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DATA EVALUATION REPORT

STUDY TYPE: Oral Range Finder - Dog

TOX. CHEM. NO.: 219AA

P.C. CODE: 059101

MRID NO.: 421449-08

TEST MATERIAL: Chlorpyrifos

SYNONYMS: Pyrinex

STUDY NUMBER: MBS 30/88675

SPONSOR: Makhteshim-Agan (America)

TESTING FACILITY: Huntingdon Research Centre, Ltd.
P.O. Box 2
Huntingdon, Cambridgeshire
PE18 6ES England

TITLE OF REPORT: Chlorpyrifos Oral Dose Range Finding Toxicity Study in Beagle Dogs

AUTHOR: Michael H. Barker

REPORT ISSUED: 3 May 1989

CONCLUSIONS: Male and female dogs were treated orally with the test article (0, 0.01, 0.03, 0.5 and 5.0 mg/kg/day) for 4 weeks. The test article inhibited plasma, RBC and brain cholinesterase at dosages of 0.03, 0.5 and 5 mg/kg/day, respectively.

NOEL 0.01 mg/kg/day (LDT)

LOEL 0.03 mg/kg/day (MDT)

LOEL based on inhibition of plasma cholinesterase.

CLASSIFICATION: core - Supplementary

This is not a guideline study.

A. MATERIALS:

1. Test compound: Chlorpyrifos, technical Description: Off-white waxy solid, Batch #: 489205, Purity: 95.8% Contaminants: not given

2. Test animals: Species: Dog Strain: Pure-bred beagles Age: 19 to 20 weeks Weight (kg): 7.8 - 9.9 (males), 6.9 - 8.9 (females) Source: Interfauna UK Ltd, Abbots Ripton Rd, Wyton, Huntingdon, UK.

B. STUDY DESIGN:

1. Animal assignment: Animals were assigned randomly to test groups as shown in Table 1.

Table 1: Animal Assignment to Study Groups

Test Group	Dosage (mg/kg/day)	Main Study (4 weeks)	
		Male	Female
Control (CON)	0	1	1
Low (LDT)	0.01	2	2
Mid 1 (MDT1)	0.03	2	2
Mid 2 (MDT2)	0.05	1	1
High (HDT)	5.0	2	2

2. Dosage: Test article was mixed with lactose (Thorton & Ross, Linthwaite Laboratory, Huddersfield, UK, Lot No. JO18, Exp 11 Feb 90) to yield a final concentration of 1 %. Samples of the mixture were analyzed and found to be homogeneous (1.18 % coefficient of variation) and within 96.8 and 100 % of the nominal concentration. Appropriate amount of test article-lactose mixture was weighed and placed in gelatin capsules (Parke-Davis prefit capsules, size 000). Dogs in the control group received 500 mg/kg/day of lactose. Dogs received one capsule/day for the duration of the study.

3. Animals received 400 grams of standard dry diet (Diet A, Specialty Diets Services) each day and water ad libitum.

4. Statistics: This range finding study used a limited number of animals to assess the toxicological effects of the test article. Therefore, detailed statistical analyses are inappropriate. Where possible, the means and standard deviations were calculated.

5. Quality assurance was documented by signed and dated GLP and quality assurance statements.

C. METHODS AND RESULTS:

1. Observations: Animals were inspected daily for signs of

toxicity, moribundity and mortality.

a. Toxicity: There were no clinical observations attributable to the administration of the test article.

b. Mortality (survival): All animals survived until the scheduled sacrifice.

2. Body weight: Animals were weighed daily during the 4 week treatment period.

Results: There were no significant dose-related changes in the body weights of either the male or female dogs.

3. Food consumption: Food consumption was determined daily.

a. Food consumption results: Daily food consumption (g/animal/day) for both male and female dogs was not altered by treatment.

b. Food efficiency results: Not determined

4. Urinalysis: Not performed.

5. Ophthalmological examinations: Examinations were performed on all animals at the termination of the study. No treatment-related eye lesions were observed.

