NIOSH/EDGEWOOD ARSENAL

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Parathion -- Inhalation and Oral Toxicity Studies on Rats and Dogs

INHALATION AND ORAL STUDIES OF ETHYL PARATHION ADMINISTERED ACUTELY AND SUB-ACUTELY TO THE RAT AND DOG

Performed for NIOSH by the Toxicology Division, Edgewood Arsenal, Aberdeen Proving Ground, Maryland

89 pages

TABLE OF CONTENT

ABSTRACT

The effect of ethyl parathion in male rats and dogs exposed acutely and subacutely by the inhalation and oral routes were determined. In acute inhalation tests, groups of four dogs were exposed four hours to five dose levels of parathion ranging from 0.0152 to 37.13 mg/cu m. Due to the pronounced effect on ChE activity and the shortage of dogs, no ChE_{50} or LC_{50} values could be obtained. The LC_{50} is greater than 37.13 mg/cu m. Groups of thirty-four rats were exposed four hours to thirteen levels of parathion ranging from 0.035 to 35.0 mg/cu m. The plasma ChE_{50} with 95% confidence limits is 7.28 (5.24 - 10.12) mg/cu m. The RBC ChE_{50} is 5.43 (4.2 - 7.03) mg/cu m. Groups of thirty-four rats were exposed to eight parathion levels ranging from 31.36 to 230.5 mg/cu m. The LC_{50} is 84.0 (78.9 - 90.4) mg/cu m. In acute oral studies groups of four dogs were exposed to seven dose levels ranging from 0.5 to 10.0 mg/kg. The plasma ChE_{50} is 1.67 (0.94 - 2.96) mg/kg and the RBC ChE_{50} is 1.5 (1.06-2.12) mg/kg. Groups of four dogs were exposed to five levels of parathion ranging from 2.5 to 20.0 mg/kg. The LD_{50} is 8.27 (4.79 to 14.29) mg/kg. Toxic signs, i. e. , tremors, convulsions and death were noted in dogs at doses above 2.5 mg/kg. The plasma ChE_{50} for rats exposed acutely by the oral route is 2.5 (2.14 to 3.1) mg/kg, and the RBC ChE_{50} value is 2.58 (2.12 to 3.14) mg/kg. The LD_{50} is 6.85 (6.19 to 7.59) mg/kg.

In sub-acute studies groups of six dogs were exposed by inhalation to three dose levels of parathion, 0.001, 0.01 and 0.20 mg/cu m seven hours per day, five days per week for six weeks. RBC ChE and plasma ChE determinations were made at 1, 2, 4 and 6 weeks of the exposure period

and post -exposure period. The 0.001 mg/cu m dose level was a no effect dose for both plasma and RBC ChE activity, while the 0.01 mg/cu m and 0.20 mg/cu m levels had moderate pronounced ChE effects respectively. RBC ChE activity in dogs exposed to 0.20 mg/cu m did not return to normal until the 6th post-exposure week. Rats in groups of eighty were tested subacute by the inhalation route at dose levels of 0.01, 0.10 and 0.74 mg/cu m seven hours/day, five days/week for six weeks. Blood samples were obtained at various weeks during the exposure and post-exposure period for ChE determinations. The 0.01 mg/cu m dose level was considered to be a no-effect level for plasma and RBC ChE activity while the 0.10 and 0.74 mg/cu m levels had moderate and pronounced ChE effects respectively. RBC ChE activity in rats exposed to 0.74 mg/cu m did not return to normal until the sixth post-exposure week. In subacute oral studies on dogs, groups of six dogs were exposed to 0.05, 0.10 and 0.50 mg/kg for six weeks during exposure and post-exposure periods. Each dog served as his own control. The least effect on ChE activity was observed at the 0.05 mg/kg dose, while 0.10 and 0.50 mg/kg doses produced moderate and pronounced effects on plasma and RBC ChE activity. Subacute rats were exposed orally to parathion doses of 0.05, 0.10 and 0.25 mg/kg for six weeks. The 0.05 mg/kg dose is a no-effect dose on both plasma and RBC ChE activity. The 0.10 mg/kg dose could be considered as having a moderate effect on the ChE activity. The highest parathion dose, 0.25 mg/kg produced pronounced effects on both plasma and RBC ChE activity.

List of Tables in Text

List of Tables in Text (continued)

List of Tables in Appendix

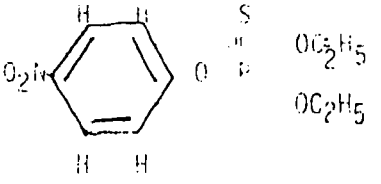
List of Tables in Appendix (continued)

List of Tables in Appendix (continued)

INHALATION AND ORAL STUDIES OF ETHYL PARATHION ADMINISTERED ACUTELY AND SUB-ACUTELY TO THE RAT AND DOG

I. INTRODUCTION.

Parathion is an "organophosphorus" insecticide developed by G. Schrader* in 1944. It has a molecular weight of 291.27. Its chemical structure is as follows:



Parathion is highly toxic to mammals and should not be used by man unless necessary safety precautions are observed and personal protective equipment is used. The parathion hazard is directed to personnel employed in agriculture especially those who handle the insecticide and are involved in spraying procedures. Employees of industrial plants where parathion is packaged and synthesized should also be aware of the parathion hazard.

The National Institute of Occupational Safety and Health (NIOSH) in order to establish the threshold limit value (TLV) for ethyl parathion, required additional acute and subacute toxicity studies on rats and dogs exposed by the oral and inhalation routes.

The effect of the insecticide on both erythrocyte (RBC) and plasma cholinesterase (ChE) activity in dogs and rats was to be used to establish

* Handbook of Toxicology Volume III, National Academy of Sciences, National Research Council by William O. Negherbon, 1959. W.B. Saunders Co. Philadelphia and London.

inhalation-to-oral toxicity ratios. From these experimental results in animals it is expected that one could predict levels of human exposure based upon the effects of RBC and plasma ChE activity or inhibition levels.

These studies were funded by NIOSH and the work was conducted by the Biomedical Laboratory, Toxicology Division located at the Edgewood Arsenal area of Aberdeen Proving Ground, Maryland.

II. EXPERIMENTAL.

A. Inhalation Toxicty.

A technical grade of Parathion, made by the Monsanto Company, was used in these tests. The diazo assay was 99.33%.

Adult male colony rats (Sprague-Dawley crossed with Wistar) and pure bred male adult beagle dogs were used for the inhalation and oral tests.

A description of the method used to determine cholinesterase values in blood samples obtained from rats and dogs exposed to ethyl parathion by both the inhalation and intragastric routes is shown below.

The blood samples from rats and dogs exposed to ethyl parathion were analyzed by Technicon Autoanalyzer method N17P. Each sample as received was spun down in an International Portable Refrigerated Centrifuge at 2000 rpm (approximately 700G) for 20 minutes at 4°C. The red cells and plasma were separated and 0.4 ml of each was diluted to 2.0 ml with saline. When 0.4 ml of red cells or plasma were not available a lesser volume was used but the proportions of sample to saline diluent was kept at 1:4.

Operating Conditions

50 samples/hr 1-1 sampling rate
20 mM acetyl thiocholine diodide substrate
flow cell - 15 mm tubular
analytical wavelength - 420 mm
buffer - 50 nM Tris* pH 7.4
color reagent - 0.1 gm 5.5'Ditniobis-2-nitrobenzoic acid qs to 1 liter with pH 7.4 tris buffer.

Standardization --- activity is measured in Deca International units of thiocholine formed by enzyme per liter at 37°C under the operating conditions for method N17P.

Preparation of Thiocholine Standard

a. Weigh out 0.1446 grams pure Acetyl Thiocholine Iodide.

b. Dissolve completely in 5 ml 0.2N NAOH.

c. Qs to 100 ml with distilled water. This stock solution is 5.0 mM in thiocholine, ph is approximately 9.0.

d. Make up a serial set of dilutions from the stock of 5 (0.25 mM), 10 (0.5 mM), 20 (1.0 mM), 40 (2.0 mM), and 60 (3.0 mM).

Calculations - Stock is 5 mM or $\frac{5000 \text{ micro moles}}{\text{liter}}$

The IUB** defines 1 unit of enzyme activity as the amount of enzyme that will catalyze the transformation of one micromole of substrate per minute under specified reaction conditions.

10 IUB International Units = 1 deca unit

The incubation time in method N17P runs between 5-6 minutes.

Problem - A sample peak is identical in peak height to the stock standard. Assume the incubation time is 5.50 minutes. What is the activity of the sample as expressed in Deca Units per liter?

* Tris(hydroxymethyl)aminomethane

** The International Union of Biochemistry (IUB).

Solution - $\frac{\text{micro moles/liter}}{\text{incubation time} \times 10}$ = Deca Units

$$\frac{5000}{5.5 \times 10} = 90.9$$

The stock solution is equivalent to a sample of 90.9 deca units per liter activity; however, the sample was diluted 1:4 with saline and is only 20% (v/v) in red cells or plasma. The samples original activity was 5 (90.9) or 454.5. The analytical procedure is not accurate to 4 significant figures and the answer should be rounded off to 454 Deca Units per liter of undiluted red cells or plasma.

Quality Control - Paper strip controls were made up and run. The paper strips were made up by the method of Fleisher, Analytical Chemistry Volume 27, pp 1080-83.

Normal serum of equine origin was diluted ad runs as a control periodically. This equine serum was obtained from the Pitman-Moore Company, Indianapolis, Indiana.

1. Acute Toxicity in Male Rats.

Groups of thirty-four male rats were exposed to parathion aerosol in a 1000 liter dyamic flow chamber for four hours. Chamber air samples were collected on two fiberglass filter pads. The parathion on the pads was diluted with isopropyl alcohol and analyzed by a gas chromatographic technique. Particle size was determined by use of a Rochester cascade impactor.

During exposure the rats wre observed for toxic signs and death. Blood samples for red blood cell (RBC) and plasma cholinesterase (ChE) determinations were obtained from groups of six rats at 4 hours and 1, 2, 7 and fourteen days exposure. Ch_{50} and LCT_{50} values were calculated.

Seventy-one male rats as baseline unexposed controls and additional unexposed rats were used as controls for various concentration levels. Twenty parathion concentration levels ranging from 0.035 to 230.0 mg/cu m were used in the acute studies.

The instrumentation and procedures for measuring ethyl parathion by the gas chromatographic technique are as follows.

Instrument: Micro-Tek Model MT 220 supplied by Micro-Tek Instruments Corporation a subsidiary of Tractor, Inc., Austin, Texas 78721.

Detector: Flame Photometric Detector, Model FPD 100 with phosphrous filter supplied by Melphar, Inc., a subsidiary of Westinghouse Air Brake Co., Falls Church, VA.

Column: 6 ft., glass (OD - 0.4 mm, ID 0.2 mm) 10% OV-], Chromsorb W, 80/100 mesh supplied by Applied Science Laboratories, Inc., PO Box 440, State College, PA

Carrier Gas: Nitrogen, prepurified grade, supplied by Linda Gas Products.

Recorder: (1) Autolab System IV, B, Computing Integrator for chromatography supplied by Autolab, a division of Spectra-Physics, 655 Clyde Avenue, Mountain View, CA 94401 and (2) Spectrum 1021 Filter and Amplifier supplied by Spectrum Scientific Corp., 2401 Ogletown Road, Newark, DEL. 19711.

Syringe: 10 ul Hamilton (#701) supplied by the Hamilton Co., Reno, Nevada.

Sample Size: 4.0 ul with 1.0 ul isopropanol pusher, and ca. 1.0 ul air space in between.

Temperature: Injection Port - 255°C
Column - 225°C
Detector = 160°C (max. for this FPD set-up)

Flow Rate:

	Pressure (psig)	Rotameter Setting	Flow cc/min STP
Carrier gas, nitrogen	40	10.0	105
Oxygen*	40	25.0	NA
Hydrogen**	40	180.0	NA
Air**	40	30.0	NA

* supplied by Linda Gas Products, prepurified
** supplied by Aberdeen Pro[illegible]

Retention Time: Parathion - 4.6 minutes

Procedures: A parathion reference standard solution was obtained from Monsanto Company on 15 May 1975 and had a purity by diazo assay of 99.33 Using this standard, the following solutions were prepared in isopropanol.

Experimental Concn Level	Standard Concn Level
1.0 /liter	4.96 /ml
0.1 /liter	0.518 /ml
0.01 /liter	0.0518 /ml

The concentration of parathion is samples (/liter) was calculated as follows:

$$\frac{(PA_S)\ (\text{Concn. Std})\ (\text{Vol. Solvent})}{(PA_{std})\ (\text{Vol. Air})}$$

PA_s = Peak area counts of sample

PA_{std} = Peak area counts of standard solution

$Concn._{std}$ = Concentration of standard solution in mg/ml.

$Vol_{solvent}$ = Vol of isopropanol used for extraction in ml.

Vol_{air} = Volume of sampled air in liter.

2. Acute Toxicity in Male Dogs.

Groups of four dogs were exposed to five concentration levels of parathion aerosol for four hours. The parathion concentrations were 0.0153, 0.145, 3.42, 8.93 and 37.15 mg/cu m. The animals were observed for toxic signs during and after exposure. Blood samples were obtained from the dogs prior to exposure for baseline control red blood cell ChE and plasma ChE values. Additional blood samples were obtained from the dogs just prior to exposure and at 4 hours, 1 day, 2 day, 7 days and 14 days post exposure for ChE determinations.

3. Subacute Toxicity in Male Rats.

Eighty male rats were exposed to parathion aerosol for seven hours per day, five days a week for six weeks to threelevels of parathion. The three levels of parathion were 0.01, 0.10 and 0.74 mg/cu m. Blood samples were obtained from 71 rats for red blood cell and plasma ChE determinations. These rats served as baseline controls. Groups of ten control rats were sacrificed for blood samples along with ten exposed rats at various weeks during the six week exposure period and the six-week post exposure period. The rats were observed for toxic signs and weighed before sampling blood and sacrifice.

4. Sub-Acute Toxicity in Male Dogs.

Groups of six dogs were exposed to three levels of parathion aerosol for seven hours per day, five days per week for six weeks. The dogs were held for six weeks post exposure observation. Blood samples were obtained from the dogs at various weeks during the exposure and the six week post-exposure period for red blood cell plasma ChE determinations. Negative control animals in groups of six were carried with the exposed dogs. The three parathion concentration levels are 0.001, 0.01 and 0.20 mg/cu m.

The dogs were observed for toxic signs. All dogs were examined by a veterinarian prior to use in this study and declared to be free of infectious disease.

The pre-exposure blood samples for ChE determinations were taken from each dog. The average RBC and plasma ChE values served as experimental controls and each dog also served as its own control.

B. Oral Toxicity.

The Parathion used in these studies was Monsanto Technical grade

Run No.	Sample Area (area count)	Std Area	Conc. of Std (γ/ml)	Final Conc. of Spike Soln (γ/ml)	Conc. of Parathion Recovered = (γ/ml)	Sample Area / Std Area	Conc. of Std	% of recovery =	Conc. of parathion recovered / Final concn of spike (100)
1	5027	3810	0.496	0.661	0.655				99.0
2	5211	3810	0.496	0.661	0.679				102.6
3	5189	3810	0.496	0.661	0.675				102.0

ethyl parathion. It was 98.5 parathion and 1.5% inert ingredient. Animals used in these experiment were adults male dogs (Beagles) and adult male rats (Sprague-Dawley/Wistar strain).

All ethyl parathion used in the following tests was administered in capsules by the oral route to dogs and by a stomach tube in rats. The parathion was diluted to working concentrations with corn oil.

III. RESULTS AND DISCUSSION.

A. Inhalation Effects of Ethyl Parathion.

1. Acute Studies - Rats.

a. Mortality and Toxic Responses.

The LC_{50} for male rats exposed for four hours to parathion aerosols is 84.00 (78.0-90.4) mg/cu m*. These data are shown in table 1. Toxic signs i. e., tremors, convulsions, salivation, respiratory difficulty, and death were seem in rats exposed to concentration ranging from 59 to 230.5 mg/cu m. The ED_{50} for tremors is 73.67 (67.15-80.83) mg/cu m and the ED_{50} for convulsions is 110.6 mg/cu m (96.0 127.4) . These data are shown in tables 2 and 3.

The ET_{50} values for tremors, convulsions and death in rats exposed to respective concentrations of 97.0, 100.6, 118.5 and 230.5 mg/cu m are shown in Appendix, tables 1A-12A. A summary of these effects is shown in table 4. Figures 1 thur 5 illustrate the 1-99% response for these toxic signs. Other observations noted at the lowest concentration level tested (26.08 mg/cu m) were as follows: 43 min - occasional sneezing, 50 min - possible nose irritation, 4 hrs- approximately 15/34 had diarrhea, scrotal area was wet with urine and 3.5 hrs post exposure - appeared lethargic and a few had "wet dog shakes".

* The Statistics of Bioassay, C. I. Bliss, Vol. II. Academic Press, Inc. New York, 1952

Probit Analysis for Mortality in R

Dose (mg/cu m)	Mortality Fraction (34 rats)
31.48	0/34
35.00	0/34
50.0 39.00	3/34
71 71.00	10/34
97 97.00	25/34
130.00	22/34
118.50	28/34
230.50	34/34

TABLE I

ats Following Inhalation Exposure to Parathion

	Bliss Statistical Analysis		
%	Dose (mg/cu m)	Lower Limit	Upper Limit
1	37.60	32.76	43.15
16	59.57	51.45	65.18
50	70.68	64.75	77.85
50	84.00	78.03	90.42
84	118.45	108.65	129.14
99	187.67	164.45	214.18

Probit Analysis (ED_{50}) T

Parathion Dose (mg/cu m)	No of Rats Showing Tremors	% Response
230. 5	31/34	1
118.5	29/34	16
100.6	26/34	30
97.0	28/34	50
71.3	19/34	84
50.0	8/34	99
35.0	0/34	
31.0	0/34	

ABLE 2

emors in Rats Exposed to Parathion

Bliss Statistical Analysis

Dose (mg/cu m)	Lower Limit	Upper Limit
25.572	15.814	40.225
45.262	35.376	57.911
56.985	48.844	66.479
75.673	67.147	80.831
119.918	94.760	151.755
230.259	136.530	588.535

TABL

Probit Analysis (ED_{50}) for

for P

Parathion Dose (mg/cu m)	No of Rats Showing Convulsions	% Response	
230.3	25/34	1	
118.5	21/34	16	
105.6	21/34	50	
97.0	19/34	50	
71.0	4/34	84	
50.0	3/34	99	
35.9	0/34		
31.9	0/34		

E 3

Convulsions in Rats Exposed to Parathion

our Hours

Bliss Statistical Analysis

Dose (mg/cu m)	Lower Limit (mg/cu m)	Upper Limit (mg/cu m)
26.3	15.2	45.5
59.8	18.3	74.1
89.3	70.5	100.8
110.6	96.0	127.4
204.3	111.4	295.5
465.9	227.4	950.9

Summary of ET_{50} Values for Trem

Parathion Co

Parathion Concentration (mg/cu m)	Tremors (min)
71.0	210.1 (201.0-219.5)
97.0	173.4 (163.7-183.6)
100.6	159.4 (144.5-175.8)
118.5	158.9 (141.2-175.3)
250.5	103.9 (96.2-112.1)

Numbers in brackets ( ) are lower and

ABLE :

ers Convulsions and Death in Rats Exposed : Ethyl
ncentration for Four Hours

RT_{50} Values

Convulsions (min)	Death (min)
184.3 (170.0 - 200.0)	218.7 (201.3-237.7)
179.2 (163.2 - 196.8)	237.0 (206.5-280.2)
167.8 (153.2 - 183.9)	208.2 (189.0-229.4)
114.1 (104.9 - 124.2)	129.5 (121.2-138.7)

upper limits

b. ChE_{50} Determinations.

Thirteen dosage levels ranging from 0.04 to 35.00 mg/cu m were used for the determination of RBC and plasma ChE values. The RBC ChE_{50} was determined to be 5.43 (4.20-7.03) mg/cu m. The plasma ChE_{50} was determined to be 7.28 mg/cu m (5.24-10.12) mgcu m. A summary of these results are shown in tables 5 and 6. The RBC and plasma ChE activities for the exposed rats sampled at 4 hours, 1, 2, 7 and 14 days post exposure are shown in table 7. A statistical evualation of these data are in Appendix, table 13A. Red blood cell and plasma ChE activity curves for rats exposed four hours to ethyl parathion aerosols are shown in figures 6 thur 13. The dashed curves ( ) illustrates the actual RBC ChE activities while the solid curves represent the statistical best fits. The dashed curves ( ) illustrates the actual plasma ChE activities while the solid curves represents the statistical best fits. Figures 1A and 2A of the Appendix summarize these data.

2. Acute Studies -Dogs

a. Mortality, Toxic Responses and ChE_{50} Determinations.

Groups of four dogs each were exposed to five parathion concentration levels: 0.0153, 0.145, 3.42, 8.93 and 37.13 mg/cu m. No deaths occurred in dogs exposed to these concentrations. The exposure time for all groups was 240 minutes. Cholinesterase was significantly inhibited by all five concentrations. However, due to the high levels of depression seem in each group, and the fact that lower concentrations could not be tested due to th shortage of dogs, calculations of ChE_{50} values were not possible. A summary of theses are shown in tables 8 and 9. Figures 14 and 15 show the RBC and plasma ChE curves for dogs exposed once for 4 hours to ethyl parathion

0.01	0.01	0.08
0.38	0.17	0.85
1.33	0.81	1.95
3.45	4.20	7.05
78.20	26.13	231.34
2780.85	280.95	27525.15

1.362 + .859 Log x

TABLE 5

PROBIT ANALYSIS OF RBC

INHIBITION IN RATS FOLLOWING ORAL ADMIN
(Blood sampled 24 hours

Dose (mg/kg a)	% ChE (RBC) Inhibition (54 rats)	ChE Inhibition
0.04	7	1
0.21	8	16
0.24	28	30
0.83	17	50
0.91	8	84
1.21	11	99
2.17	30	
2.27	60	
12.80	58	
19.06	69	
26.08	85	
31.56	80	
35.00	68	

Probit Y=

TABLE 6

PROBIT ANALYSIS FOR PLASMA CHE IN

RATS FOLLOWING FOUR HOUR INHALATION EXPOSURES TO ETHYL PARATHION
(Blood sampled 24 hours post exposure)

Dose (mg/cu m)	%ChE (plasma) Inhibition (34 rats)	Bliss Statistical Analysis			
		ChE Inhibition	Dose (mg/cu m)	95% Confidence Lower Limit	95% Confidence Upper Li
0.04	0	1	0.02	0.002	0.14
0.21	0	16	0.51	0.31	1.18
0.24	24	30	1.79	1.24	2.59
0.83	37	50	7.28	5.24	10.12
0.91	12	84	103.85	27.23	396.05
1.21	0	99	3648.22	231.53	57485.56
2.17	28				
2.27	58				
12.80	69				
19.06	72	Probit Y=4.257 + .862 Log x			
26.08	58				
31.36	77				
35.00	74				

TABLE 7

RED BLOOD CELL AND PLASMA CHOLINESTERASE VALUES OF RATS EXPOSED BY INHALATION TO PARATHION AEROSOLS FOR FOUR HOURS

Parathion Conc	Percent ChE Activity From Start of Exposure									
mg/cu.m	4 Hrs		24 Hrs		48 Hrs		168 Hrs		336 Hrs	
	RBC	PLASMA	RBC	PLASMA	RBC	PLASMA	RBC	PLASMA	RBC	PLASMA
0.055	83.61	100.0	93.0	100.00	90.78	100.00	91.43	100.00	82.90	100.00
0.206	67.31	80.51	92.45	100.00	100.0	100.00	97.67	100.00	70.45	100.00
0.255	100.0	79.72	72.52	75.80	86.17	80.41	100.0	76.49	73.84	66.81
0.825	66.15	62.67	82.62	62.67	66.15	75.80	74.33	90.09	85.04	68.98
0.905	100.0	88.47	91.90	88.01	81.34	68.42	87.89	80.64	77.04	75.60
1.21	100.0	100.0	89.48	100.0	78.95	100.0	79.75	99.68	94.71	100.0
2.17	83.78	65.49	69.95	71.95	69.05	69.37	74.28	73.98	77.62	70.98
2.265	56.35	52.03	39.76	42.25	71.74	68.08	77.87	80.62	52.82	50.27
12.80	66.36	47.97	42.37	31.18	45.74	44.46	59.94	73.06	61.39	67.22
19.06	42.90	46.70	31.02	47.97	18.46	58.86	49.0	59.59	78.25	77.51
26.08	24.44	33.39	15.10	42.25	42.30	37.82	46.0	64.20	57.57	58.36
31.36	42.12	39.63	19.74	22.58	19.01	26.95	57.42	67.05	74.14	63.04
35.0	43.76	24.42	32.48	25.57	27.11	27.88	48.95	61.05	60.11	77.28

TABLE 8

Summary Of Parathion Dog Exposures

Date	Run No.	Parathion Concentration	Exposure Time	Ct	Toxic Signs	(Avg of 4 Dogs) Cholinesterase % of Normal Time	RBC	Plasma	Mortality 24-hour
		mg/cu M	min	mg min/cu m			%	%	
4 Sep74	1	8.93*	240	2143.20	Lacrimation - 1/4	4-hour	64.15	13.91	0/4
						24-hour	42.41	6.70	
						48-hour	37.08	7.10	
						7-day	26.79	20.52	
						14-day	37.08	31.93	
10Sep74	2	3.42*	240	821.0		4-hour	70.8	23.20	0/4
						24-hour	44.4	12.72	
						48-hour	38.8	3.85	
						7-day	19.06	9.41	
						14-day	24.48	30.05	
24Sep74	3	0.145*	240	34.8		4-hour	69.89	39.61	0/4
						24-hour	55.69	20.23	
						48-hour	56.70	17.26	
						7-day	56.70	27.96	
						14-day	59.86	37.28	
	4	0.0153*	240	3.672		4-hour	62.1	17.80	0/4
						24-hour	49.27	14.2	
						48-hour	44.01	15.12	
						7-day	71.57	35.40	
						14-day	58.02	75.03	

TABLE 8 CONTINUED

Date	Run No.	Parathion Concentration	Exposure Time	Ct	Toxic Signs	(Avg of 4 Dogs) Cholinesterase % of Normal			Mortality
						Time	RBC	Plasma	
		mg/cu M	min	mg min/cu m			%	%	
	5	37.13 *	240	8912		4-hour	72.53	19.69	0/4
						24-hour	45.11	8.30	
						48-hour	77.81	16.14	
						7-day	64.91	38.01	
						14-day	85.34	76.39	

* Average of 2 chamber samples collected at 1 and 2 hours

TABLE 9

Red Blood Cell and Plasma Cholinesterase Values of Dogs Exposed by Inhalation To Parathion Aerosols for Four Hours

Percent ChE Activity From Start of Exposure

Conc. mg/cu m	4 hr		24hr		48hr		168hr		336hr	
	RBC	Plasma	RBC	Plasma	RBC	Plasma	RBC	Plasma	RBC	Plasma
0.0153	62.10	17.92	49.27	14.20	44.01	15.12	71.57	35.40	58.02	75.03
0.15	69.90	39.61	55.70	20.23	56.70	17.26	56.40	27.96	59.86	37.28
3.4	70.80	23.20	44.40	12.72	38.80	3.85	19.06	9.41	24.5	30.05
8.9	64.15	13.91	42.41	6.70	37.09	7.10	26.79	20.52	37.09	31.93
37.13	72.53	19.69	45.11	8.30	77.81	16.14	64.91	38.01	85.34	76.39

The individual curves for plasma and RBC ChE activity for each dose level are shown in figures 3A thur 7A of the Appendix. The solid lines represent the statistical best fit curve while the dashed lines connect the individual points.

