10 batches prepared during the study) and stored at ambient temperatures. For the control groups acetone was mixed with the diet. Each animal was given approximately 350 g of the appropriate test or control diet daily. Immediately before feeding, the diet was mixed with approximately 350 mL of water. Food was available for a 4-hour period daily, 7 days/week.

Samples of test and basal diets were analyzed by the sponsor for determining the concentration levels, stability and homogeneity of ~~MO~~ 70616 in the diet.

All dogs were observed twice daily for mortality, general health, and behavior. Body weights were recorded weekly throughout the study. Food consumption was recorded qualitatively (0, 25, 50, 75, or 100% food consumed) 6 days/week and quantitatively 1 day/week for the duration of the study.

Ophthalmological examinations were performed on all animals before the initiation and at termination of the study. Prior to examination, the eyes of the dogs were diluted with 1% Mydriacyl and then examined with a Fison indirect ophthalmoscope.

For hematology and clinical chemistry measurements, blood was collected from the jugular vein of each animal before the initiation of the study and at weeks 13, 26, and 52 after overnight fasting. For urinalysis measurements each dog was given 20 mL of water/kg body weight (by intubation) and urine was collected for 24 hours before the initiation of the study and at weeks 13, 26, and 52. All hematology, clinical chemistry, and urinalysis parameters measured are listed in Table 1.

Table 1.

Hematology

Parameter	Abbreviation
Erythrocyte count	RBC
Mean corpuscular volume	MCV
Mean corpuscular hemoglobin	MCH
Mean corpuscular hemoglobin concentration	MCHC
Hematocrit	HCT
Hemoglobin	HGB
Reticulocyte count	RETIC
Leukocyte count, total	WBC
Leukocyte count, differential	
Neutrophils	N-SEG
Lymphocytes	L
Monocytes	M
Eosinophils	E
Basophils	B
Immature neutrophils	BANDS-N
Platelet count	PLT
Nucleated red blood cells	NRBC

Table 1. (continued)

Clinical Chemistry

Albumin	ALB
Globulin	GLOB
Urea nitrogen	UN
Calcium	CA
Chloride	CL
Creatinine phosphokinase	CK
Creatinine	CREAT
Glucose	GLU
Inorganic phosphorus	I PHOS
Potassium	K
Serum glutamic-oxaloacetic transaminase	AST/SGOT
Serum glutamic-pyruvic transaminase	ALT/SGPT
Alkaline phosphatase	ALK PHOS
Sodium	NA
Total bilirubin	T BILI
Direct bilirubin	D BILI
Total cholesterol	CHOL
Total protein	T PRO
Lactate dehydrogenase	LDH

Urinalysis

Parameter	Abbreviation
Physical appearance	URINE APP.
pH	PH
Specific gravity	SP GR
Urine volume	U. VOL
Bilirubin	U BILI
Blood	U BLOOD
Glucose	U GLU
Ketones	U KET
Protein	U PRO
Urobilinogen	UROBILI
Microscopic examination of sediment	--

At termination, all animals were killed by exsanguination under sodium pentobarbital anesthesia and subjected to gross pathological examination. Major tissues were dissected from each animal examined macroscopically and preserved in 10% phosphate-buffered neutral formalin (eyes were preserved in Zenker's solution; testes and epididymides were preserved in Bouin's solution). All tissues from all dogs were sectioned, mounted on slides and

stained with hematoxylin-eosin for microscopic examinations. The following checked (X) tissues were collected from all animals for histological examination. The (XX) organs in addition were weighed.

X		X		X	
	Digestive system		Cardiovasc./Hemat.		Neurologic
	Tongue	X	Aorta*	XX	Brain*
X	Salivary glands*	XX	Heart*		Perip. nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	XX	Spleen*		Eyes (optic n.)*
X	Jejunum*	X	Thymus*		Glandular
X	Ileum*		Urogenital	XX	Adrenals*
X	Cecum*	XX	Kidneys*	X	Lacrimal gland
X	Colon*	X	Urinary bladder*	XX	Mammary gland*
X	Rectum*	XX	Testes*	XX	Parathyroids*
XX	Liver*	X	Epididymides	XX	Thyroids*
X	Gallbladder*	X	Prostate		Other
X	Pancreas*		Seminal vesicle	X	Bone*
	Respiratory	XX	Ovaries	X	Skeletal muscle*
X	Trachea*	X	Uterus*	X	Skin
XX	Lung*			X	All gross lesions and masses

*Recommended by Subdivision F (Oct. 1982)guidelines for chronic studies.