6. Hematology and Clinical Chemistry: Clinical chemistry analyses were performed during the pre-dosing and dosing periods. The checked (X) parameters were examined.

a. Hematology: Not performed

b. Clinical Chemistry

	Electrolytes	Other
	Calcium	Albumin
	Chloride	Blood creatinine
	Magnesium	Blood urea nitrogen
	Phosphorous	Cholesterol
	Potassium	Globulins
	Sodium	Glucose
	Enzymes	Total Bilirubin
	Alkaline phosphatase	Triglycerides
X	Cholinesterase	Total Protein
	Creatinine phosphokinase	
	Lactic acid dehydrogenase	
	Serum alanine aminotransferase (SGPT/ALT)	
	Serum aspartate aminotransferase (SGOT/AST)	

Results: Plasma cholinesterase activity was markedly (> 20%) inhibited from day 1 in animals in the 0.5 and 5.0 mg/kg/day groups (Table 2). From day 7 smaller reductions were also apparent in animals in the 0.03 mg/kg/day group. The inhibition of plasma cholinesterase by the test

compound was very persistent, with marked reductions still apparent 24 hours after dosing. The inhibition of RBC cholinesterase activities was less pronounced than the plasma cholinesterase. Marked reduction in RBC cholinesterase activity was found in animals in the 5.0 mg/kg/day group from day 7; no treatment-related effects were seen in the other dosages groups (Table 3).

7. Sacrifice and Pathology: Detailed pathological examination was performed on male and female mice in the control and treatment groups. The checked (X) tissues were collected for histological examination; the checked (XX) organs were also weighed.

Digestive system	Cardiovas./Hematol	Neurologic
X Tongue	X Aorta	XX Brain
X Salivary glands	XX Heart	X Periph. nerve
X Esophagus	X Bone marrow	X Spinal cord (3x)
X Stomach	X Lymph nodes	XX Pituitary
X Duodenum	XX Spleen	X Eyes
X Jejunum	XX Thymus	Glandular
X Ileum	Urogenital	XX Adrenals
X Cecum	XX Kidneys	Lacrimal gland
X Colon	X Urinary bladder	X Mammary gland
X Rectum	X Testes	X Parathyroids
XX Liver	Epididymides	XX Thyroids
X Gall bladder	X Prostate	Other
X Pancreas	Seminal vesicle	X Bone
Respiratory	X Ovaries	X Skeletal muscle
X Trachea	X Uterus	X Skin
XX Lungs	X Vagina	X Gross lesions
Nasal Passages	Cervix	

a. Organ Weights: The organ weights of the treated animals were not significantly different from the control values.

b. Gross pathology: Minor changes not related to treatment were observed in some of the control and treated animals.

c. Brain Cholinesterase: As summarized in Table 4, below, brain cholinesterase activity was markedly inhibited in the 5.0 mg/kg/day group (Table 3).

TABLE 4

Plasma cholinesterase activity - group mean values - combined - µmol/ml/min

Dosage mg/kg/ day	Day number/hours after dose											
	-9	-6	1	1	1	1	1	1	1	1	1	2
	0	0	0	0.5	1.0	1.5	2.0	3.0	4.0	5.0	6.0	0
Control	(1.34)	(1.42)	(1.29)	(1.22)	(1.25)	(1.34)	(1.32)	(1.36)	(1.46)	(1.38)	(1.37)	(1.32)
0.01	1.42	1.61	1.37	1.40	1.36	1.36	1.32	1.36	1.47	1.37	1.49	1.38
0.03	1.53	1.65	1.56	1.55	1.34	1.26	1.46	1.39	1.47	1.45	1.38	1.37
0.5	(1.35)	(1.27)	(1.23)	(1.02)	(0.88)	(0.71)	(0.65)	(0.74)	(0.67)	(0.71)	(0.73)	(0.82)
5	1.49	1.56	1.54	0.76	0.50	0.48	0.44	0.40	0.53	0.63	0.55	0.62