3. Sub-Acute Studies.

a. Rats.

Based on the information obtained from acutely exposing rats, the estimated no effect dose (0.01 mg/cu m) was selected for subacute testing. Two additional dose levels 0.10 and 0.74 mg/cu m were tested to obtain moderate and pronounced effects on ChE.

These data are summarized in table 10 and illustrated in figures 16 thru 19. The levels selected for testing were experimentally verified. The 0.01 mg/cu m concentration was determined to be a no-effect dose while the 0.10 mg/cu m level produced moderate effects. A pronounced effect was produced by the highest dose level 0.74 mg/cu m. Table 14A thru 19A show the statistical evaluations of these data.

Three chamber samples were collected during each 7 hour exposure for analysis of parathion. The results, including the mean concentration for all three dose levels, are shown in Appendix, table 20A. The average parathion concentrations, daily Ct's, cumulative Ct's and toxic signs are in Appendix tables 21A, 22A and 23A.

No toxic signs were seen in the rats exposed to 0.01 and 0.10 mg/cu m. However, one rat died on the 1st exposure day at the lowest level. Pathological examination showed that the rat had lung congestion but no significant lesions due to parathion exposure. One unexposed control rat from the 0.10 mg/cu m group died on the ninth day. This rat showed acute kidney, ureter and bladder inflammation.

TABLE 10

Red Blood Cell and Plasma Cholinesterase Values of Rats Exposed By Inhalation to Parathion Aerosols

Concentration (mg/cu m)	Percent ChE Activity from Start of Exposure											
	Week No.1		Week No.2		Week No.3		Week No.4		Week No.5		Week No.6	
	RBC	Plasma	RBC	Plasma	RBC	Plasma	RBC	Plasma	RBC	Plasma	RBC	Plasma
0.01	88	96	93	100	-	-	69	97	69.6	76.8	97.5	99.2
0.10	57	99	60	66	-	-	65	79	66.7	92.3	Exposure Terminated	
0.74	58	68	50	67	23.8	22.7	33.2	21.0	15.5	31.8	25.5	40.0
	Percent ChE Activity - Post-Exposure Period											
0.01	82	97	84.4	127	-	-	94	99.4	-	-	118.5	141.3
0.10	61	116.4	76.4	133.3	82	118.6	-	-	81	113	-	-
0.74	44	112.6	-	-	65	100	-	-	-	-	87.5	116.6

There were no other significant lesions. The cause of death could not be definitely related to the action of parathion. At the highest parathion level, 0.74 mg/cu m, two rats died, one on the 10th day of exposure and one on the 23th day of exposure. The rat that died on the tenth day of exposure showed congested lungs on gross examination and edema on microscopic examination. This was an agent related lesion. The rat that died on the 22th day showed acute lung congestion and no significant lesions.

Two rats were sacrificed at the highest parathion level after 5 and 15 days exposure due to their poor physical appearance. The rat that was sacrificed on the 5th day of exposure had severe malecclusion. The other rats showed tremors and ataxia twenty-four hours before sacrifice. This rat had escaped from its cage and was loose in the chamber.

Blood hematocrit values were obtained on four controls and nine exposed rats after the last exposure to a parathion concentration of 0.74 mg/cu m. The values for the four controls were 47.8, 49.0, 51.0 and 45.9 mg%. The values for the nine exposed rats were 47.2, 44.9, 49.3, 47.8, 45.5, 47.3, 48.8, 47.8, 46.6 mg%. The average was 47.2 mg%. This value is not significantly different from the control average.

The rats were weighed just prior to obtaining blood samples, during the exposure and post-exposure period. The body weights of the rats exposed to all three subacute parathion concentrations are shown in Appendix table 24A. Rats gained weight throughout the exposure and post exposure periods at all three parathion levels. These body weights are shown graphically in figures 20 and 21.

b. Dogs.

Repsective groups of six dogs each were exposed to airborne parathion concentrations of 0.001, 0.01 and 0.20 mg/cu m. The RBC and plasma ChE % activity values are shown in table 11. Figures 8A through 11A of the Appendix illustrates the cholinesterase activities for the exposure and post exposure periods.

Red blood cell and plasma ChE activities tested at the 0.001 mg/cu m dose level remained essentially unchanged during the six week exposure period and post exposure recovery period. This dose level would be considered a no-effect level. At the 0.01 mg/cu m dose level, ChE activity was 78.6% for RBC and 69.6% for plasma at the end of the 2nd week of exposure. This level would be considered as having an intermediate effect. The high dose, 0.2 mg/cu m, could be considered as having a severe effect. By the end of the 2nd week RBC ChE activity was 53.0% and plasma activity was 25.5%. RBC ChE activity did not return to normal until the 4th week of the post exposure recovery period. No other toxic signs were observed in these dogs.

Figures 22 and 23 show the growth curves for the subchronic dogs Appendix table 25A lists the daily concentration for dogs exposed to parathion with the mean concentration and 95% confidence limits. Appendix tables 26A, 27A and 28A show the daily CTs and 30-day cumulative CTs for the dogs.

B. Oral Effect of Parathion.

1. Acute Studies - Rat.

a. Mortality and Toxic Effects.

Fifty adult male rats were used to determine the acute 24-hour LD_{50} following a single oral dose of ethyl parathion in corn oil. Five

groups of rats, 10 per group, received doses of ethyl parathion ranging from 10.0 mg/kg to 4.0 mg/kg. The results of this study are shown in table 12. The 24-hour LD50 was found to be 6.83 (6.13-7.60) mg/kg. Table 13 lists the toxic signs observed during this LD_{50} study and gives the ET_{50}'s for toxic signs as well as the ED_{50} for each group. Figures 24 through 27 illustrate the 1-99% response for these signs.

b. ChE_{50} Determinations.

The acute ChE_{50} determinations in adult male rats required the use of 80 rats, 10 of which served as controls. All rats received a constant dose volume of 5 ml/kg of the parathion/corn oil solution. The concentration of parathion per ml of corn oil was varied in order to maintain the constant dose volume. The results of this study are shown in table 14 (RBC) and table 15 (plasma). The RBC ChE_{50} was determined to be 2.579 (2.117-3.141) mg/kg and the plasma ChE_{50} was 2.546 (2.123-3.054) mg/kg.

2. Acute Studies - Dogs.

a. Mortality, Toxic Responses and ChE Determinations.

Twenty adult male dogs were used to determine the 24-hour LD_{50} following oral dosing with ethyl parathion. Table 16 lists the five dose levels (mg/kg) used, the per cent of dogs responding at each dose level and the Bliss statistical analysis for the LD_{50} (8.17 mg/kg). Toxic signs and times to death are listed in table 17. Because of the limited numbers of dogs used to determine the LD_{50} no statistical analysis of time to response was done.

The acute ChE_{50} for both RBC and plasma ChE activity in dogs is shown in tables 18 (RBC) and 19 (plasma). Dogs in groups of four

TABLE 11

Subacute Inhalation Toxicity Studies of Ethyl Parathion in Six Dogs

Exposed Seven Hours/Day, Five Days/Week, For Six Weeks.

Parathion Concentration		Exposure Period (Day & Weeks)							Post Exposure (Weeks)					
mg/cu m	ChE	1 (Day)	1	2	3	4	5	6	1	2	3	4	5	6
		% Activity (average of six dogs)							% Activity (average of six dogs)					
	RBC	101	134.5	129	106.0	-	135	135	95	95	-	86.5	90	98
0.001	Plasma	88	88	96	95	-	102	91	99	78.5	-	97	131	105
	RBC	124	105.7	78.6	86.0	-	96.9	101.3	97.9	103.8				
0.01	Plasma	113	92.3	69.9	71.9	-	71.6	58.4	91.4	90.8				
	RBC	88.5	75	53.6	74.4	-	57	41	77	61	-	86	84	79
0.20	Plasma	46	41	25.9	34.5	-	53	36	72	94	-	115	134	112

TABLE 12

Rat 24 Hr. LD_{50} Following Oral Administration of Ethyl Parathion

Dose mg/kg	% Mortality 10 Rats/dose	Bliss Statistical Analysis 95%			
		Percent	Dose mg/kg	Lower Limit	Upper Limit
10.0	100.0	1	4.49	3.59	5.62
7.9	80.0	16	5.72	5.01	6.53
6.3	20.0	30	6.23	5.57	6.97
5.0	10.0	50	6.85	6.18	7.60
4.0	0.0	84	8.21	7.17	9.40
		99	10.45	8.33	13.16

247

TABLE 13

ED_{50}'s (minute) ED_{50}'s and LD_{50} For Toxic Signs and Death in Male Rats Following a Single Oral Exposure to Ethyl Parathion

Dose (mg/kg	Tremors	Salivation	Convulsions	Prostration	Death
10.0	10/10 28.1 (23.5 - 33.5)	10/10 36.9 (28.7 - 47.4)	10/10 33.1 (25.8 - 42.4)	10/10 42.5 (34.1 - 52.4)	10/10 45.6 (36.5 - 56.8)
7.9	10/10 46.1 (34.1 - 62.3)	9/10 72.1 (48.4 - 107.4)	8/10 75.5 (45.1 - 125.7)	7/10 80.4 (50.7 - 127.7)	8/10 108.3 (5.15 - 227.4)
6.3	10/10 69.1 (48.8 097.7)	4/10 ——	2/10 ——	2/10 ——	2/10 ——
5.0	10/10 43.8 (39.9 - 48.1)	2/10 ——	2/10 ——	1/10 ——	1/10 ——
4.0	0/10 ——	——	——	——	——
ED_{50} And LD_{50} (95% C. L. (mg/kg)	4.43 (4.48 - 4.48)	6.27 (5.64 - 6.98)	6.69 (5.98 - 7.84)	7.01 (6.30 - 7.80)	6.85 (6.18 - 7.3

a/ Number of animals Responding

TABLE 1:

Rat Acute RBC ChE_{50} Following Oral Adminstration of Ethyl Parathion

Dose mg//kg	% Inhibition 10/rats/dose	Bliss Statistical Analysis 95% C. L.			
		Per cent	Dose mg/kg	Lower Limit	Upper Limit
0.175	8.1	1	0.035	0.021	0.057
0.350	12.6	16	0.410	0.318	0.527
0.700	27.4	30	0.977	0.799	1.195
1.400	32.2	50	2.579	2.117	3.141
2.800	51.8	84	16.236	11.716	22.499
5.600	69.7	99	190.792	106.402	342.114
7.000	69.0				

TABLE 15

Rat Acute Plasma ChE_{50} Following Oral Administration of Ethyl Parathion

Dose mg/kg	% Inhibition 10 Rat/dose	Bliss Statistical Analysis 95%			
		Per Cent	Dose mg/kg	Lower Limit	Upper Limit
0.175	0.00	1	0.094	0.034	0.259
0.350	8.7	16	0.622	0.416	0.930
0.700	22.5				
1.400	44.7	30	1.211	0.976	1.503
2.800	55.5	50	2.546	2.123	3.054
5.600	78.4				
7.000	75.2	84	10.424	5.813	18.692
		99	68.853	20.747	228.367

TABLE 16

LD_{50} In Adult Male Dogs Following Oral Exposure to Ethyl Parathion in Corn Oil

Dose mg/kg	Mortality 4 Dogs/dose	Bliss Statistical Analysis 95% C. L.			
		Per Cent	Dose mg/kg	Lower Limit	Upper Limit
20.0	100	1	1.91	0.18	20.67
15.8	75	16	4.42	1.29	15.07
10.0	50	50	5.94	2.53	13.98
6.3	50	50	8.27	4.79	14.29
2.5	0	84	15.50	6.61	36.34
		99	35.92	5.04	256.10

TABLE 17

Observed Toxic Signs and Times To Death

In Male Dogs Exposed Orally To Ethyl Parathion

Dose mg/kg	Time To Toxic Sign (minutes)					
	Tremors	Ataxia	Salivation	Convulsions	Prestration	Death
20.0	15.0 15.0	12.0 15.0	-- --	20.0 18.0,120.0	25.0 20.0,120.0	30.0,65.0 120.0 on
15.8	27.0,28.0 58.0	-- --	-- --	50.0 58.0	55.0 67.0	71.0 1320.0 30.0
10.0	90.0 97.0	90.0 97.0	90.0,97.0 137.0	93.0 98.0	-- --	120.0, on
6.3	55.0,65.0 68.0	40.0 50.0	-- --	85.0 178.0	90.0 185.0	195.0 on
2.5	--	--	--	--	--	--

TABLE 18

Dog Acute RBC ChE_{50} Following Oral Adminstration of Ethyl Parathion

Dose mg/kg	% Inhibition 4 dogs/dose	Bliss Statistical Analysis 95% C. L.			
		Percent	Dose mg/kg	Lower Limit	Upper Limit
10.0	73.0	1	0.004	0.000	0.059
2.5	64.0	16	0.114	0.032	0.412
1.26	50.0	30	0.385	0.178	0.837
0.50	29.0	50	1.497	1.060	2.115
		84	19.619	6.620	58.141
		99	615.423	46.685	8112.696

TABLE 19

Dog Acute Plasma ChE_{50} Following Oral Administration of Ethyl Parathion

Dose	% Inhibition	Bliss Statistical Analysis 95% C. L.			
mg/kg	4 dogs/dose	Percent	Dose mg/kg	Lower Limit	Upper Limit
10.0	65.0	1	0.000	0.000	0.299
2.5	59.0				
1.26	40.0	16	0.020	0.000	0.693
0.50	42.0				
		30	0.161	0.019	1.348
		50	1.670	0.942	2.960
		84	141.422	4.061	4294.465
		99	53974.909	12.157	239,629,444.000

were given one of four dose levels of ethyl parathion in corn oil and blood samples for ChE activity analysis were taken 24 hours post exposure. The RBC ChE_{50} was found to be 1.497(1.060-2.115) mg/kg and the plasma ChE_{50} was 1.670(0.942-2.960) mg/kg.

3. Sub-Acute Studies.

a. Rats.

A total of 480 adult male rats were used to determine the effects of repeated daily exposure to ethyl parathion. One half of the rats received daily doses of corn oil (5 days/week for 6 weeks) and served as solvent controls while the other 240 rats received daily doses of ethyl parathion in corn oil. All rats were weighed daily and doses were given on a ml/kg basis. Control rats received 1 ml/kg of corn oil and exposed (test) rats received 1 ml/kg of corn oil containing the ethyl parathion in concentrations of 0.25 mg/ml, 0.10 mg/ml or 0.05 mg/ml. There were 80 rats per dose level in the exposed groups.

The bleeding schedule for ChE determination was 10 control and 10 exposed rats for each dose level at 1, 2, 4 and 6 weeks during exposure and at 1, 2, 4 and 6 weeks post exposure if required.

The results of this study are shown in table 20. The high dose (0.25 mg/kg) produced about a 55% inhibition in RBC ChE activity and 48% inhibition of the plasma ChE activity. No signficant inhibition resulted from the 0.05 mg/kg dose while the 0.1 mg/kg dose produced about 20% inhibition of RBC ChE activity. The 0.25 mg/kg dose rats were recovered to normal levels at six weeks post exposure, while the two lower dose levels were recovered at one week post exposure.

Table 20

ChE Determination in Male Rat Following Daily (5day/wk/6wks) Oral Exposure to Ethyl Parathion in Corn Oil

Daily Dose mg/kg	ChE Type	Percent Residual ChE Activity											
		Week of Exposure						Week Post Exposure					
		1	2	3	4	5	6	1	2	3	4	5	6
0.25	RBC	74.1	—	66.4	43.5	56.6	45.5	44.4	69.0	—	67.7	—	159.0
	Plasma	103.0	—	106.0	115.0	53.9	52.1	75.5	101.0	—	106.0	—	119.0
0.10	RBC	87.4	78.5	—	77.9	—	80.8	119.0	141.0	—	71.6	—	
	Plasma	106.0	19.9	—	94.2	—	115.0	109.0	117.0	—	103.0	—	
0.05	RBC	85.1	95.0	—	119.0	—	115.0	85.3		—		—	
	Plasma	98.2	127.0	—	133.0	—	156.0	96.0		—		—	

4

The rat data are illustrated in figures 28 thru 31. These are computed lines designed to give the best statistical fit to the actual data. Figures 28 and 29 represent the RBC and plasma ChE values during the exposure period. Figures 30 and 31 show the post exposure ChE values for RBC and plasma ChE.

No toxic signs were observed in any of these test or control rats during or after exposure. Weight gained by controls was not significantly different from that gained by the exposed rat groups. Figures 32 through 34 show the growth curves for rats exposed to 0.05, 0.10 and 0.25 mg/kg respectively.

b. Dogs.

Twenty-four adult male dogs were exposed orally, 5 days/week for 6 weeks to one of three dose levels of ethyl parathion in solution with corn oil. The dogs were divided into three groups of eight each. Each group had six dogs exposed to parathion and two dogs (control) to neat corn oil. All dogs were weighed on a weekly schedule and doses were given on a mg/kg basis.

Blood samples for ChE determination were taken at 1, 2, 4 and 6 weeks during exposure and at 1, 2, 4 and 6 weeks post exposure if needed. Post exposure dogs were bled only until normal or near normal levels of ChE activity had returned.

The results of these daily repeated doses of ethyl parathion are shown in table 21. The 0.50 mg/kg dose produced after 6 weeks exposure an approximate 58% inhibition of RBC ChE and 85% inhibition of the plasma ChE activity. Recovery at six weeks post exposure was incomplete but had reached 67% of normal for RBC ChE and 74% of normal for plasma ChE. Inhibition from the 0.10 mg/kg and 0.05 mg/kg dose of

Table 21

ChE Determination in Male Dogs Following Daily (5day/wk/6wks) Oral Exposure To Ethyl Parathion In Corn Oil

Daily Dose mg/kg	ChE Type	Per Cent Residual ChE Activity											
		Week of Exposure						Week Post Exposure					
		1	2	3	4	5	6	1	2	3	4	5	6
0.5	RBC	74.3	64.6	—	50.7	—	42.4	50.0	49.0	—	68.0	—	67.0
	Plasma	21.9	36.6	—	80.0	—	15.0	70.0	90.0	—	93.0	—	74.0
0.1	RBC	72.6	85.7	—	81.1	—	80.0	77.1	89.5	—	90.8	—	—
	Plasma	24.3	31.9	—	44.4	—	61.1	165.0	94.0	—	90.3	—	—
0.05	RBC	81.5	105.2	—	101.3	—	82.6	69.8	95.3	—	101.3	—	—
	Plasma	44.4	67.7	—	87.3	—	54.2	73.9	92.3	—	99.3	—	—

parathion were similar. The 0.1 mg/kg dose did inhibit ChE activity slightly more but recovery rates were very close and near normal levels of ChE activity were reached by two-weeks post exposure. Figures 35 through 38 show this same data graphically based on per cent residual ChE activity. These graphs are computed lines drawn to give the best statistical fit to the actual data.

No toxic signs were observed in any of the dogs during or after their exposure to these levels of parathion. Also there was no significant weight loss or gain in any of the animals tested. Figure 39 shows the growth curves for these dogs.

4. ChE Recovery Rate.

a. Rats.

A total of 80 male rats were used to determine the recovery rate of RBC and plasma ChE activity following a single oral dose of 2.80 mg/kg of ethyl parathion. Sixty of the rats were exposed to the parathion and 20 rats received neat corn oil and served as controls. Rats were bled at 4, 24, 48, 72, 168, and 336 hours post exposure.

Recovery rates of the RBC and plasma ChE activity are shown in table 22. After 336 hours, recovery of the RBC ChE activity was only 67 per cent of normal while the plasma ChE was still 11 per cent inhibited.

These data are graphically represented in figure 40. These lines are computed statistically to best fit the actual data points.

b. Dogs.

Four adult male dogs were given a single oral dose of ethyl parathion (2.5 mg/kg) and post exposure blood samples were taken at 24, 264, 360, 696 and 864 hours post exposure. At 24 hours post exposure RBC ChE activity was 64% inhibited and plasma ChE activity was 59% inhibited.

Table 22

ChE Recovery in Male Rats Following a Single Oral Dose (2.80 mg/kg) of Ethyl Parathion

Time Post Exposure	% Residual ChE Activity	
	RBC	Plasma
4 Hrs	44.2	34.9
24 Hrs	44.5	48.8
48 Hrs	55.7	51.5
72 Hrs	50.9	85.2
168 Hrs	60.1	69.5
336 Hrs	66.7	89.3

.36
29|864
72
144

Recovery to near normal levels was reached at 864 hours post exposure for the RBC ChE activity and at 696 hours post exposure for the plasma ChE activity. Results of this experiment are listed in table 23 and a graphic representation of the data is given in figure 41. This figure is a statistical representation of the best fit of the acutal data as drawn by computer.

TABLE 25

ChE Recovery in Male Dogs Following a Single Oral Dose (2.5 mg/kg) of Ethyl Parathion

Time Post Exposure	% Residual ChE Activity	
	RBC	Plasma
24 Hrs	56.0	41.0
264 Hrs	53.0	78.0
360 Hrs	58.0	85.0
696 Hrs	67.0	117.0
864 Hrs	89.0	112.0

IV. SUMMARY AND CONCLUSIONS.

The effect of ethyl parathion in male rats and dogs exposed acutely and subacutely by the inhalation and oral routes were determined. In acute inhalation tests, groups of four dogs were exposed four hours to five dose levels of parathion ranging from 0.0153 to 37.13 mg/cu m. Due to the pronounced effect on ChE activity and the shortage of dogs, no ChE_{50} or LC_{50} values could be obtained. The LC_{50} is greater than 37.13 mg/cu m. Groups of thirty-four rats were exposed four hours to thirteen levels of parathion ranging from 0.035 to 35.0 mg/cu m. The plasma ChE_{50} with 95% confidence limits is 7.28 (5.24-10.12) mg/cu m. The RBC ChE_{50} is 5.43 (4.2-7.03) mg/cu m. Groups of thirty-four rats were exposed to eight parathion levels ranging from 31.36 to 230.5 mg/cu m. The LC_{50} is 84.0 (78.9 - 90.4) mg/cu m. In acute oral studies groups of four dogs were exposed to seven dose levels ranging from 0.5 to 10.0 mg/kg. The plasma ChE_{50} is 1.67 (0.94-2.96) mg/kg and the RBC ChE_{50} is 1.5 (1.06- 2.12) mg/kg. Groups of four dogs were exposed to five levels of parathion ranging from 2.5 to 20.0 mg/kg. The LD_{50} is 8.27 (4.79 to 14.29) mg/kg. Toxic signs, i. e., tremors, convulsions and death were noted in dogs at doses above 2.5 mg/kg. The plasma ChE_{50} for rats exposed acutely by the oral route is 2.5 (2.14 to 3.1) mg/kg, and the RBC ChE_{50} value is 2.58 (2.12 to 3.14) mg/kg. The LD_{50} is 6.85 (6.18 to 7.59) mg/kg.