Statistical Analysis (Abstracted from the original report):

Body weight; food consumption; hematology; clinical chemistry; urine pH, volume, and specific gravity; organ weight data; and organ-to-body weight ratios were analyzed separately for each sex using one-way analysis of variance (ANOVA) using the raw data or transformations as appropriate to attain variance homogeneity. For analysis of body weight, Day 0 weights were used as a covariate in the analysis of covariance (ANCOVA) at weekly weighing intervals. If the ANOVA or ANCOVA was significant, comparisons between control and treatment groups were analyzed by one-tailed Dunnett's t-test except relative organ weights were analyzed by two-tailed test. All group comparisons found to be statistically significant at $p < 0.05$ were documented.

Protocol Deviations (Abstracted from the original report):

1. The animals used for this study were housed in two separate rooms, not one as stated in the protocol.

2. There were several deviations from the protocol--specified ranges for room temperature and relative humidity.

3. Due to a delay in animal arrival, the dogs were acclimated for 13 days instead of 2 weeks as specified in the protocol.

4. HLA routinely analyzes samples of tap water on a quarterly basis. The results of all analyses performed during the study are reported instead of the results of analyses for the specified contaminants at the three time intervals listed in the protocol.

5. Because HLA routinely analyzes samples of tap water, the samples analyzed during this study were not necessarily taken from the animal rooms used for this study as specified in the protocol.

6. Diets were inadvertently fed to the dogs up to 4 weeks past the proven stability date.

7. On several occasions during the days of quantitative food consumption measurements, the dogs were offered more than 350 g of diet moistened with 350 mL of water as stated in the protocol. However, actual food consumption measurements were recorded.

8. Although not required by the protocol, statistical analyses were performed on urine volume, pH, and specific gravity values.

9. As stated in the protocol, the results of the neurologic examination are to be included in the final report; however, the neurologic examination was not required, and therefore, results are not presented.

10. Although the protocol specified an endoparasite screen on five dogs from the shipment, all dogs had fecal flotation examinations as per HLA standard operating procedures.

11. On several occasions prior to collection of urine, the specified dosing of water could not be completed due to animal behavior.

12. Although the protocol specified eyes were to be preserved in 10% neutral buffered formalin, they were actually preserved in Zenker's solution.

13. The dates specified in the protocol for issuing the draft final report and final report were not met.

14. Missing tissues not examined microscopically were rectum from a Group 1 male (H00712), parathyroid from a Group 3 female (H00743), and the right mandibular lymph node from a Group 4 male (H00746).

Results:

Analysis of test diets at each dose level indicated, according to the authors that (a) diets contained an average of 99 percent of their nominal values in MO 70616 with a range of 92 to 104 percent; (b) the test article was stable in the diet (dog chow) for at least 3.5 months when stored at ambient temperature; (c) the test article was homogeneously distributed in the diet at all dose levels tested; and (d) isomer ratio was unchanged during mixing and storage.

Clinical signs: The main clinical signs of toxicity reported by the authors included soft stool, mucoid stool, and food-like vomitus. These signs, however, were observed in all treated and control groups of male and female dogs. Thus, none of these clinical signs of toxicity appear to be compound related.

Mortality: There was no mortality reported in male or female dogs during the study.

Body weight gains appeared to be, for the most part, comparable between the treated and control groups throughout the study in both sexes. Statistically significant decrease in body weight gain was observed in male dogs of Groups 3 (50 ppm) and 5 (200 ppm) on week 6 and in Groups 3, 4, and 5 on week 7. The mean body weights at sacrifice were comparable between treated and control groups in both sexes.

Mean food consumption was approximately similar between treated and control male and female groups throughout the study as seen from the weekly measurements. Statistically significant increase in food consumption was observed only in female dogs of Group 3 on day 351 on study. Upon review of the individual animal food consumption (on a weekly basis) it was apparent that there was a great variation in consumption between animals of the same group as well as consumption by the same animal from week to week.