Dosage mg/kg/ day	Day number/hours after dose										
	7	7	7	7	8	14	27	27	27	27	28
	0	1.0	2.0	4.0	0	0	0	1.0	2.0	4.0	0
Control	(1.22)	(1.51)	(1.30)	(1.34)	(1.29)	(1.22)	(1.27)	(1.21)	(1.18)	(1.36)	(1.30)
0.01	1.28	1.29	1.27	1.30	1.25	1.28	1.28	1.17	1.18	1.24	1.24
0.03	1.25	1.14	1.09	1.11	1.16	1.24	1.10	1.06	1.05	1.02	1.09
0.5	(0.68)	(0.46)	(0.45)	(0.53)	(0.54)	(0.70)	(0.58)	(0.45)	(0.48)	(0.50)	(0.44)
5	0.49	0.32	0.36	0.40	0.41	0.53	0.48	0.30	0.34	0.25	0.37

() Mean of two values

Table 3: RBC Cholinesterase activity

TABLE 5

Erythrocyte cholinesterase activity - group mean values - combined - µmol/ml/min

Dosage mg/kg/ day	Day number/hours after dose											
	-9	-6	1	1	1	1	1	1	1	1	1	2
	0	0	0	0.5	1.0	1.5	2.0	3.0	4.0	5.0	6.0	0
Control	(1.72)	(1.69)	(1.66)	(1.69)	(1.64)	(1.97)	(1.86)	(1.72)	(1.98)	(1.74)	(1.73)	(1.67)
0.01	2.11	2.04	1.96	1.98	1.98	2.20	2.10	2.30	2.19	2.10	2.01	2.23
0.03	2.38	2.28	2.22	2.16	2.26	2.45	2.49	2.50	2.38	2.39	2.28	2.43
0.5	(2.18)	(2.19)	(2.20)	(2.31)	(2.11)	(2.40)	(2.26)	(2.62)	(2.29)	(2.21)	(2.11)	(2.32)
5	1.90	1.93	1.90	1.84	1.82	1.90	1.96	1.81	1.82	1.61	1.71	1.76

Dosage mg/kg/ day	Day number/hours after dose										
	7	7	7	7	8	14	27	27	27	27	28
	0	1.0	2.0	4.0	0	0	0	1.0	2.0	4.0	0
Control	(1.75)	(1.67)	(1.61)	(1.77)	(1.78)	(1.94)	(1.71)	(1.65)	(1.61)	(1.59)	(1.86)
0.01	1.91	1.88	2.10	2.02	2.02	2.05	1.99	1.96	1.96	2.06	1.97
0.03	2.22	2.29	2.28	2.17	2.23	2.28	2.22	2.05	2.05	2.17	2.19
0.5	(1.97)	(1.89)	(2.10)	(1.85)	(1.94)	(1.90)	(1.66)	(1.50)	(1.49)	(1.48)	(1.52)
5	0.92	0.92	1.04	1.13	0.95	0.77	0.44	0.37	0.36	0.45	0.53

() Mean of two values

Table 4: Brain Cholinesterase Activity

Dosage (mg/kg/day)	µmol/g/min	% Difference
Control	(4.71)	---
0.01	5.09	+8.0
0.03	5.02	+6.6
0.5	(4.34)	-8.0
5.0	3.18	-32.6

() represents the mean of two values

c. Microscopic pathology

1) Non-neoplastic: Possible treatment-related histopathological changes were noted in animals in the 5.0 mg/kg/day group. These changes included thickened muscular coat of the duodenum of one male and one female and an area of papillomatous hyperplasia (pyloric) in one female.

2) Neoplastic: Not noted

D. DISCUSSION: Male and female dogs were treated orally with the test article (0, 0.01, 0.03, 0.5 and 5.0 mg/kg/day) for 4 weeks. The test article inhibited plasma, RBC and brain cholinesterase at dosages of 0.03, 0.5 and 5 mg/kg/day, respectively.

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