In sub-acute studies groups of six dogs were exposed by inhalation to three dose levels of parathion, 0.001, 0.01 and 0.20 mg/cu m seven hours per day, five days per week for six weeks. RBC ChE and plasma ChE determinations were made at 1, 2, 4 and 6 weeks of the exposure period

and post -exposure period. The o.ool mg/cu m dose level was a no effect dose for both plasma and RBC ChE activity, while the 0.01 mg/cu m and 0.20 mg/cu m levels had moderate pronounced ChE effects respectively. RBC ChE activity in dogs exposed to 0.20 mg/cu m did not return to normal until the 6th post-exposure week. Rats in groups of eighty were tested subacute by the inhalation route at dose levels of 0.01, 0.10 and 0.74 mg/cu m seven hours/day, five days/week for six weeks. Blood samples were obtained at various weeks during the exposure and post-exposure period for ChE determinations. The 0.01 mg/cu m dose level was considered to be a no-effect level for plasma and RBC ChE activity while the 0.10 and 0.74 mg/cu m levels had moderate and pronounced ChE effects respectively. RBC ChE activity in rats exposed to 0.74 mg/cu m did not return to normal until the sixth post-exposure week. In subacute oral studies on dogs, groups of six dogs were exposed to 0.05, 0.10 and 0.50 mg/kg for six weeks during exposure and post-exposure periods. Each dog served as his own control. The least effect on ChE activity was observed at the 0.05 mg/kg dose, while 0.10 and 0.50 mg/kg doses produced moderate and pronounced effects on plasma and RBC ChE activity. Subacute rats were exposed orally to parathion doses of 0.05, 0.10 and 0.25 mg/kg for six weeks. The 0.05 mg/kg dose is a no-effect dose on both plasma and RBC ChE activity. The 0.10 mg/kg dose could be considered as having a moderate effect on the ChE activity. The highest parathion dose, 0.25 mg/kg produced pronounced effects on both plasma and RBC ChE activity.

FIGURES IN TEXT OF PARATHION REPORT

Figure 1.
199% RESPONSE TIMES FOR TREMORS IN RATS EXPOSED ACUTELY FOR FOUR HOURS TO ETHYL PARATHION AEROSOL (DOSE-71.0 Mg/Cu M)

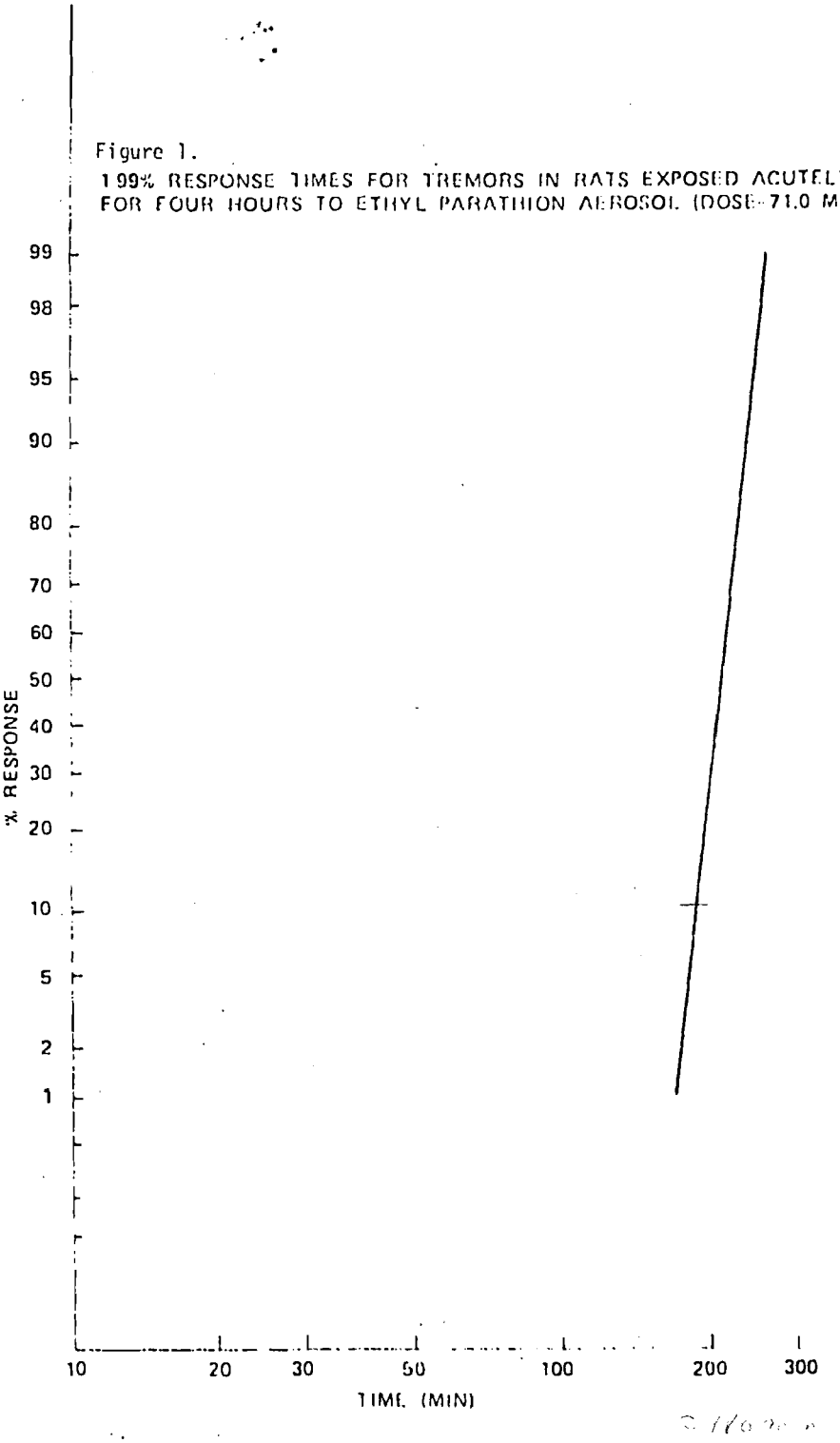


Figure 2.
1.99% RESPONSE TIMES FOR TREMORS, CONVULSIONS AND DEATH IN RATS EXPOSED ACUTELY FOR FOUR HOURS TO ETHYL PARATHION AEROSOL (DOSE = 97.0 Mg/Cu M)

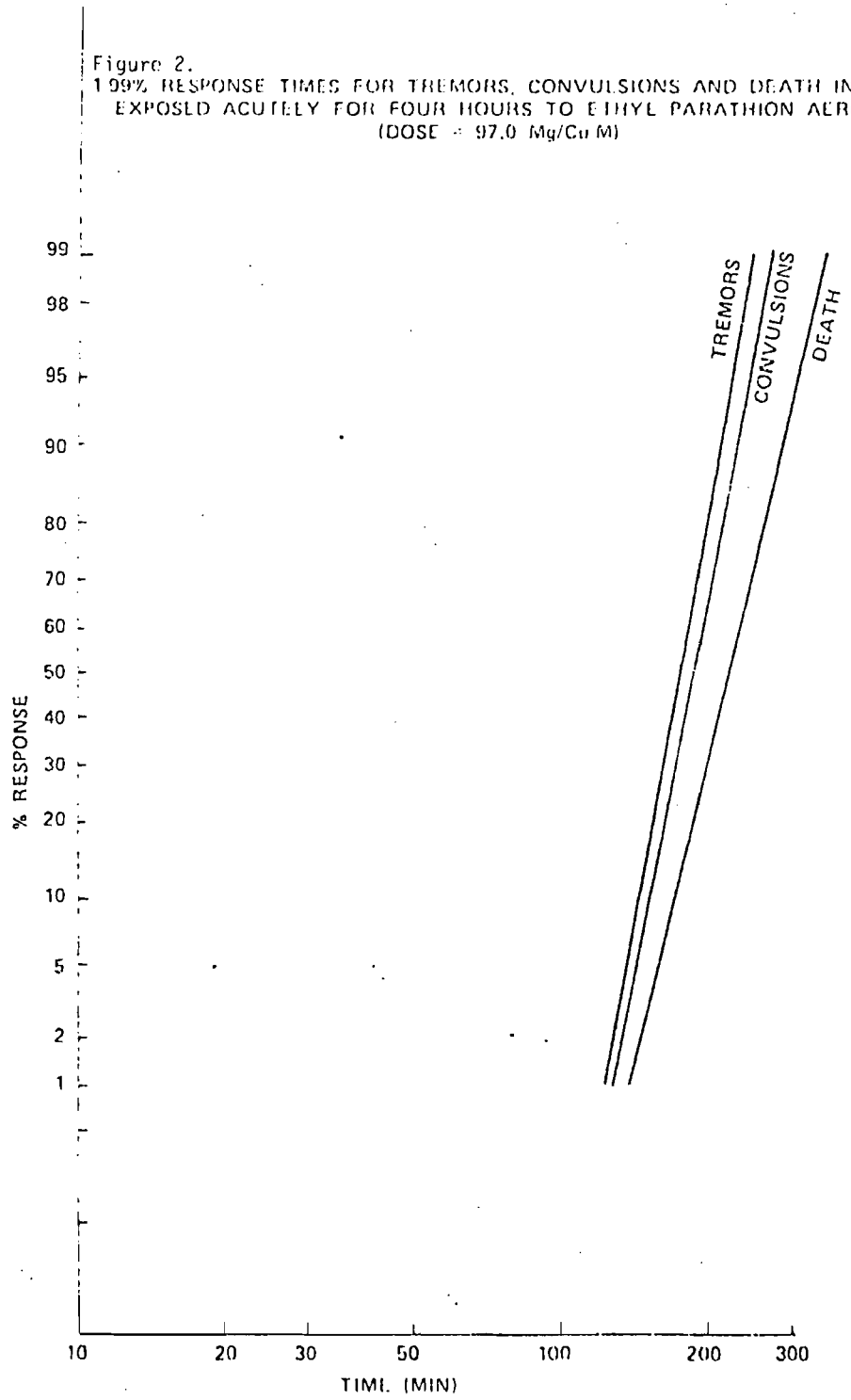


Figure 3.
1-99% RESPONSE TIMES FOR TREMORS, CONVULSIONS AND DEATH IN RATS EXPOSED ACUTELY FOR FOUR HOURS TO ETHYL PARATHION AEROSOL (DOSE = 100.6 Mg/Cu M)

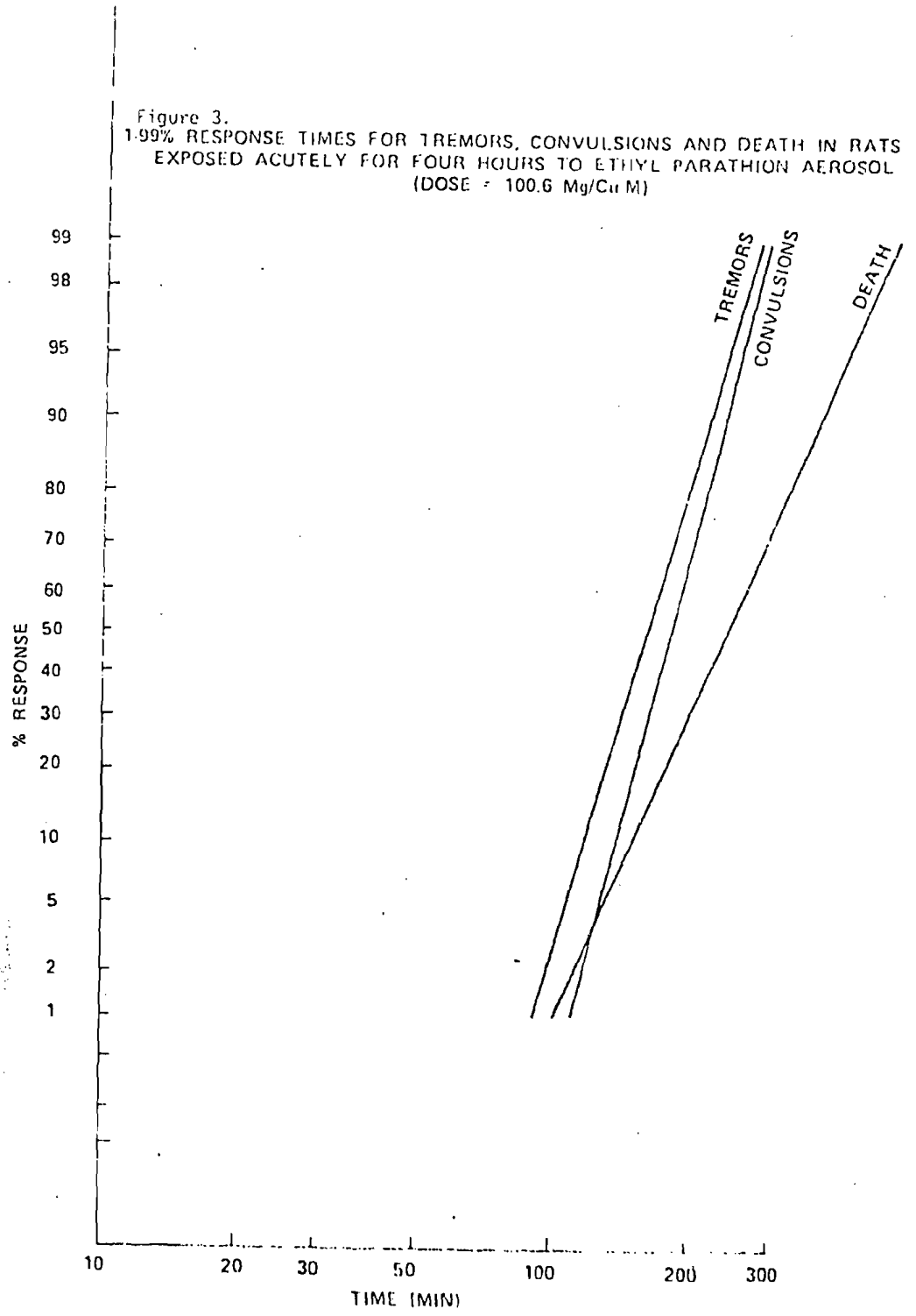


Figure 4.
1 99% RESPONSE TIMES FOR TREMORS, CONVULSIONS AND DEATH
IN RATS EXPOSED ACUTELY FOR FOUR HOURS TO ETHYL PARATHION
(DOSE = 118.5 Mg/Cu M)

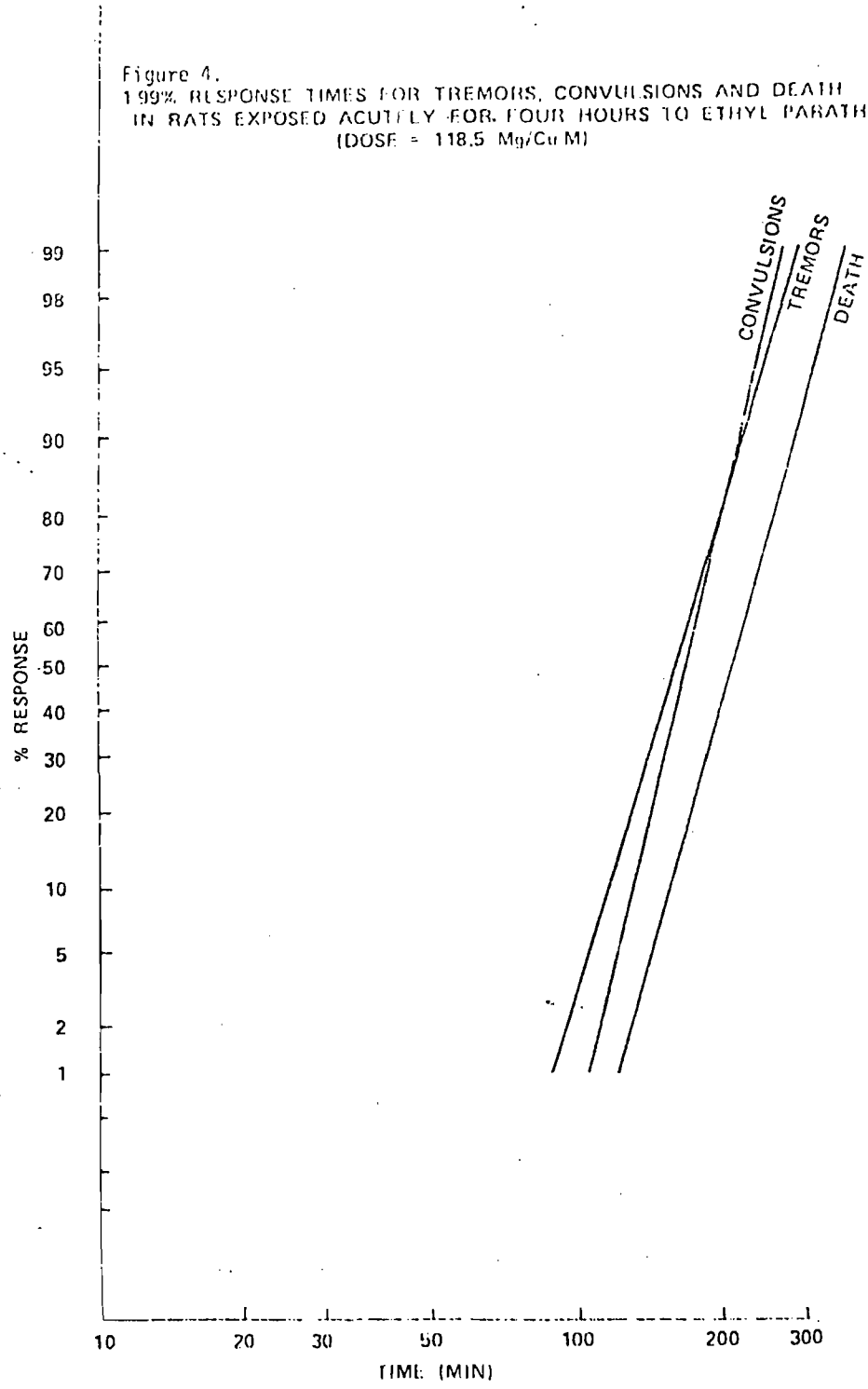


Figure 5.
1-99% RESPONSE TIMES FOR TREMORS, CONVULSIONS AND DEATH IN RATS EXPOSED ACUTELY FOR FOUR HOURS TO ETHYL PARATHION AEROSOL (DOSE=230.5 Mg/Cu M)

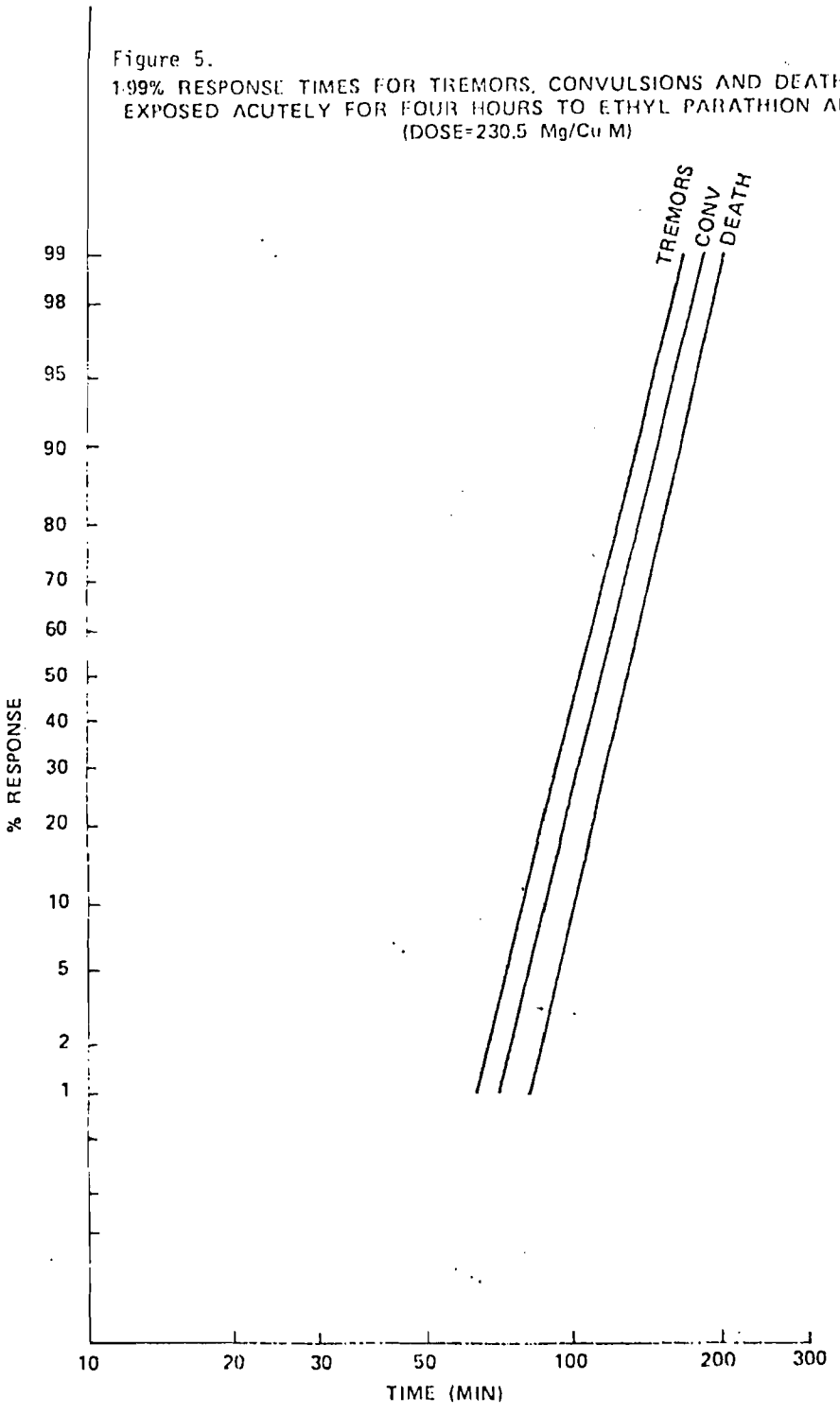


Figure 6. RED BLOOD CELL AND PLASMA CHOLINESTERASE CURVES FOR RATS EXPOSED FOUR HOURS TO ETHYL PARATHION AEROSOL (CONCENTRATION = 0.035 mg/cu m)

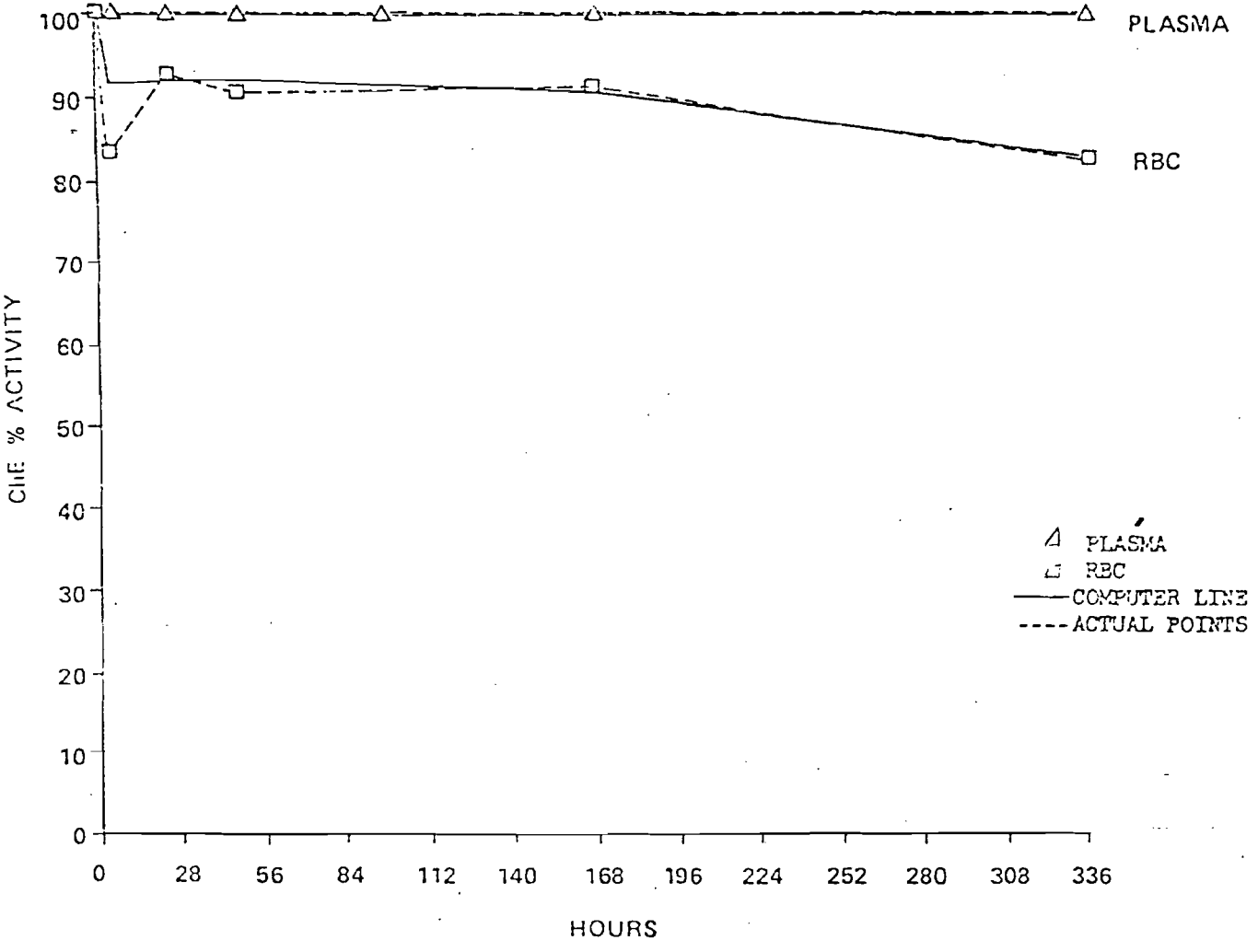


Figure 7. RED BLOOD CELL AND PLASMA CHOLINESTERASE CURVES FOR RATS EXPOSED FOUR HOURS TO ETHYL PARATHION AEROSOL (CONCENTRATION = 0.220 mg/cu m)