Based on the mean weekly food consumption, the authors estimated for each group the weekly test article consumption as mg/kg/bwt/day. The authors concluded that test article consumption was approximately the same as the specified target levels.

Eye examination performed prior to initiation and at termination of the study did not reveal, according to the authors, any treatment-related ocular lesions in any of the male or female dogs.

A number of clinical chemistry and hematology parameters were found to be statistically significantly different between the treated and control groups at the various time intervals examined. However, most of these differences did not appear to be treatment related or biologically meaningful and most probably reflected normal biological variability. Table 2 lists several clinical chemistry and hematology parameters that are of statistical significance. From the clinical chemistry parameters, inorganic phosphorus was statistically significantly lower than the control values in Groups 3, 4, and 5 at the 13-week time point in female dogs and lactate dehydrogenase was statistically significantly lower in male dogs with Groups 3 and 4 and in female dogs with Group 5 at the 26-week time point. From the hematology parameters the mean corpuscular hemoglobin concentration (MCHC) was statistically significantly lower in male dogs at the 13-week time point in Groups 4 and 5 and in females at the 26-week time point in Groups 3, 4, and 5. Reticulocyte counts were statistically significantly lower than controls in Group 5 at the 26- and 52-week time points in male dogs.

From the urinalysis parameters measured, only the pH of the urine was statistically significantly different from control in male dogs with Group 5 at the 26-week time point and in female dogs with Group 3 at the 52-week time point. These changes, however, are not considered to be biologically meaningful.

Table 2

Effect of MO 70616 on Clinical Chemistry, Hematology, and Urinalysis Parameters

Parameter	Sex	Time of Measurement (Week)	Dose Levels (ppm) 0	25	50	100	200
Clinical Chemistry							
Total Bilirubin (mg/dl)	M	13	0.4	0.3	0.3	0.2*	0.2*
		26	0.1	0.4*	0.2*	0.1	0.3*
		52	0.2	0.3	0.2	0.2	0.5*
Urea Nitrogen (mg/dl)	M	13	12.6	11.4	14.9*	13.2	13.4
		26	13.0	10.4*	11.2	10.2*	10.7*
Inorg. Phosphorus (mg/dl)	M	13	5.4	5.1	4.9	4.4*	5.0
		52	4.0	4.0	3.8	3.2*	3.8
	F	13	5.2	5.0	4.5*	4.2*	4.4*
Calcium (mg/dl)	M	13	11.6	11.3	11.2*	10.8	10.3*
	F	52	10.9	10.8	10.2*	10.5	10.5
Lact. Dehydrogenase (IU/L)	M	26	85	76	52*	38*	63
	F	26	87	70	84	52	50*
SGPT (IU/L)	F	26	22	26*	21	20	20

Table 2 (cont'd)

Effect of MO 70616 on Clinical Chemistry, Hematology, and Urinalysis Parameters

Parameter	Sex	Time of Measurement (Week)	Dose Levels (ppm) 0	25	50	100	200
Hematology							
MCHC (%)	M	13	30.8	30.3	30.3	29.8*	29.8*
	F	26	27.2	26.7	26.2*	26.1*	26.2*
MCV (Fl)	M	52	59	57*	57*	56*	59
Hemoglobin (g/dl)	M	52	16.0	15.8	14.9*	16.2	16.6
HCT.(%)	M	52	52.1	50.3	47.7*	51.2	53.5
Reticulocyte Count (%)	M	26	0.4	0.4	0.2	0.3	0.8*
		52	0.5	0.6	0.4	0.2	1.2*
Urinalysis							
pH	M	26	8.4	8.4	8.3	8.2	7.8*
	F	52	7.8	8.2	8.4*	8.2	7.6

*Statistically significantly different from control using Dunnett's t-test; $P < 0.05$

Gross pathology, performed on all tissues of treated and control animals, did not reveal any compound-related effects.

Histopathological examinations revealed various lesions that occurred randomly in organs of treated and control animals. These lesions, however, are not considered to be treatment related because of the absence of statistical significance, the absence of dose response, and the lack of any biological meaning.