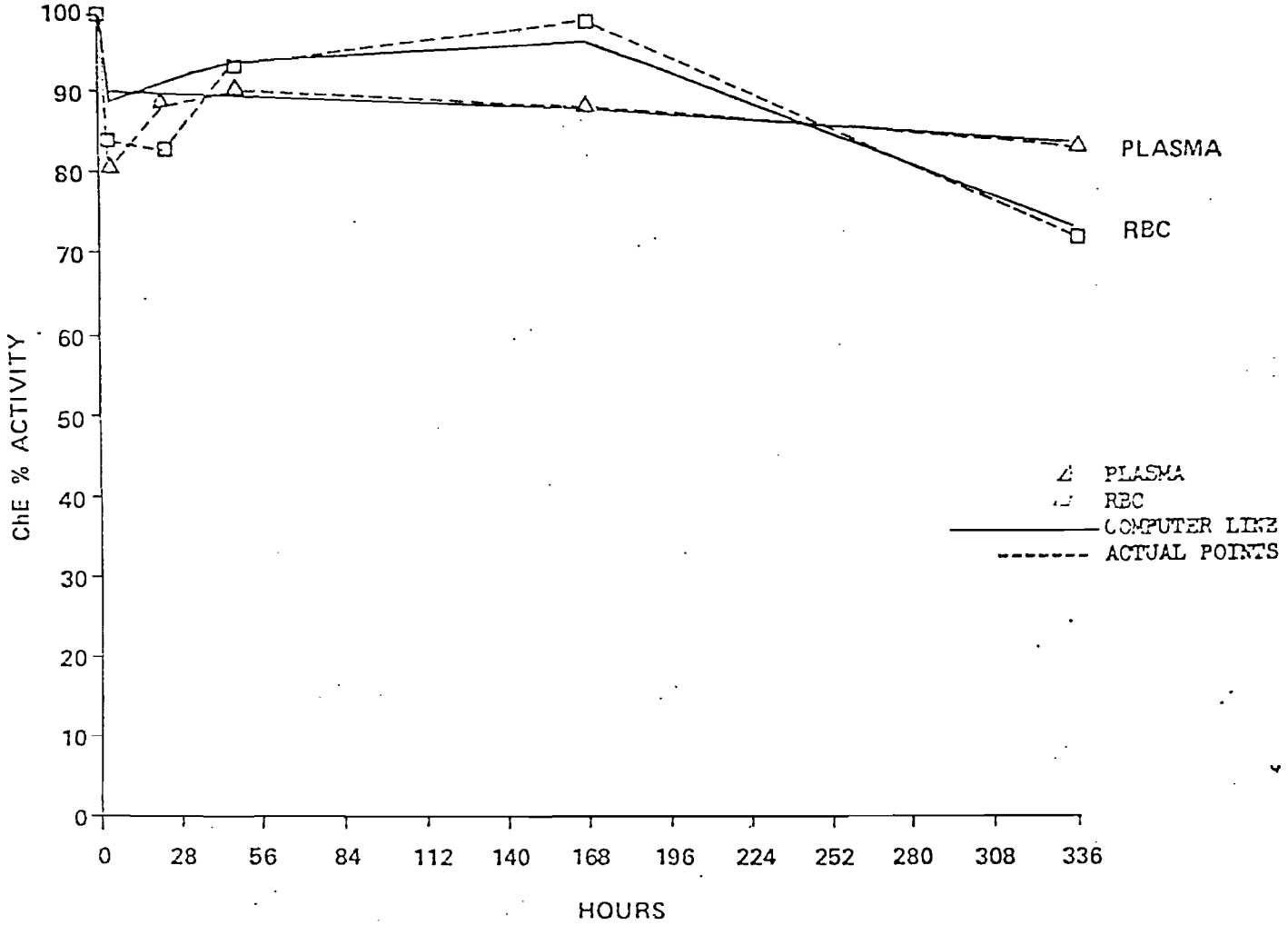


Figure 8. RED BLOOD CELL AND PLASMA CHOLINESTERASE CURVES FOR RATS EXPOSED FOUR HOURS TO ETHYL PARATHION AEROSOL (CONCENTRATION = 0.98 mg/cu m)

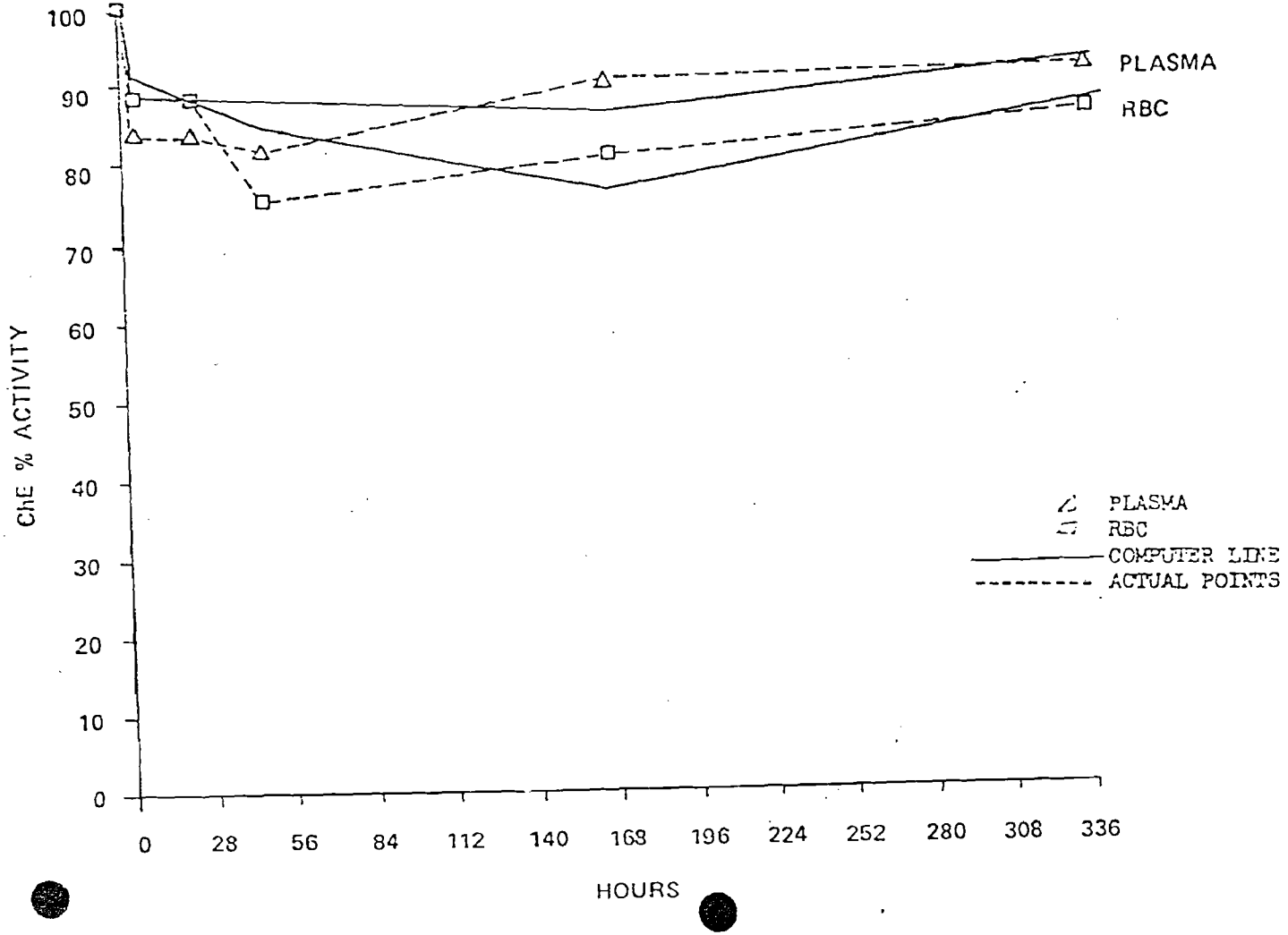


Figure 8A. RED BLOOD CELL ChE ACTIVITY IN DOGS DURING SUB-ACUTE INHALATION EXPOSURES TO ETHYL PARATHION

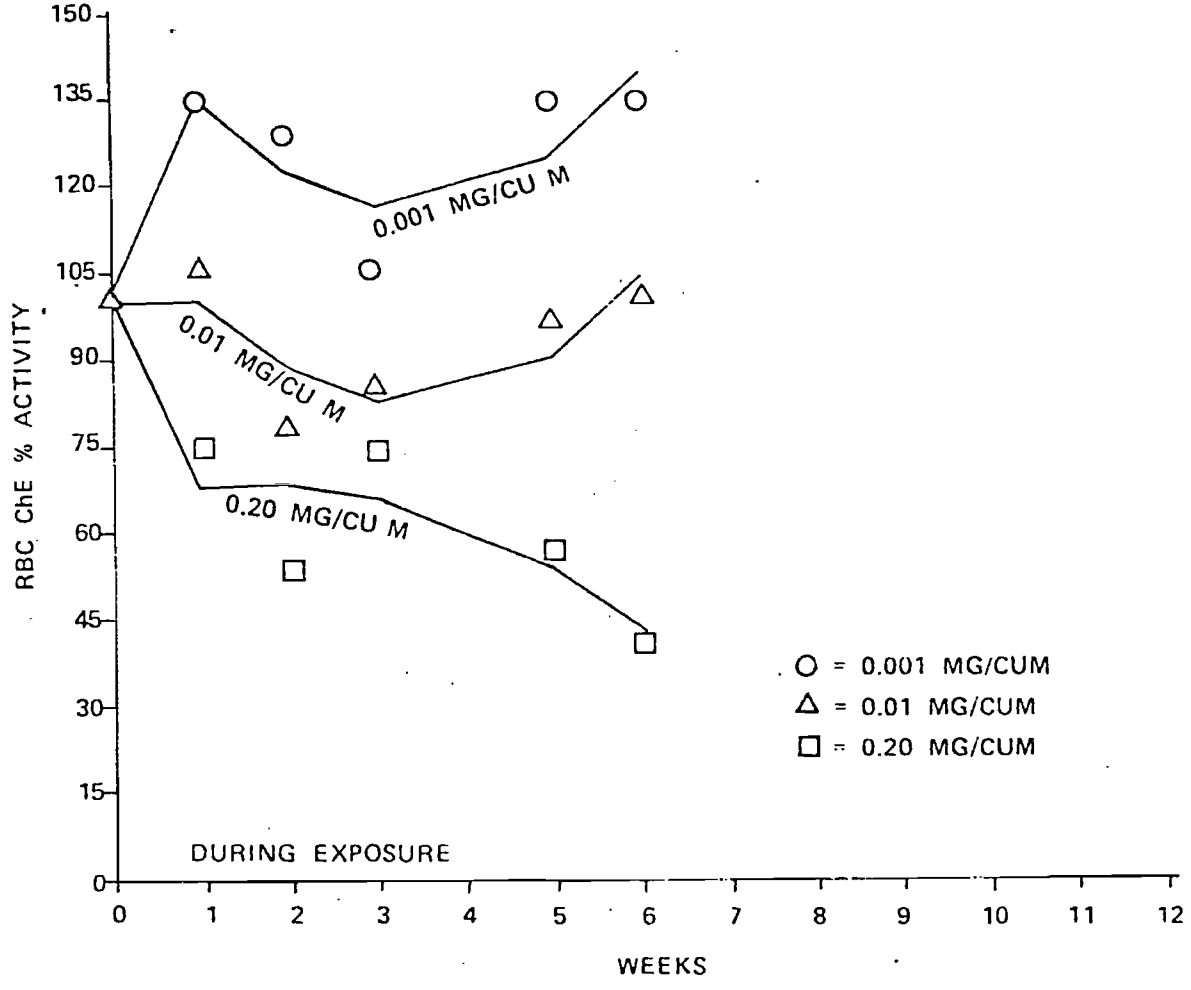


Figure 9. RED BLOOD CELL AND PLASMA CHOLINESTERASE CURVES FOR RATS EXPOSED FOUR HOURS TO ETHYL PARATHION AEROSOL (CONCENTRATION = 2.22 mg/cu m)

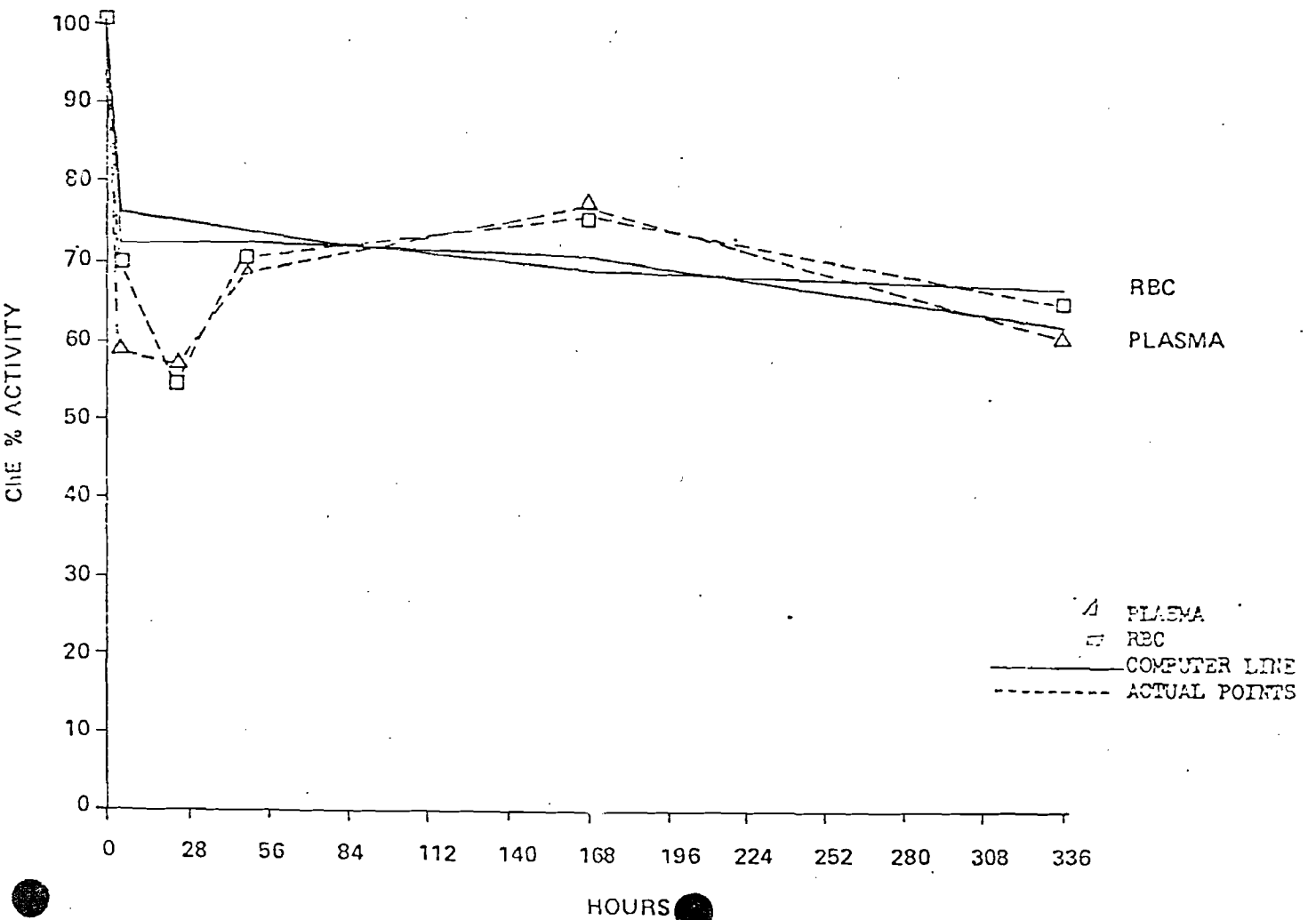


Figure 9A. RECOVERY RATE OF RBC ChE ACTIVITY IN DOGS FOLLOWING SUB-ACUTE INHALATION EXPOSURES TO ETHYL PARATHION

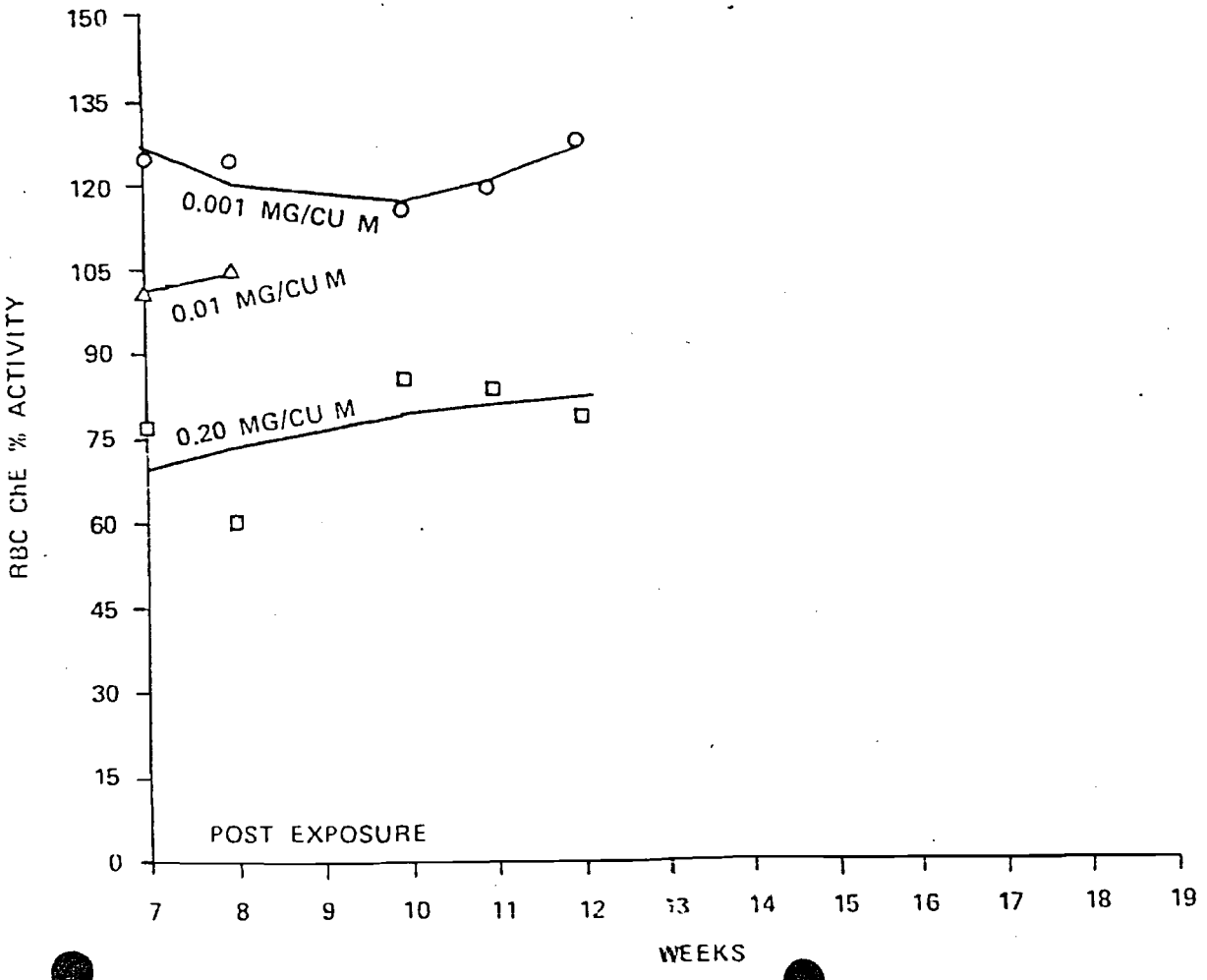


Figure 10. RED BLOOD CELL AND PLASMA CHOLINESTERASE CURVES FOR RATS EXPOSED FOUR HOURS TO ETHYL PARATHION AEROSOL (CONCENTRATION = 12.80 mg/cu m)

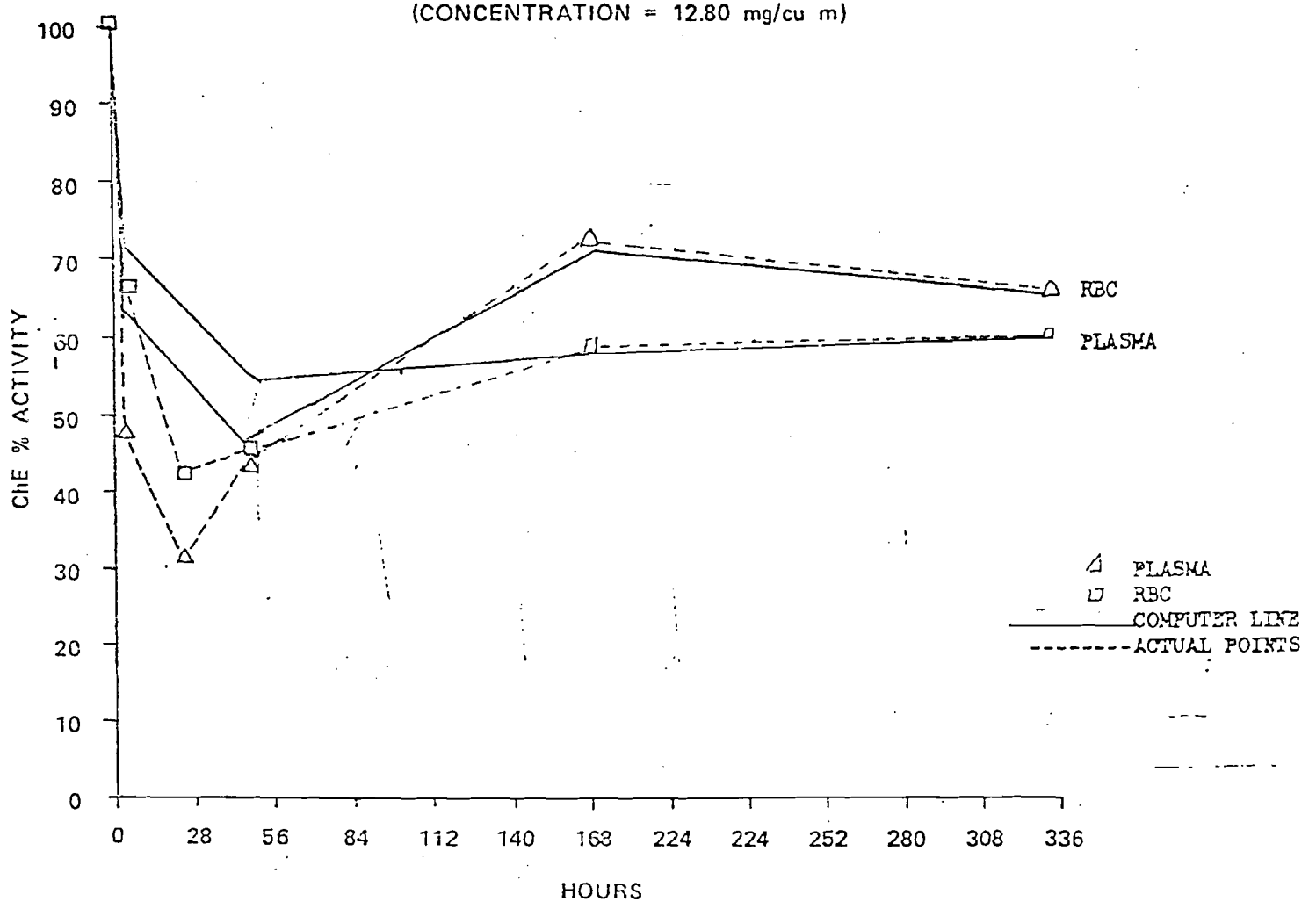


Figure 10A. PLASMA ChE ACTIVITY IN DOGS DURING SUB-ACUTE INHALATION EXPOSURES TO ETHYL PARATHION

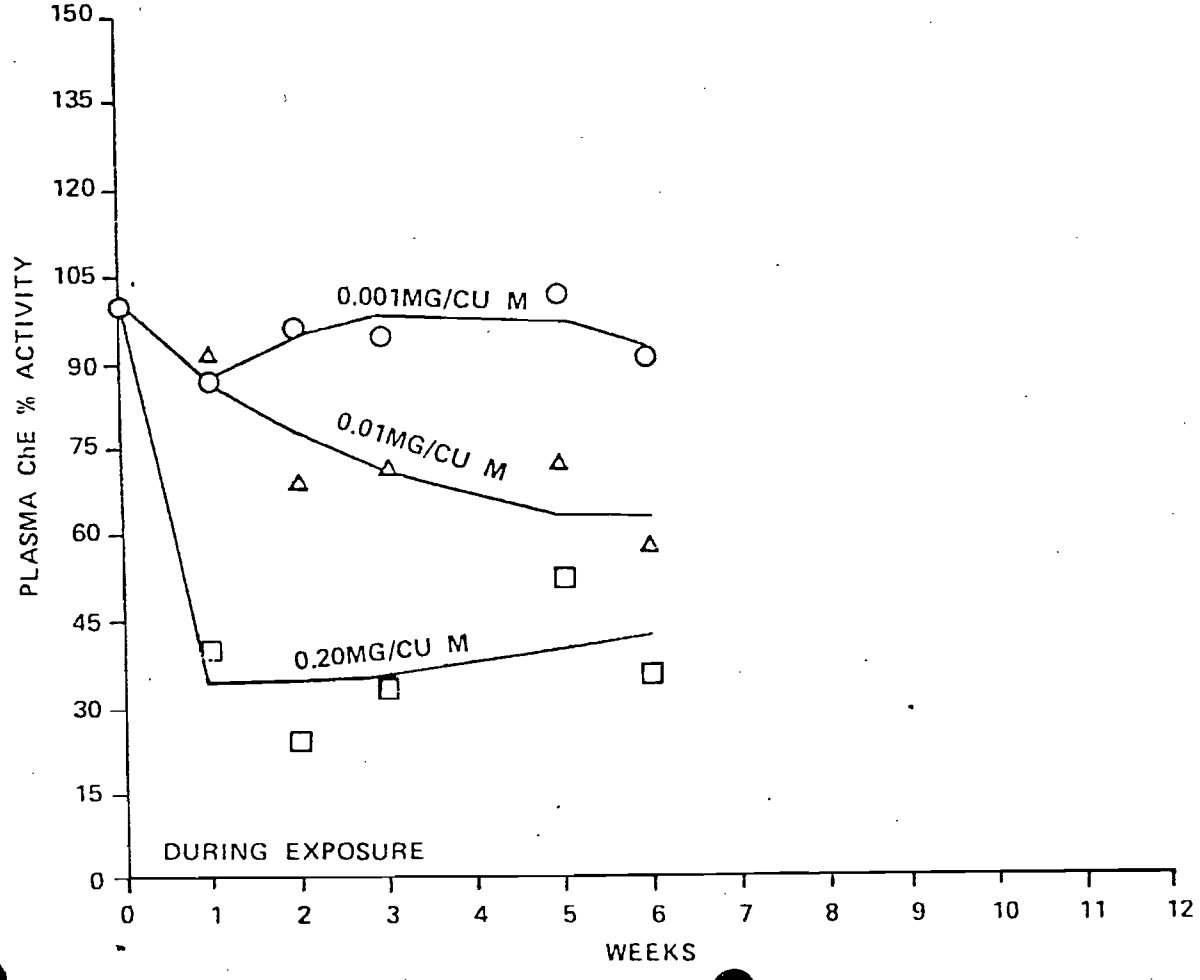


Figure 11. RED BLOOD CELL AND PLASMA CHOLINESTERASE CURVES FOR RATS EXPOSED FOUR HOURS TO ETHYL PARATHION AEROSOL (CONCENTRATION = 19.06 mg/cu m)

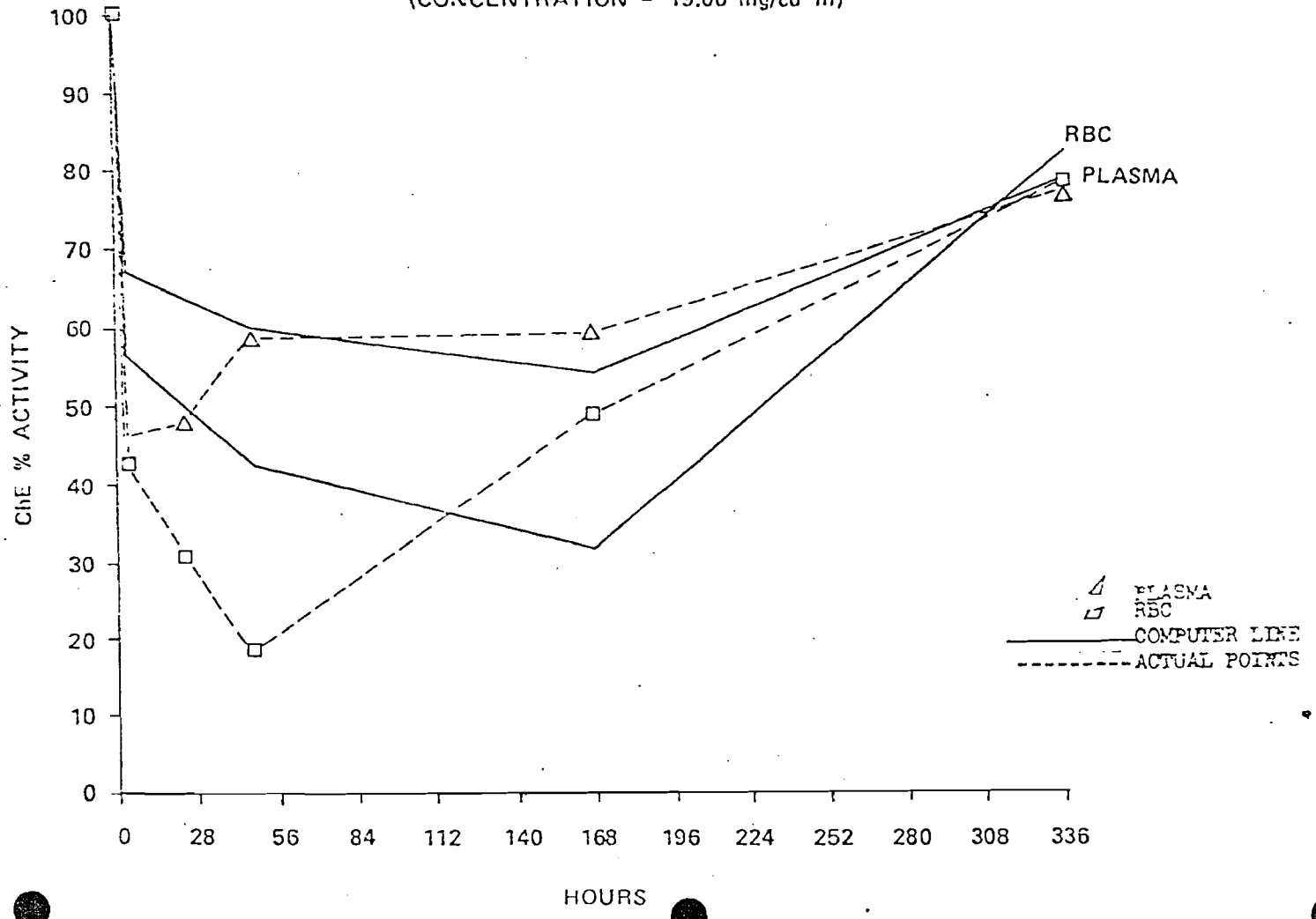


Figure 11A. RECOVERY RATE OF PLASMA ChE ACTIVITY IN DOGS FOLLOWING SUB-ACUTE INHALATION EXPOSURES TO ETHYL PARATHION

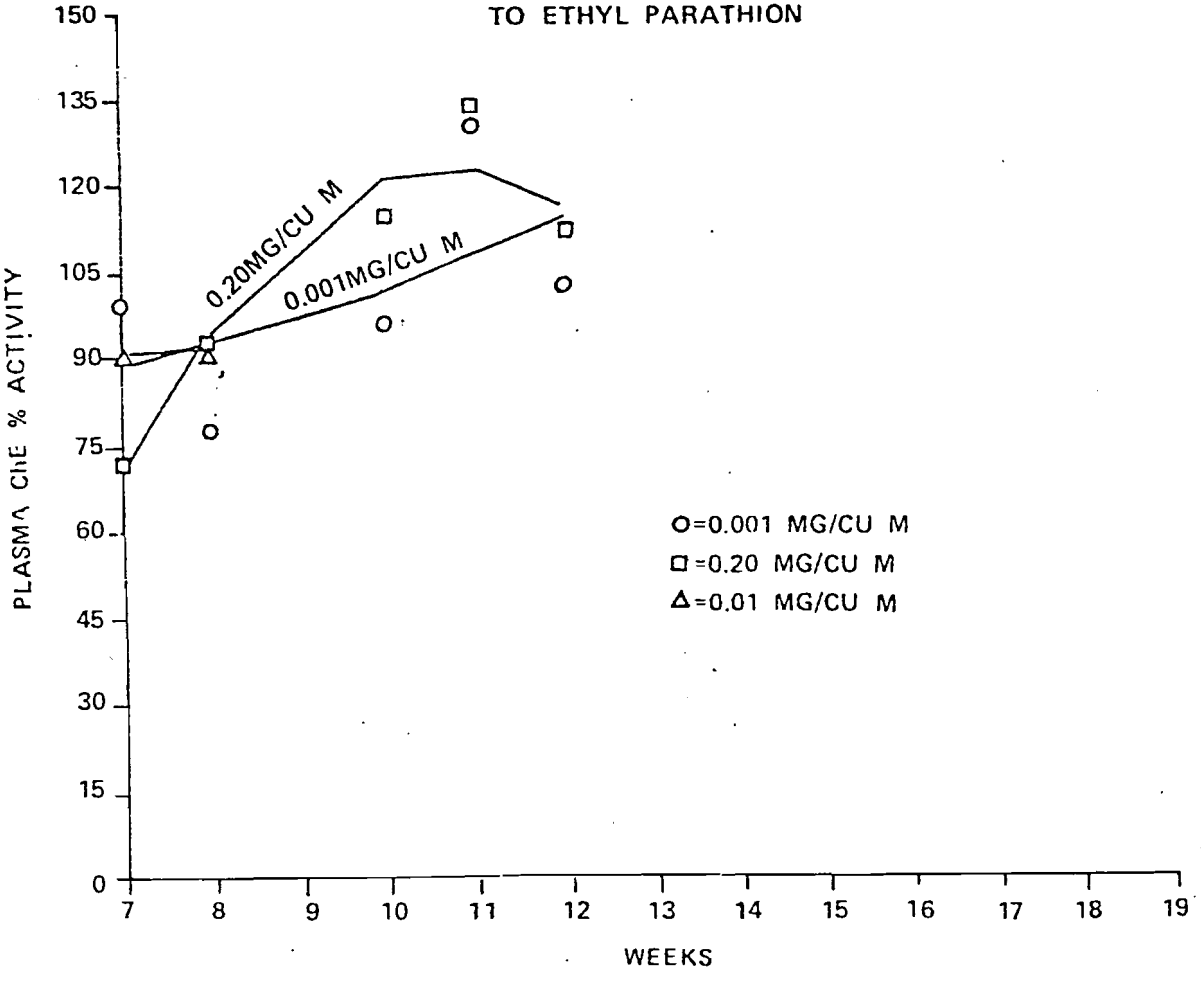


Figure 12. RED BLOOD CELL AND PLASMA CHOLINESTERASE CURVES FOR RATS EXPOSED FOUR HOURS TO ETHYL PARATHION AEROSOL (CONCENTRATION = 26.08 mg/cu m)

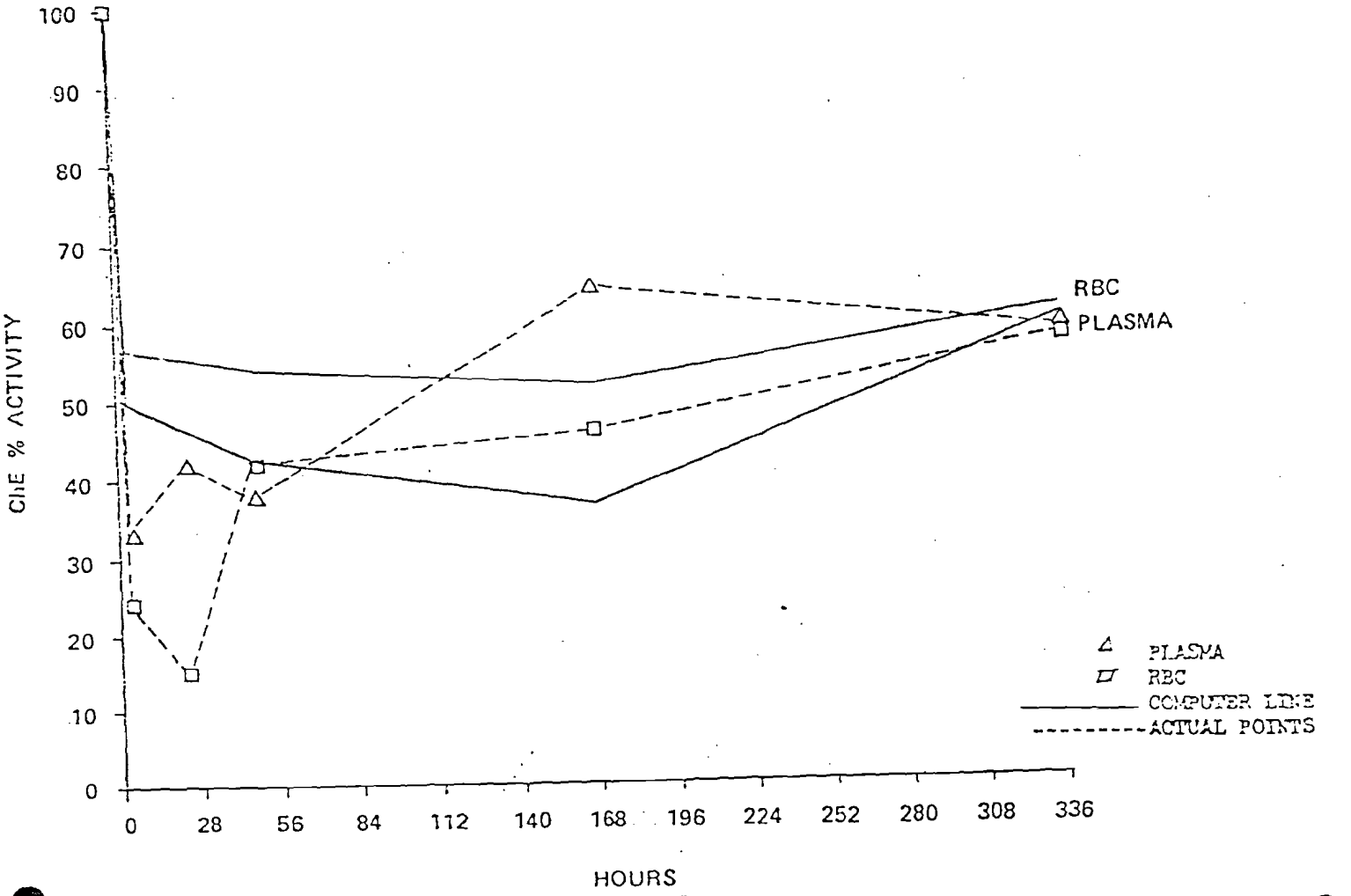


Figure 13. RED BLOOD CELL AND PLASMA CHOLINESTERASE CURVES FOR RATS EXPOSED FOUR HOURS TO ETHYL PARATHION AEROSOL (CONCENTRATION = 33.2 mg/cu m)