Mean organ weights (absolute) were found to be comparable between treated and control groups. It should be noted, however, that in some instances, the individual organ weight values varied considerably within animals of the same group. Spleen, testes, and ovaries were the main organs with varying weights. Organ weight to body weight ratios (relative weights) and organ weight to brain weight ratios were also comparable between treated and control groups. As with absolute weights, individual values for relative weight and organ to brain weight ratios also varied considerably between animals of the same group for the same organs specified above.

Discussion:

Upon request, the sponsor submitted additional analytical data which clearly show that: Concentrations of MO 70616 in the diet were similar to the nominal concentrations; the test substance was homogeneously distributed in the diet; MO 70616 isomer ratio was unchanged during mixing and storage; and that MO 70616 was relatively stable when mixed with the diet and kept at ambient temperatures for up-to 14 weeks. However, as the authors reported (see Protocol Deviations), "diets were inadvertently fed to the dogs up to 4 weeks past the proven stability date." The authors however, did not provide us with any data to indicate MO 70616 stability in the diet 18 weeks after mixing. It is not clear from the authors' report whether this deviation from the protocol was repeated with each batch of diet. For a final evaluation of the present study, we request that the registrant provides the Agency with data concerning:

1. Stability of MO 70616 in the diet for all dose levels at ambient temperatures for at least 18 weeks;

2. Clarify whether all animals were fed diets up-to 18 weeks after mixing with MO 70616 throughout the study.

Clinical signs of toxicity appeared to be randomly distributed to all groups (treated and control) and none of these signs was considered to be of any biological significance. No mortality was reported throughout the study.

Mean body weight gains were found for the most part to be comparable between the treated and control groups throughout the study. Although numerically body weight gains were consistently lower in the treated as compared to the control groups in male dogs, statistical significance was observed only in weeks 6 and 7 in some groups. The lower body weight gains correlate with a reduction in mean food consumption in animals of the same groups at the same time point (i.e., weeks 6 and 7 on study). Thus, it appears that lower body weight gains were due to lower food intake and not attributed to adverse effect(s) of the test article.

Evaluation of the clinical chemistry data revealed statistically significant differences between treated and control groups for some parameters. Although some of these changes suggested some impairment of liver and/or kidney function, no correlation was seen between clinical chemistry changes and histopathological

changes in the same tissues and/or other tissues. Additionally, the reported clinical chemistry changes occurred rather randomly with no evidence of a dose response trend. The reported changes in hematology parameters were also of random occurrence with no evidence of a dose response trend and as far as could be determined none of these changes were associated with any other changes to suggest hemolytic anemia or other blood-associated disorders. Thus, the reported changes in clinical chemistry and hematology parameters are not considered to be of any toxicological significance.

Although absolute and/or relative mean organ weights were found to be comparable between treated and control groups, individual organ weights were in some instances considerably different between animals of the same group. These differences in organ weights cannot be explained by differences in body weights between animals of the same group (organ weight not proportional to the body weight). At the same time such differences cannot be attributed to the effect of the test article since they were of random occurrence and were observed in treated as well as control groups.

Based on the evaluation of all available data, we conclude that the reported changes in the treated groups were mostly due to biological variation and not related to treatment with MO 70616. It is obvious that the high dose tested (200 ppm) did not cause any toxic effects and thus the LEL and NOEL could not be established. The authors mentioned in their report that the selection of the dose levels used for this study was based on the results of a "probe study" in which beagle dogs were fed diets containing 0, 100, 300, or 500 ppm of MO 70616 for 3 weeks. According to the authors (data not supplied), animals on the 300 and 500 ppm dose levels "demonstrated neurological clinical signs and lower body weight. In addition, food consumption was lower and absolute and relative adrenal weights were higher in the 500 ppm dose group." It appears (from the authors' description) that the 300 ppm dose can be the LEL. However, in order to evaluate fully the "probe study" as it relates to the 1-year study, we request that the sponsor provide us with all pertinent data from the "probe study."

Conclusions:

Based on the evaluation of all available data, Toxicology Branch concludes that MO 70616 when fed to dogs at 25, 50, 100, or 200 ppm for 1 year does not cause any overt toxicity or any pathological changes in male or female dogs. The LEL and NOEL appear to be higher than 200 ppm, the HDT.

Classification:

The present study is classified as Core-Supplementary for deficiencies listed above. The study can be upgraded to a Core-Minimum classification when all deficiencies are resolved.