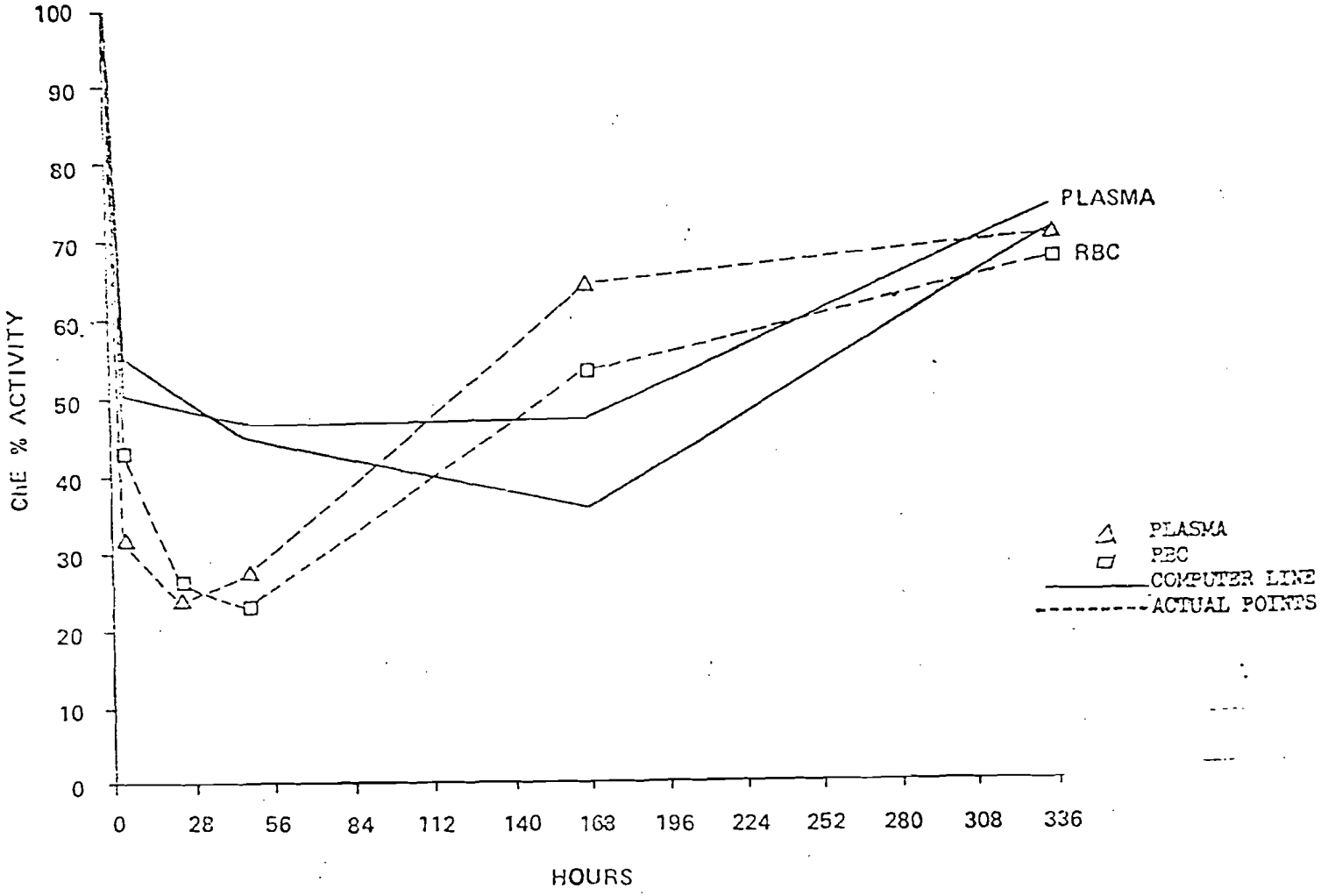


Figure 14. RED BLOOD CELL ChE CURVES FOR DOGS EXPOSED FOUR HOURS TO ETHYL PARATHION

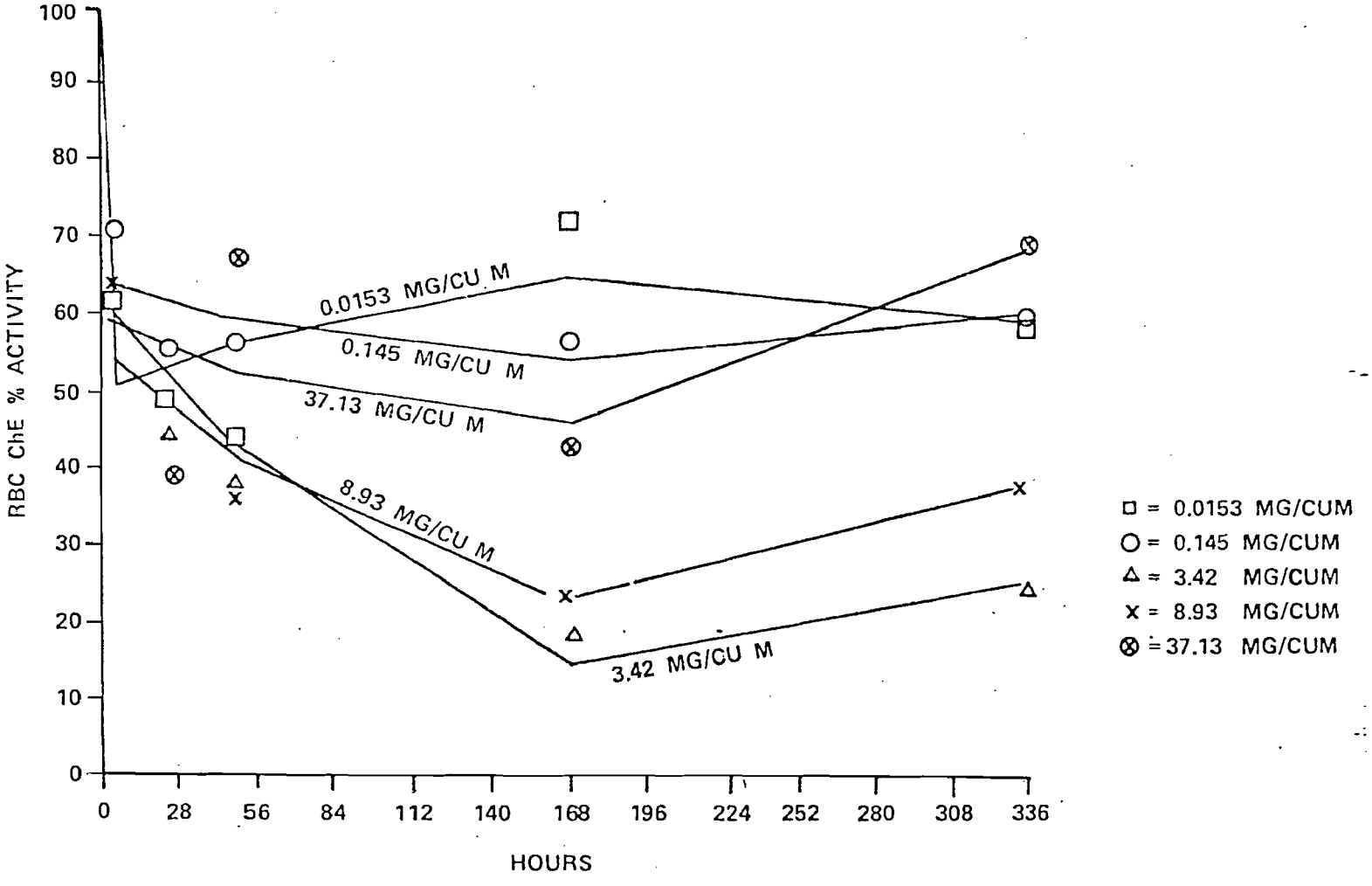


Figure 15. PLASMA ChE ACTIVITY IN DOGS EXPOSED BY INHALATION FOR FOUR HOURS TO ETHYL PARATHION

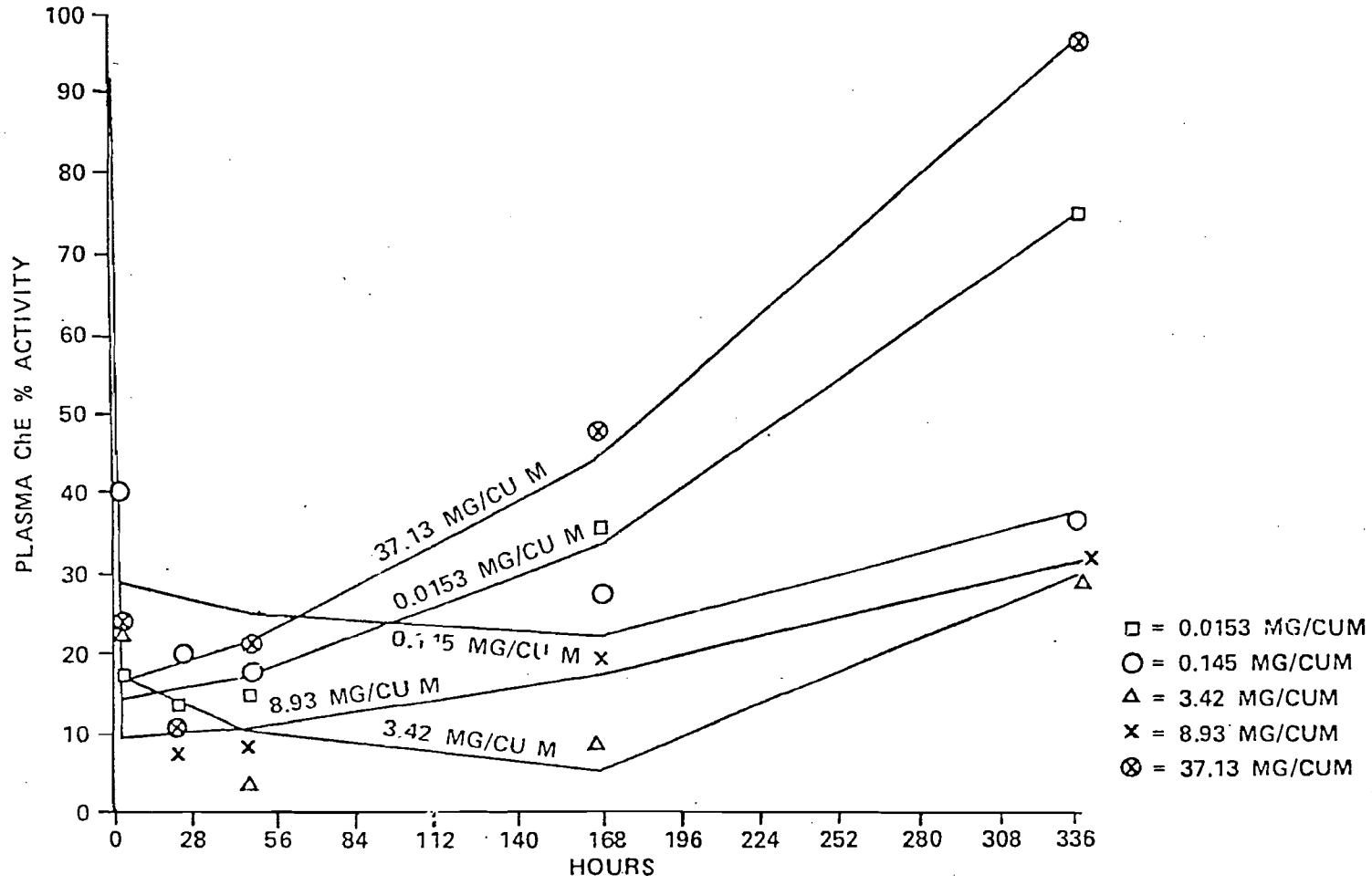


Figure 16. RED BLOOD CELL ChE ACTIVITY IN RATS DURING SUB-ACUTE INHALATION EXPOSURES TO ETHYL PARATHION

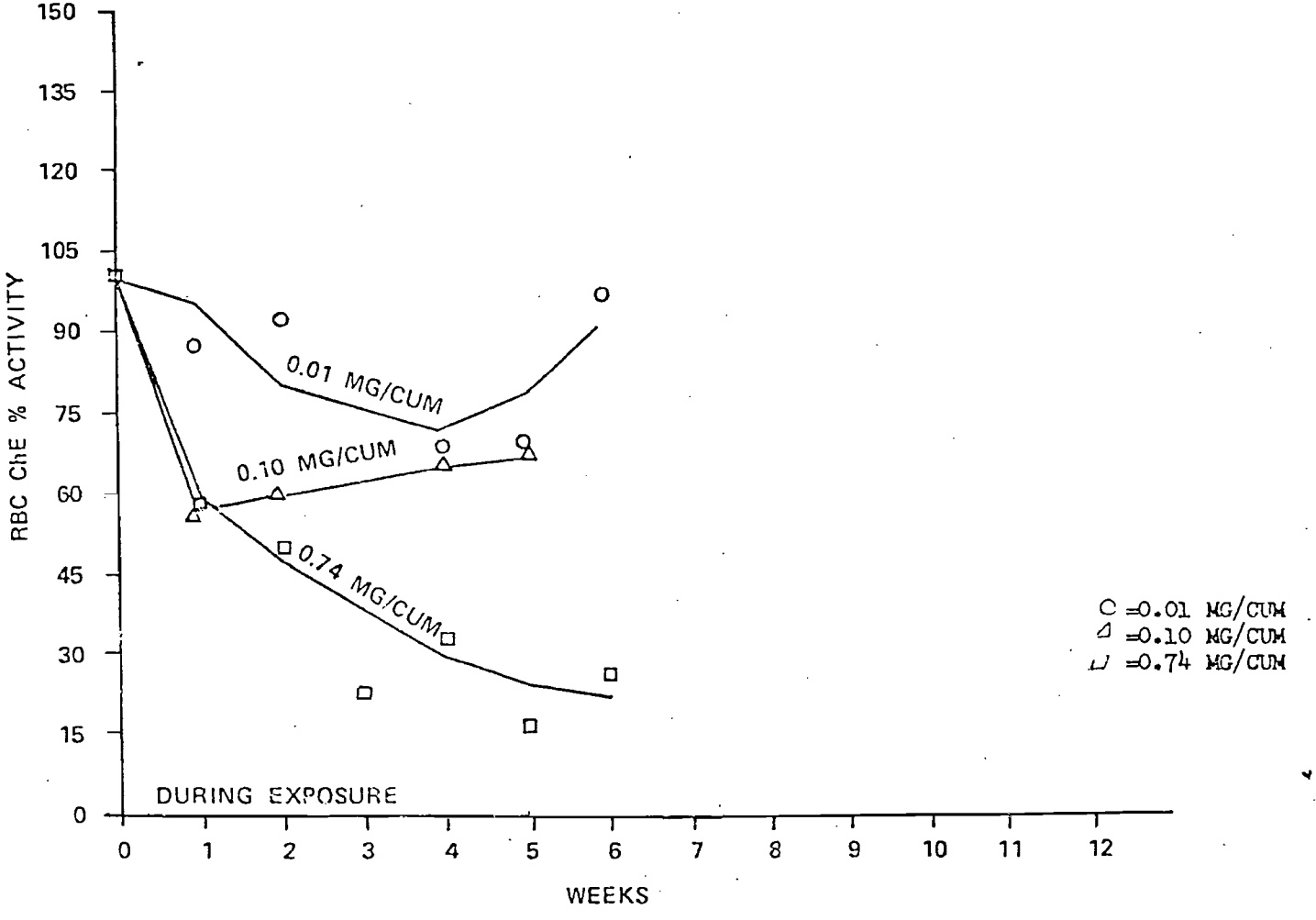
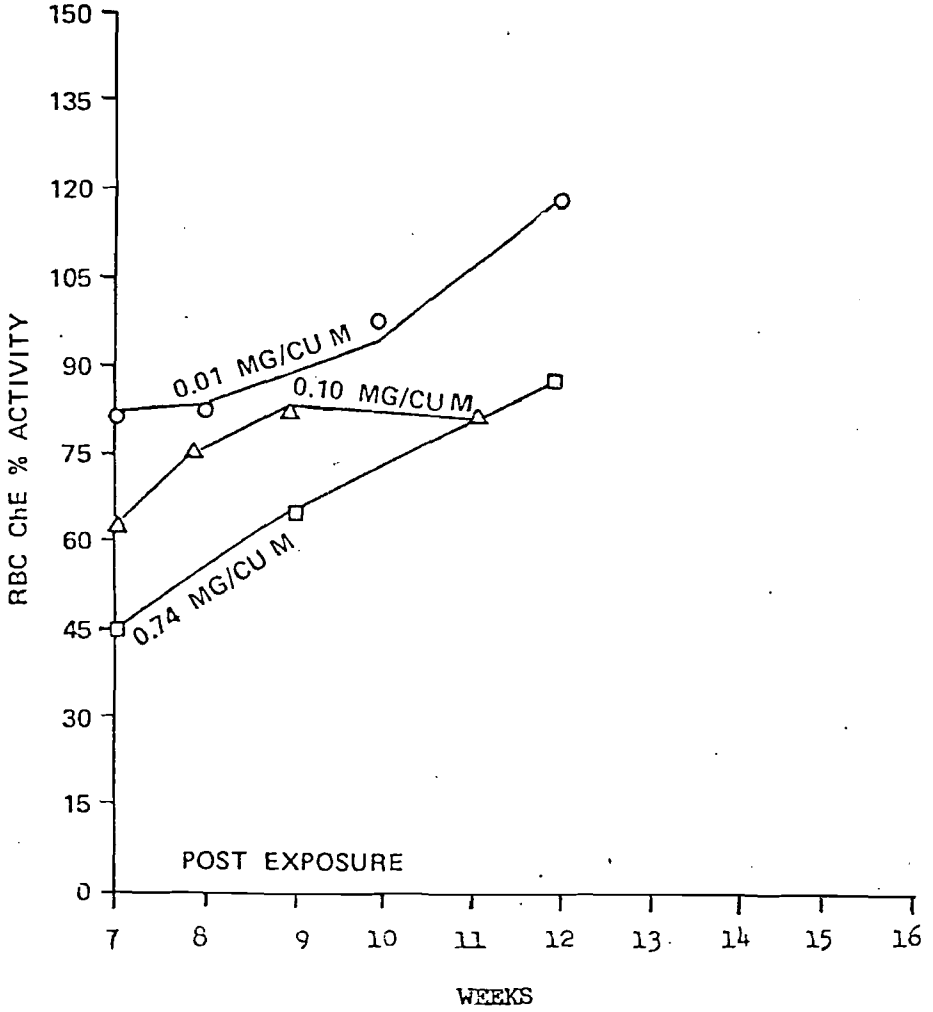


Figure 17. RECOVERY RATE OF RBC ChE ACTIVITY IN RATS FOLLOWING SUB-ACUTE INHALATION EXPOSURES TO ETHYL PARATHION



○ = 0.01 MG/CUM
△ = 0.10 MG/CUM
□ = 0.74 MG/CUM

Figure 18. PLASMA ChE ACTIVITY IN RATS DURING SUB-ACUTE INHALATION EXPOSURES TO ETHYL PARATHION

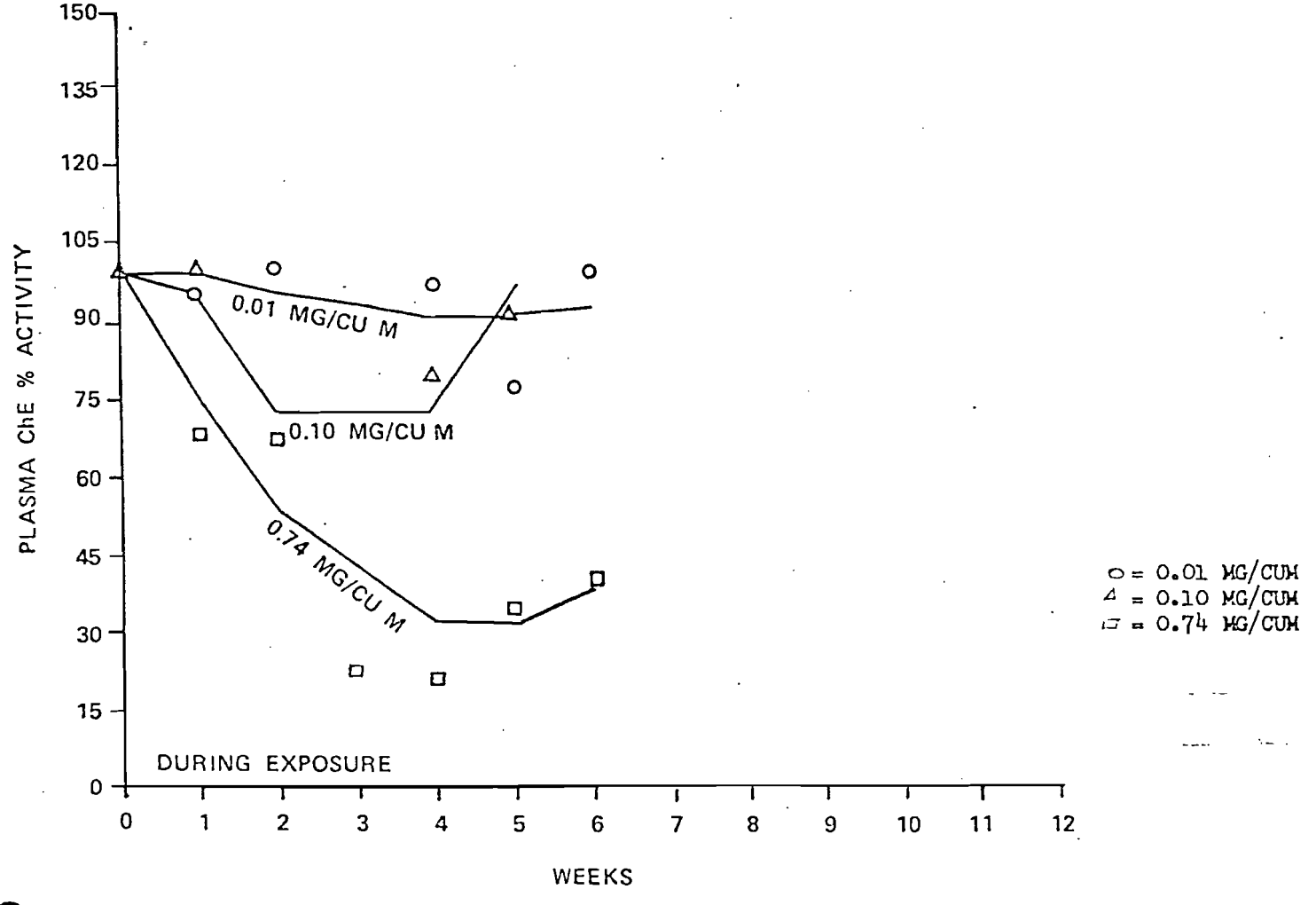


Figure 19. RECOVERY RATE OF PLASMA ChE ACTIVITY IN RATS FOLLOWING SUB-ACUTE INHALATION EXPOSURES TO ETHYL PARATHION

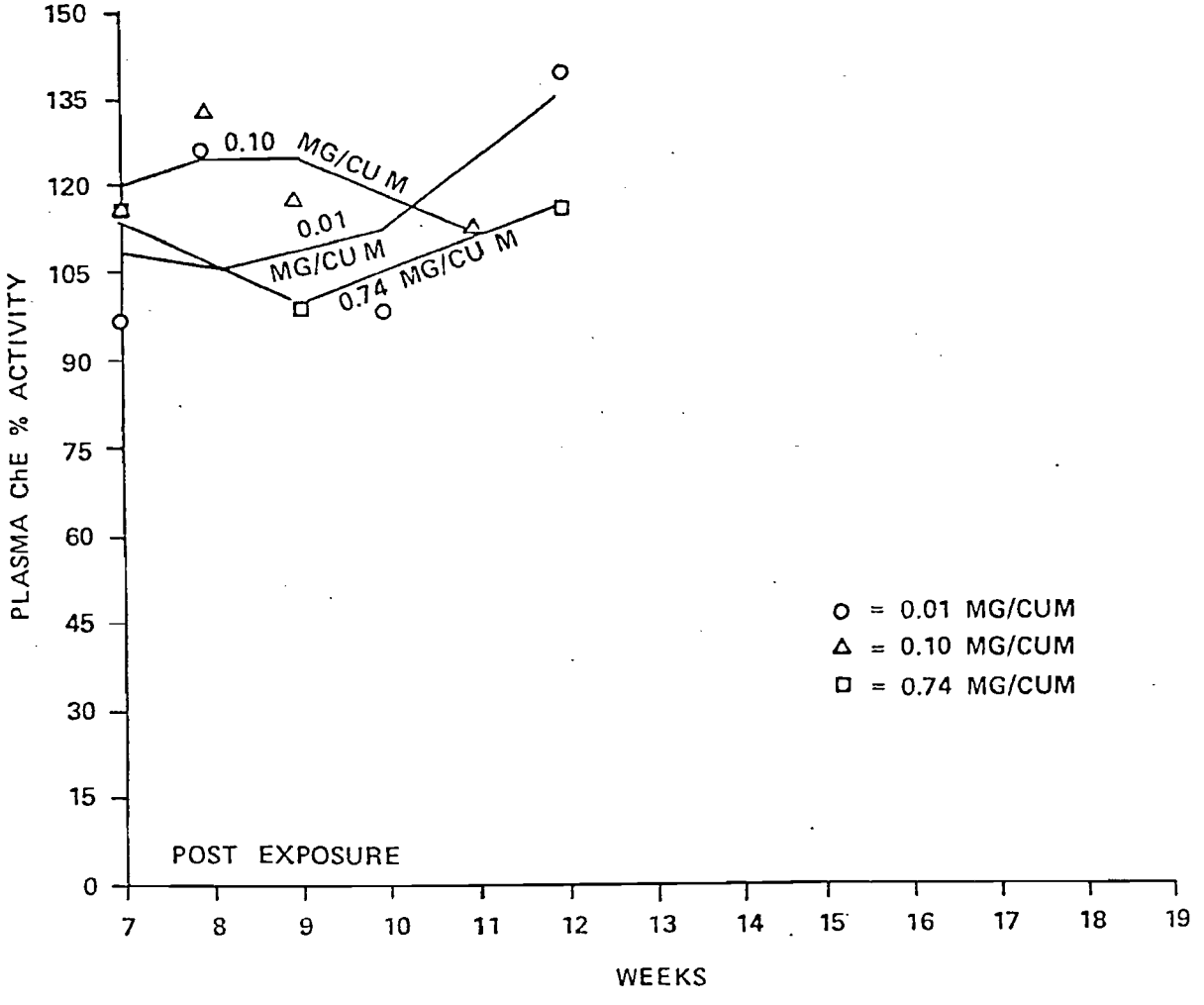


Figure 20. GROWTH CURVE OF SUBACUTE RATS EXPOSED TO ETHYL PARATHION FOR 6 WEEKS BY INHALATION ROUTE

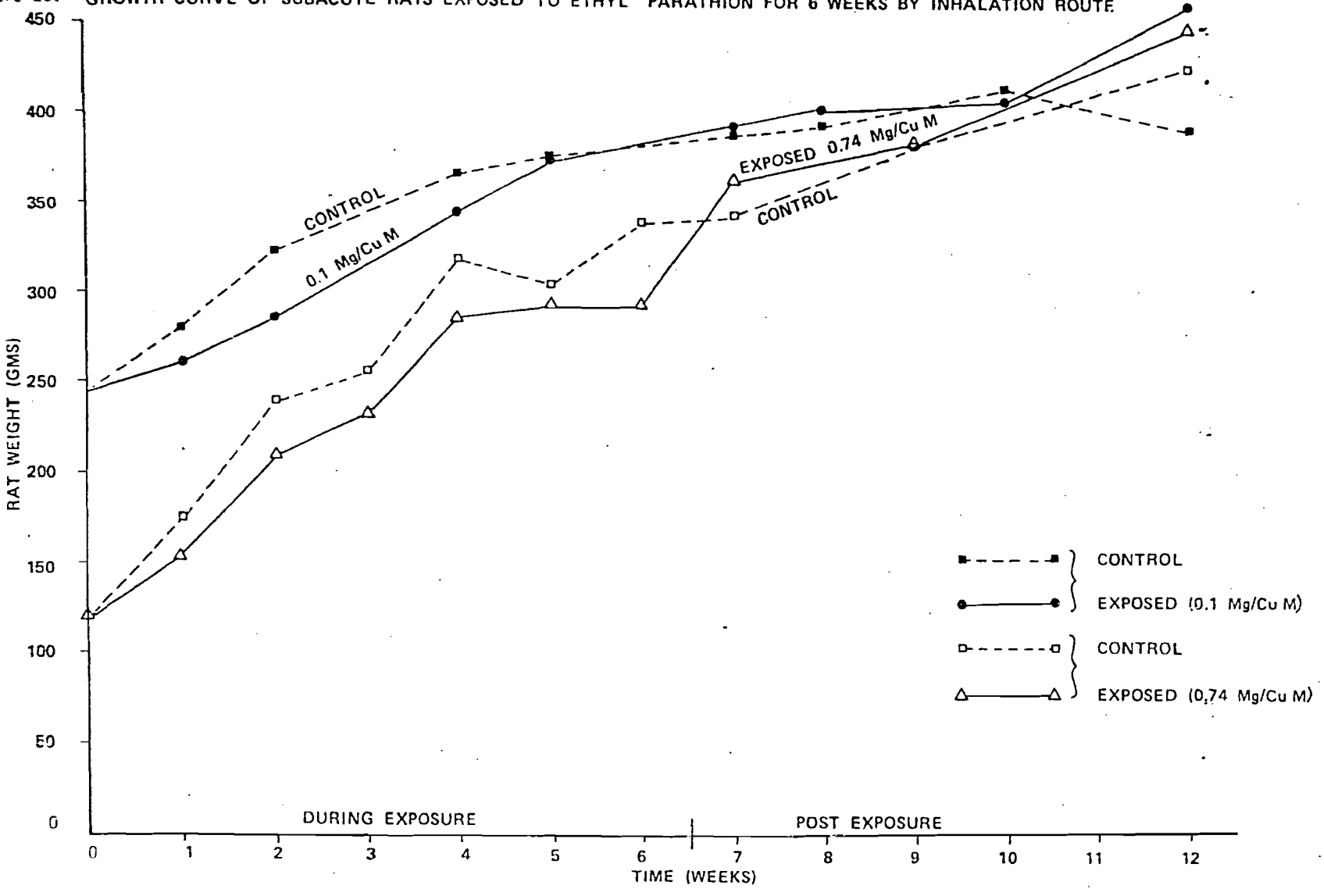


Figure 21. GROWTH CURVE OF SUBACUTE RATS EXPOSED TO ETHYL PARATHION FOR 6 WEEKS BY THE INHALATION ROUTE

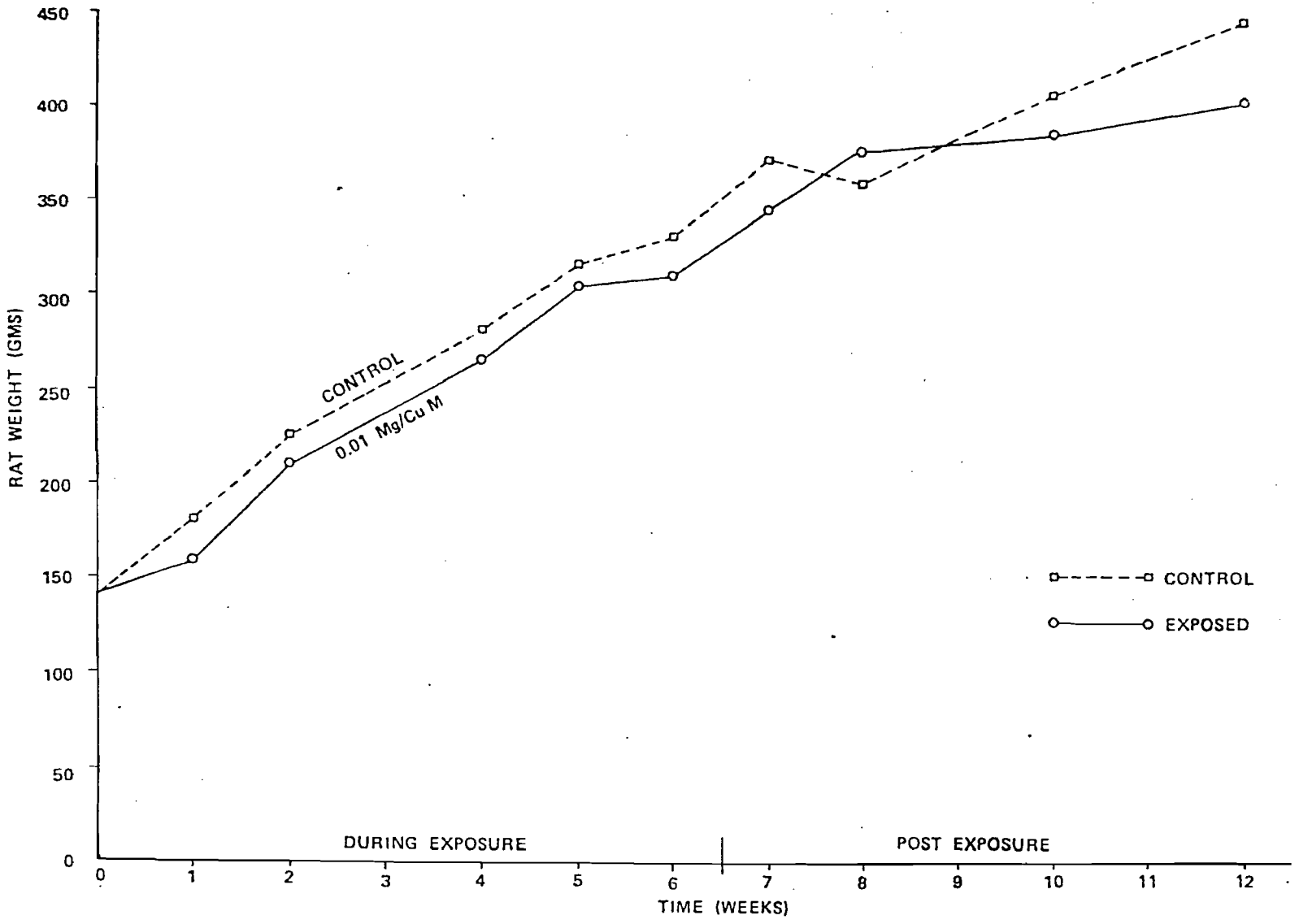


Figure 22.
GROWTH CURVE OF SUBACUTE DOGS EXPOSED TO ETHYL PARATHION FOR 6 WEEKS BY THE INHALATION ROUTE

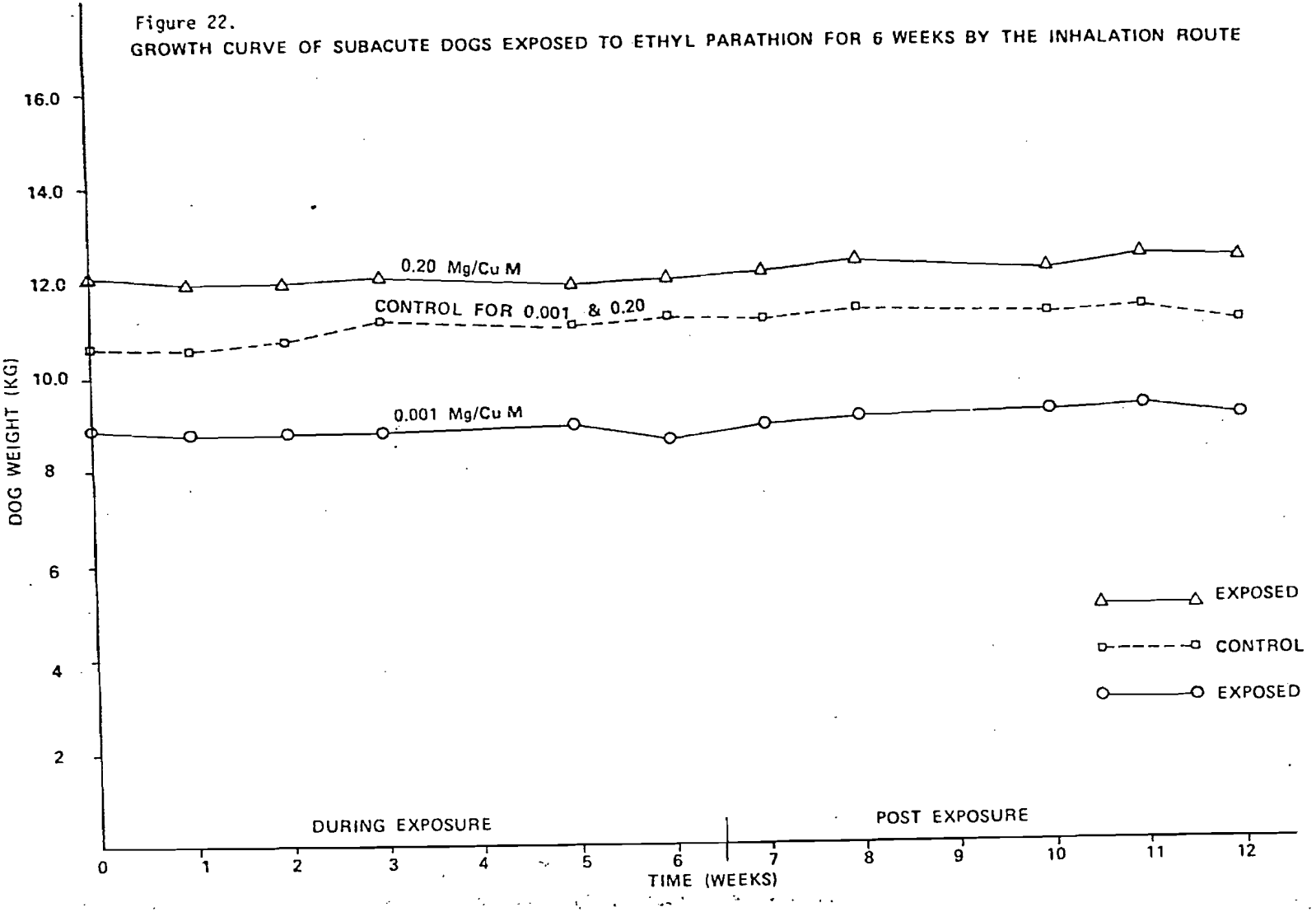


Figure 23.
GROWTH CURVE OF SUBACUTE DOGS EXPOSED TO ETHYL PARATHION FOR 6 WEEKS BY THE INHALATION ROUTE

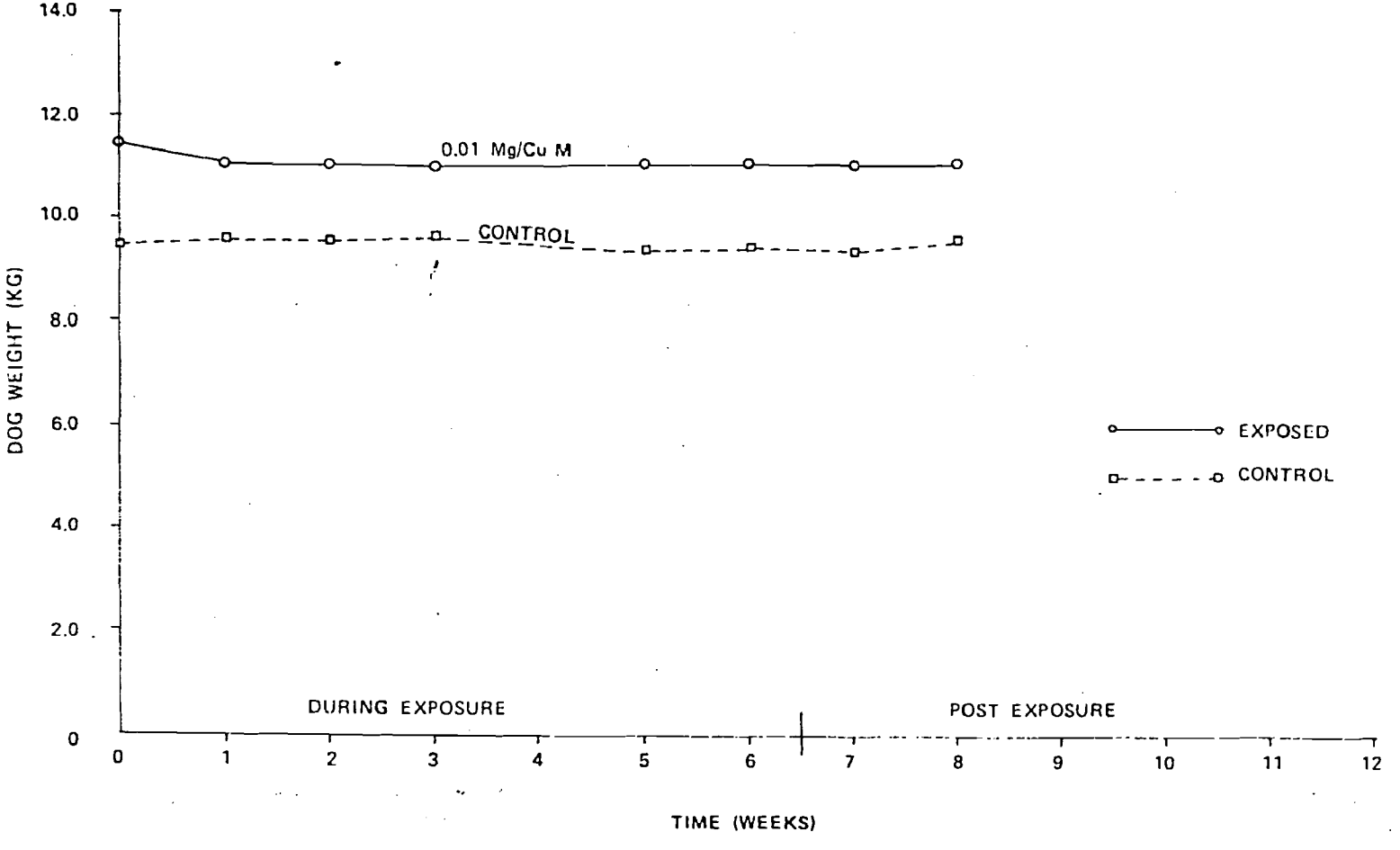


Figure 24. 1 — 99% RESPONSE TIME FOR TREMORS IN RATS EXPOSED ACUTELY TO ETHYL PARATHION

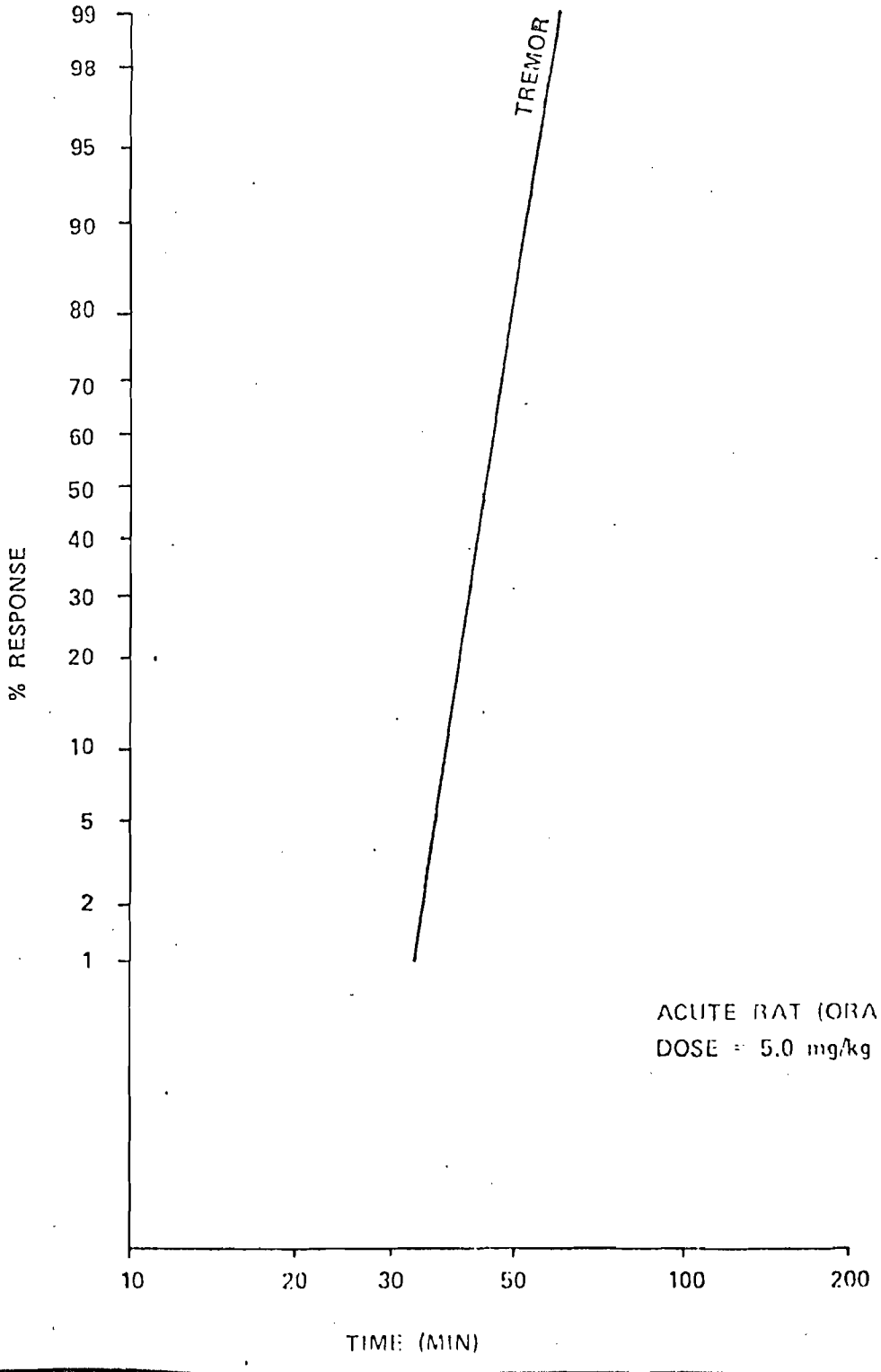


Figure 25.1 - 99% RESPONSE TIME FOR TREMORS IN RATS EXPOSED ACUTELY TO ETHYL PARATHION

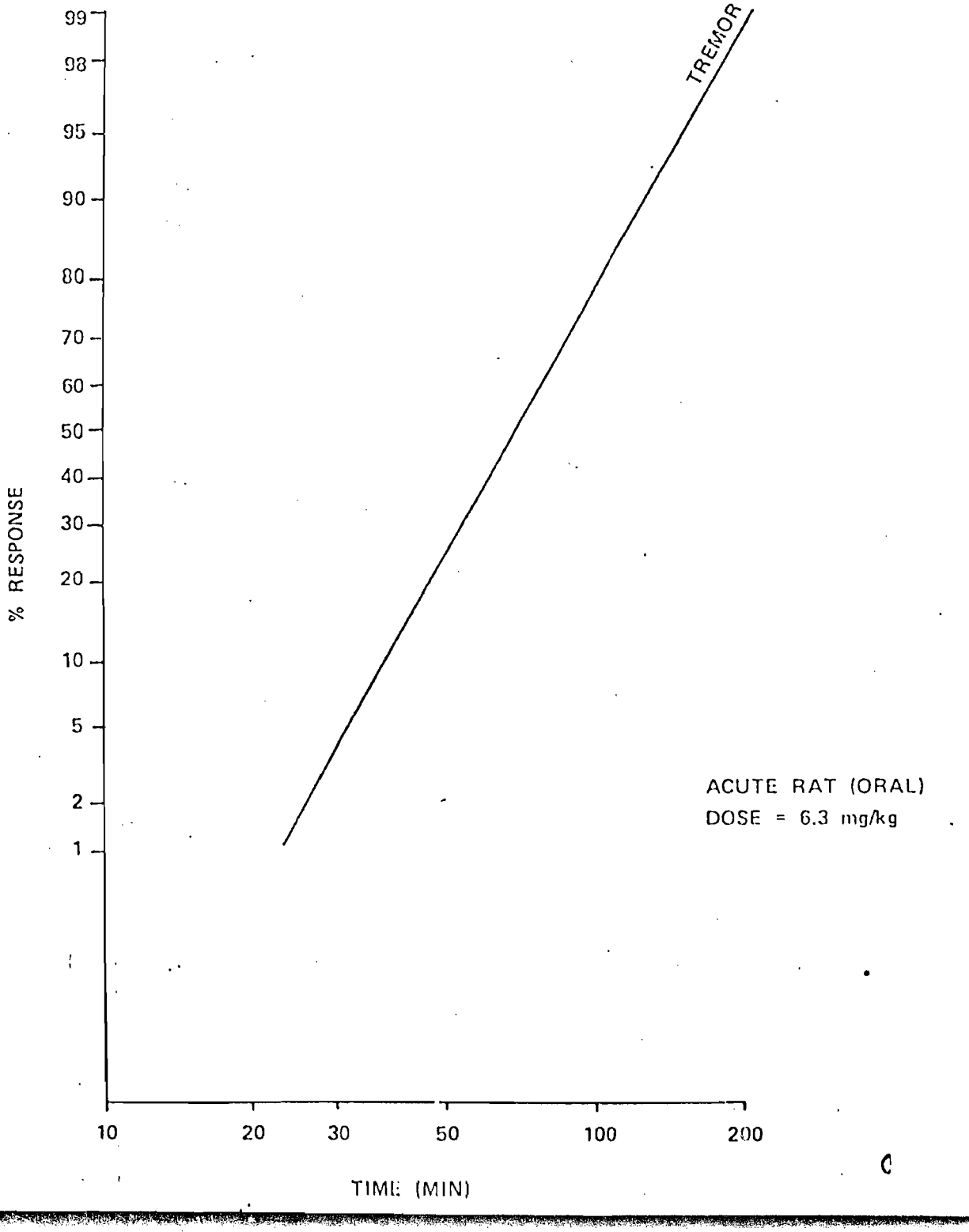


Figure 26.1 - 99% RESPONSE TIMES FOR TREMORS, CONVULSIONS AND DEATH IN RATS EXPOSED ACUTELY TO ETHYL PARATHION

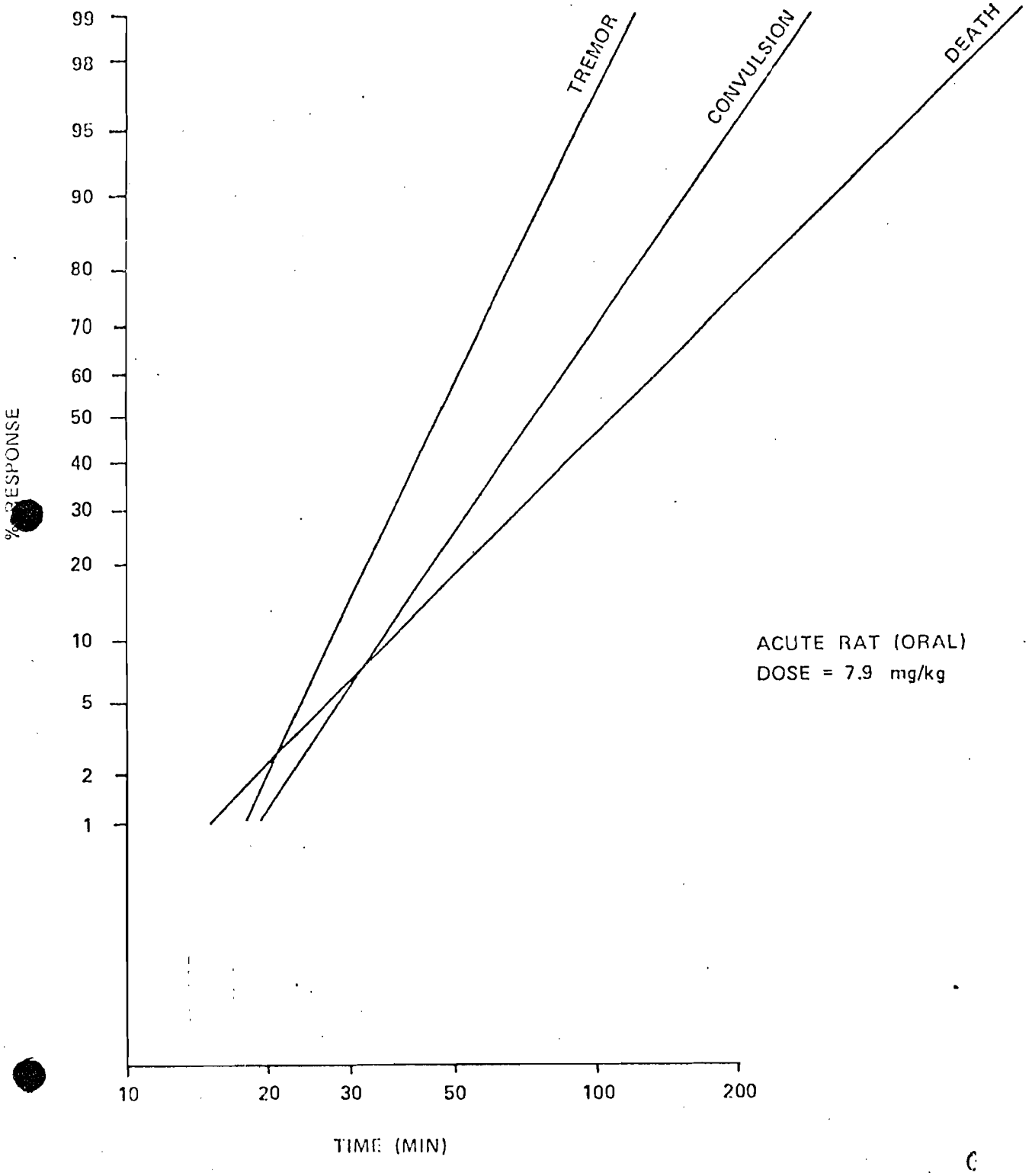


Figure 27.
1-99% RESPONSE TIMES FOR TREMORS, CONVULSIONS AND DEATH IN RATS EXPOSED ACUTELY TO ETHYL PARATHION

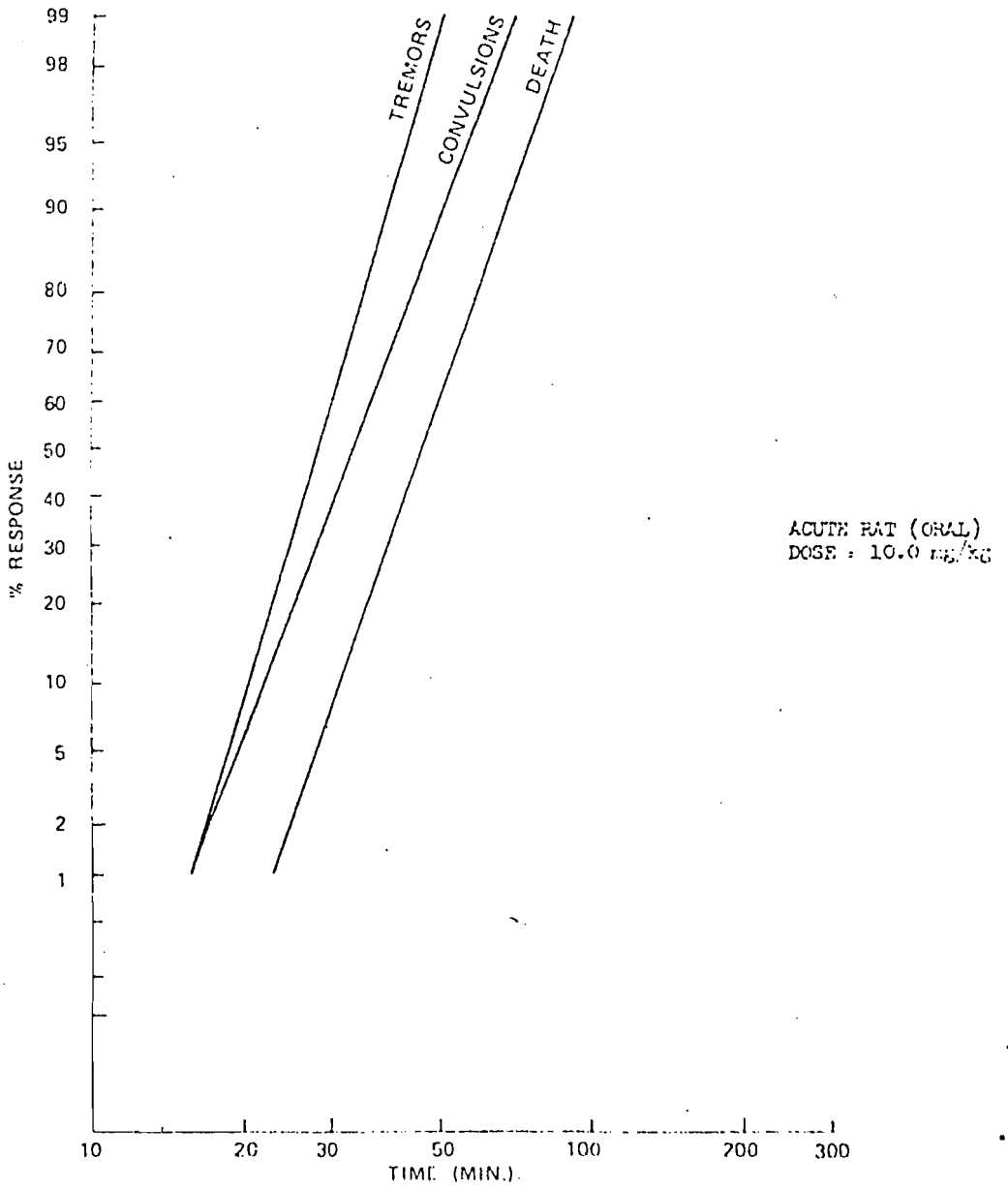


Figure 28. RESIDUAL RBC ChE ACTIVITY IN RATS EXPOSED ORALLY TO ETHYL PARATHION

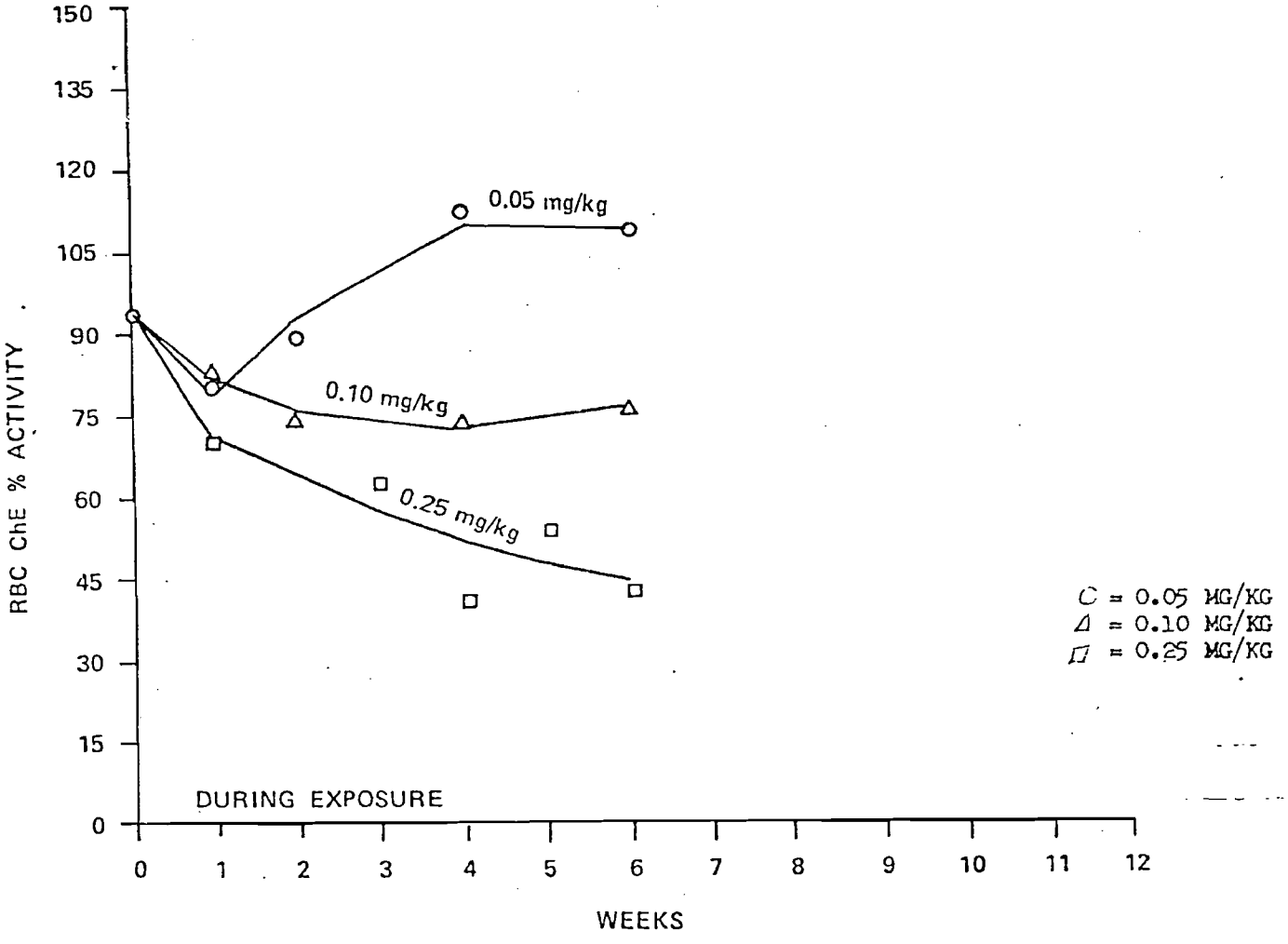


Figure 29. RESIDUAL PLASMA ChE ACTIVITY IN RATS EXPOSED ORALLY TO ETHYL PARATHION

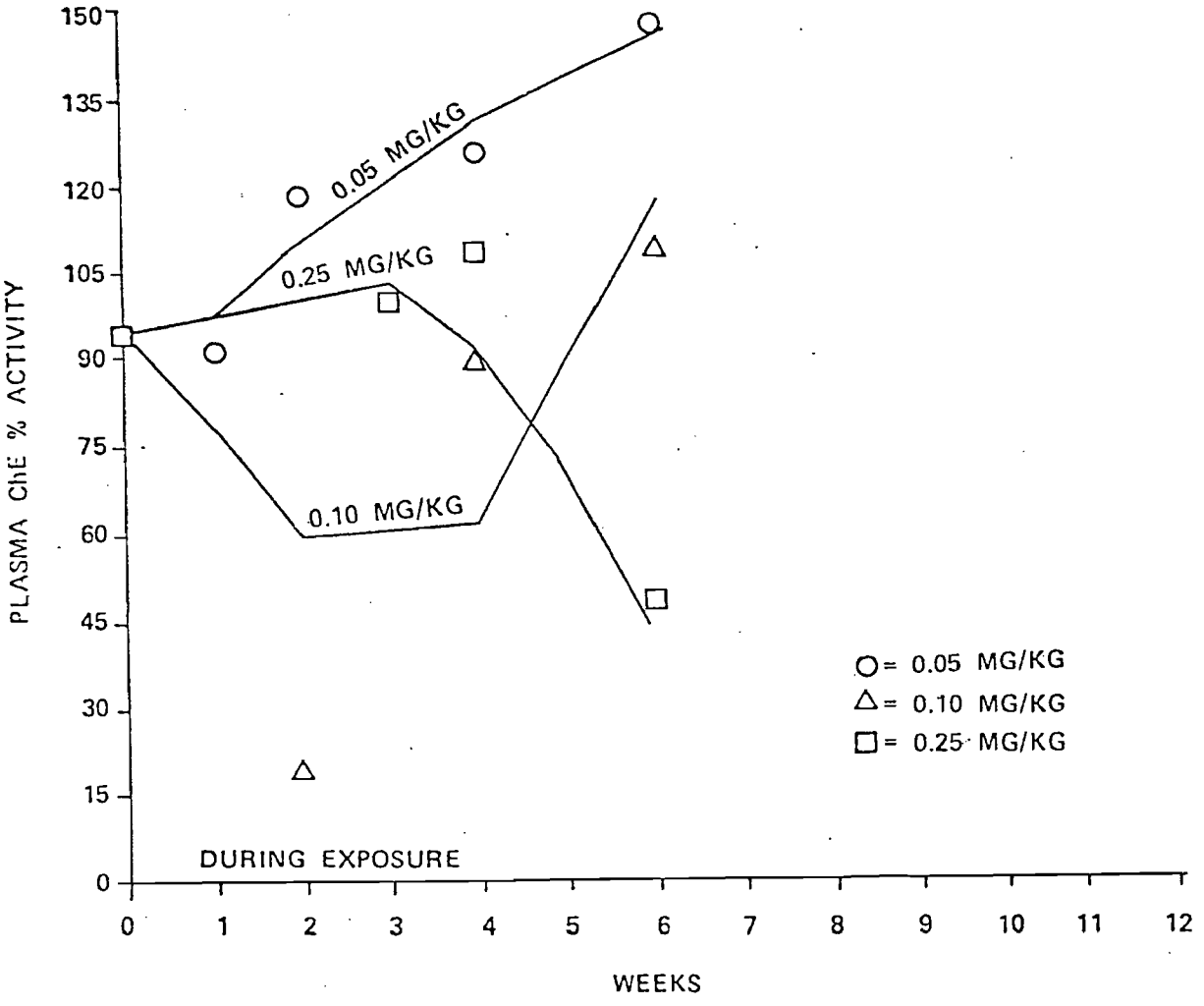


Figure 30. RECOVERY RATE OF RBC ChE ACTIVITY IN RATS FOLLOWING ORAL EXPOSURE TO ETHYL PARATHION

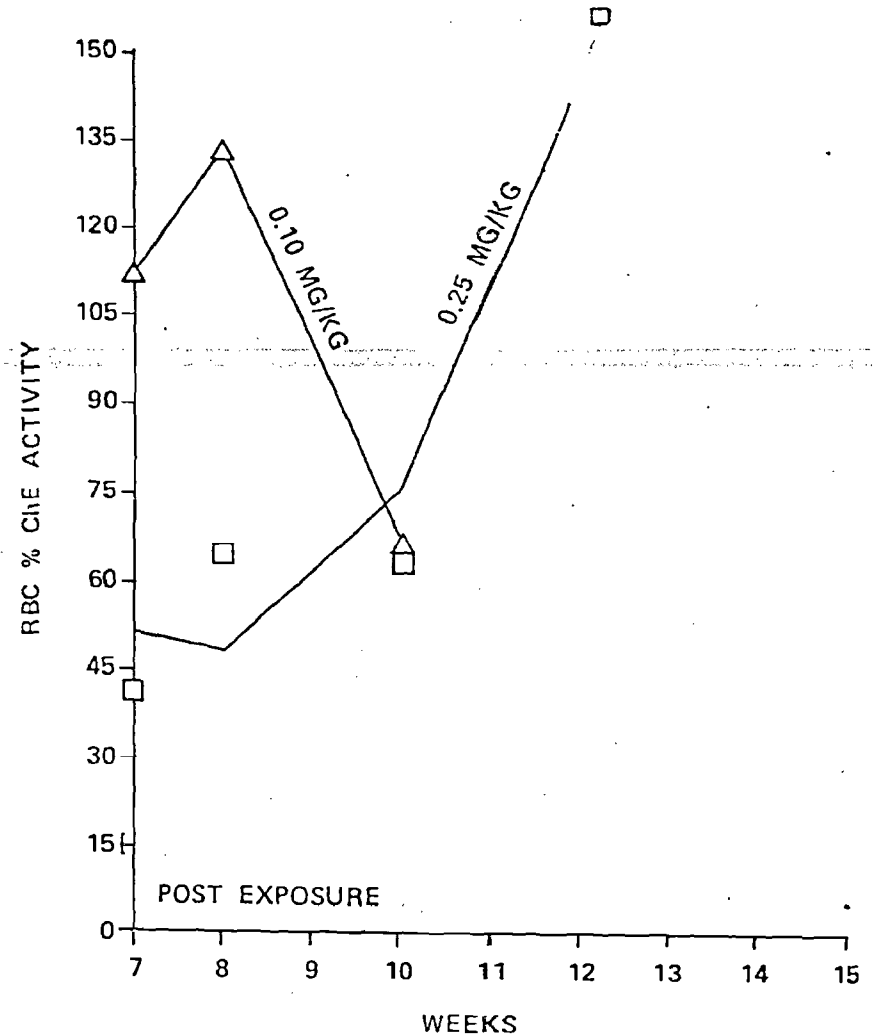


Figure 31. RECOVERY RATE OF PLASMA ChE ACTIVITY IN RATS FOLLOWING ORAL EXPOSURE TO ETHYL PARATHION

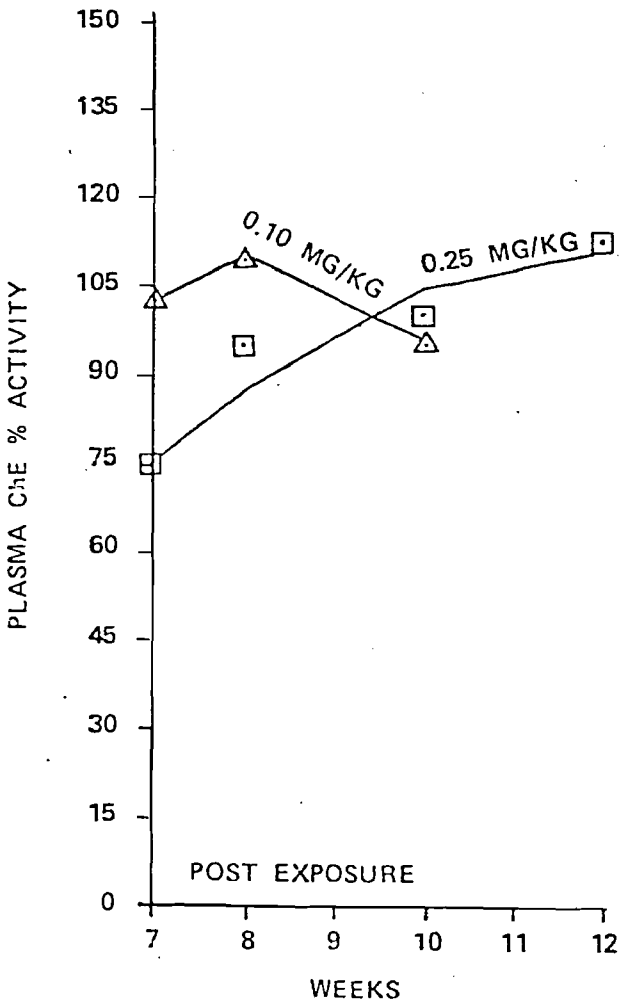


Figure 32. GROWTH CURVE OF SUB-ACUTE RATS EXPOSED TO ETHYL PARATHION FOR SIX WEEKS BY THE INTRAGASTRIC ROUTE (DOSE=0.05MG/KG)

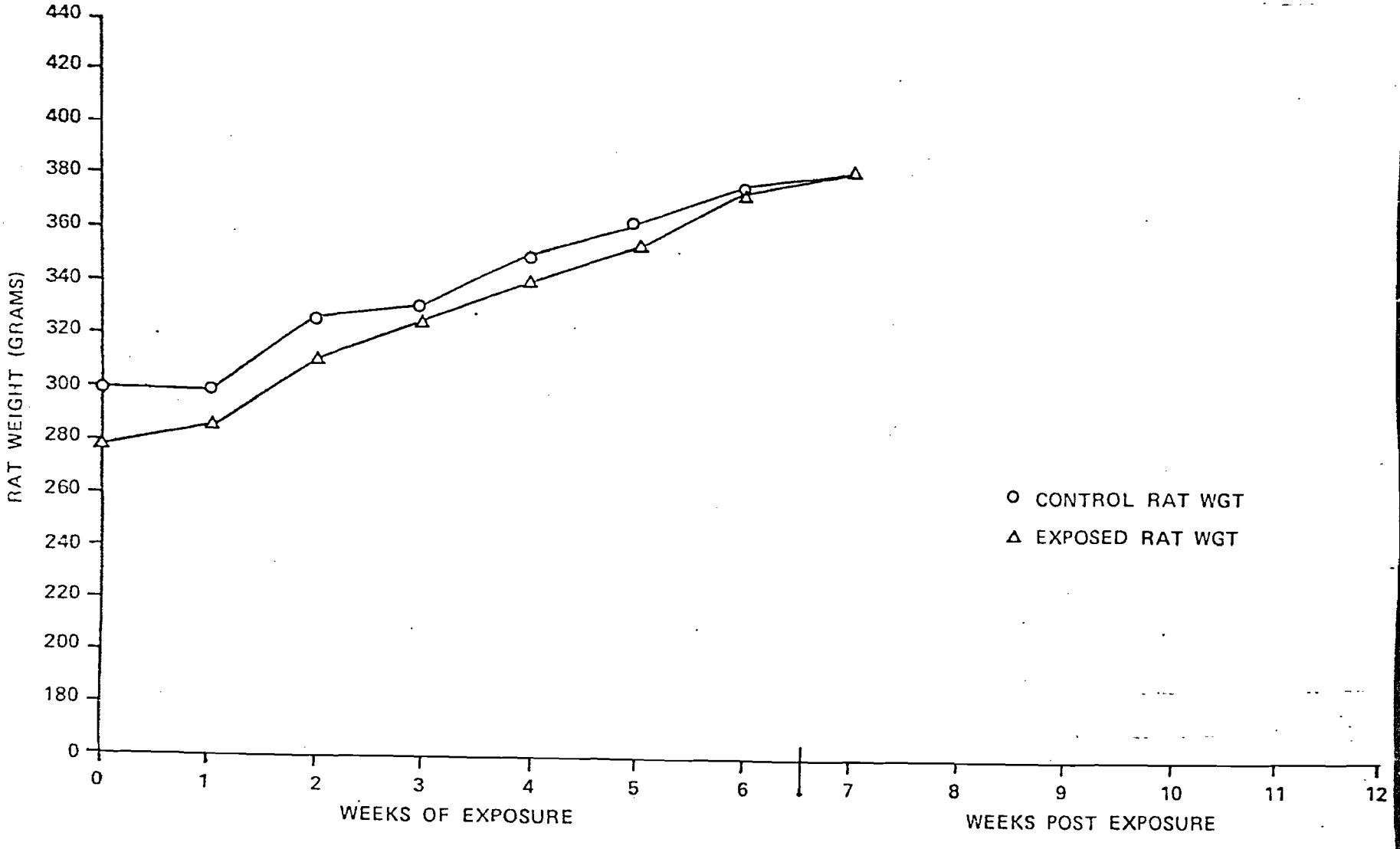


Figure 33. GROWTH CURVE OF SUB-ACUTE RATS EXPOSED TO ETHYL PARATHION FOR SIX WEEKS BY THE INTRAGASTRIC ROUTE (DOSE = 0.10 MG/KG)

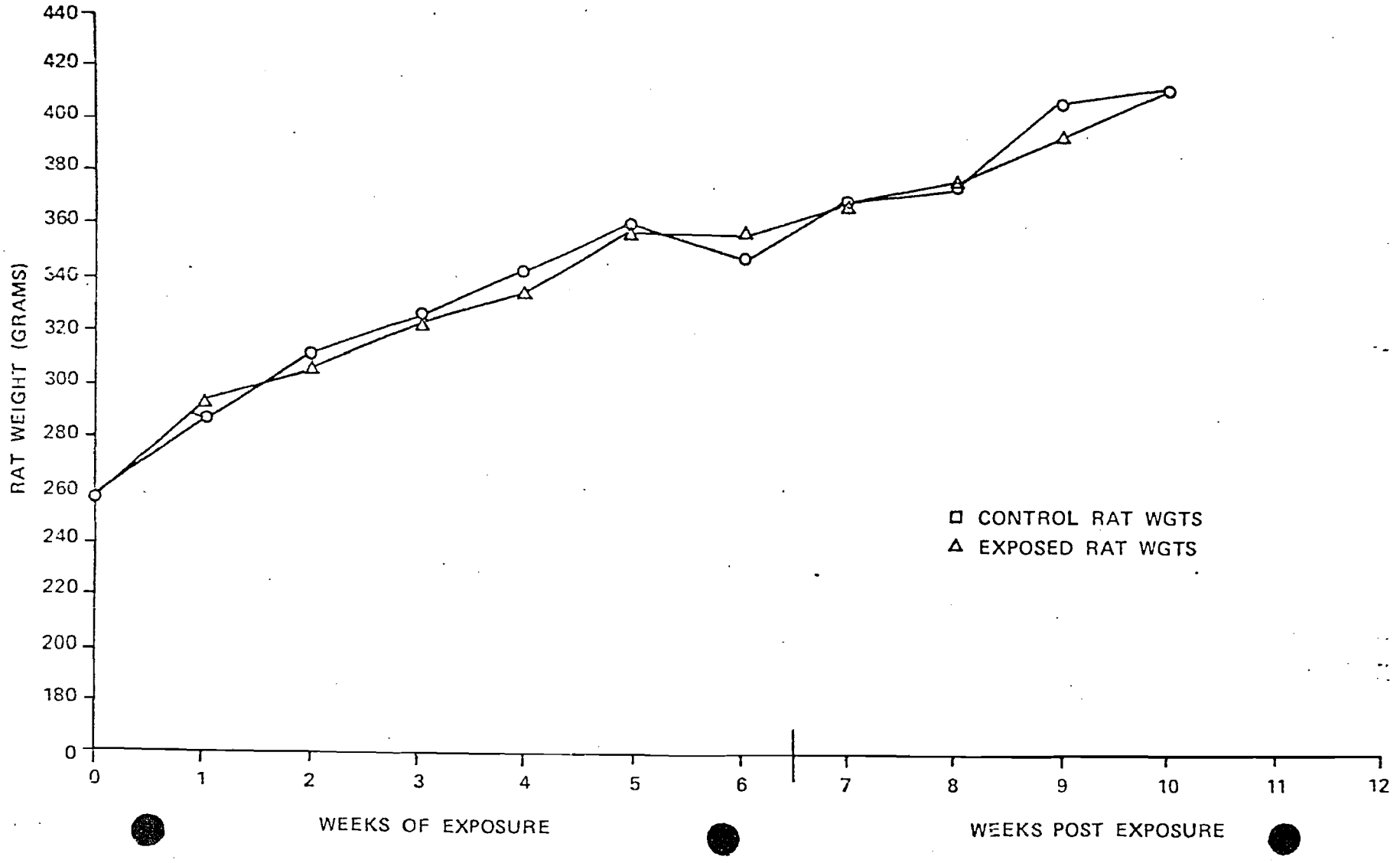


Figure 34. GROWTH CURVE OF SUB-ACUTE RATS EXPOSED TO ETHYL PARATHION FOR SIX WEEKS BY THE INTRAGASTRIC ROUTE (DOSE = 0.25 MG/KG)

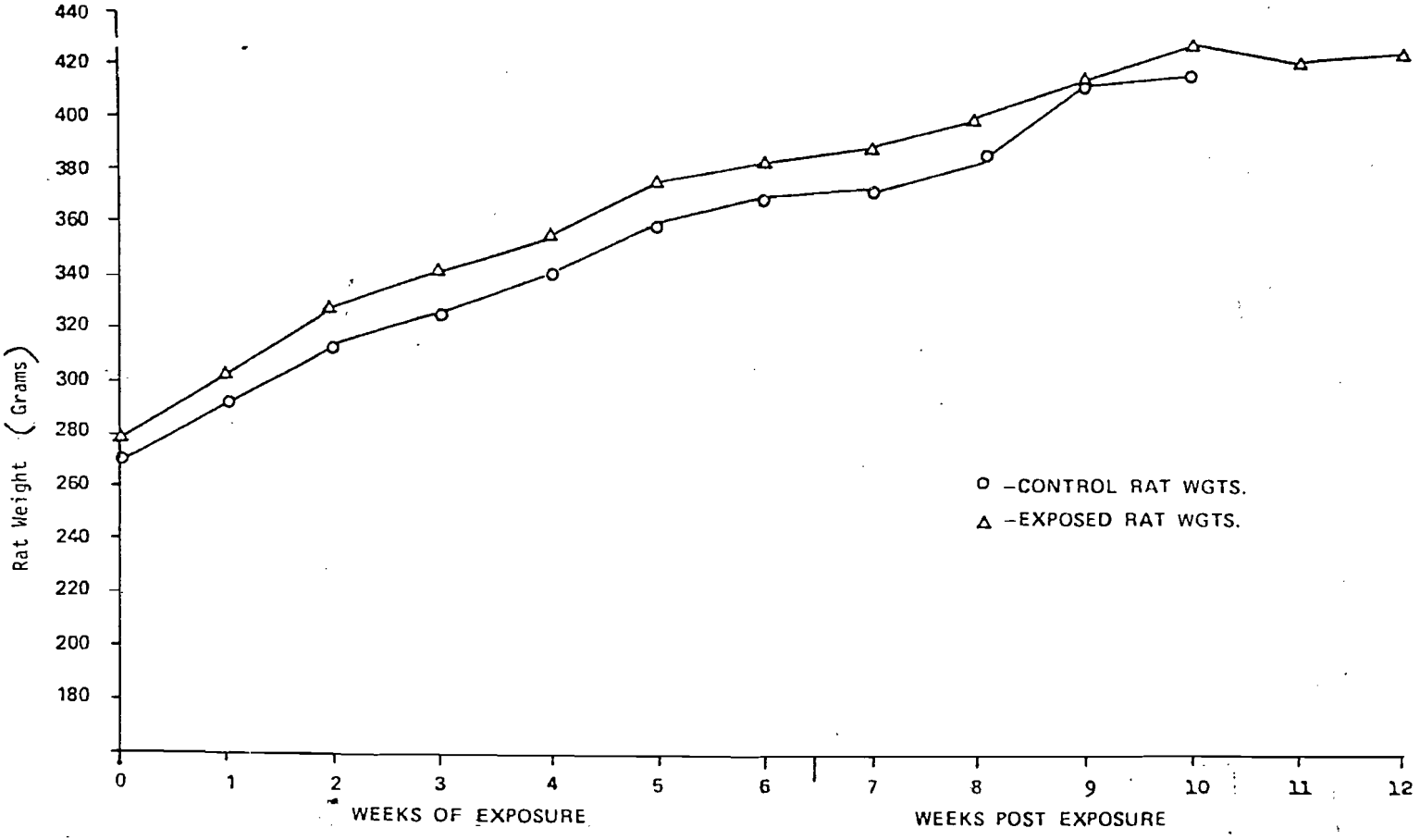


Figure 35. RESIDUAL RBC ChE ACTIVITY IN DOGS EXPOSED ORALLY TO ETHYL PARATHION

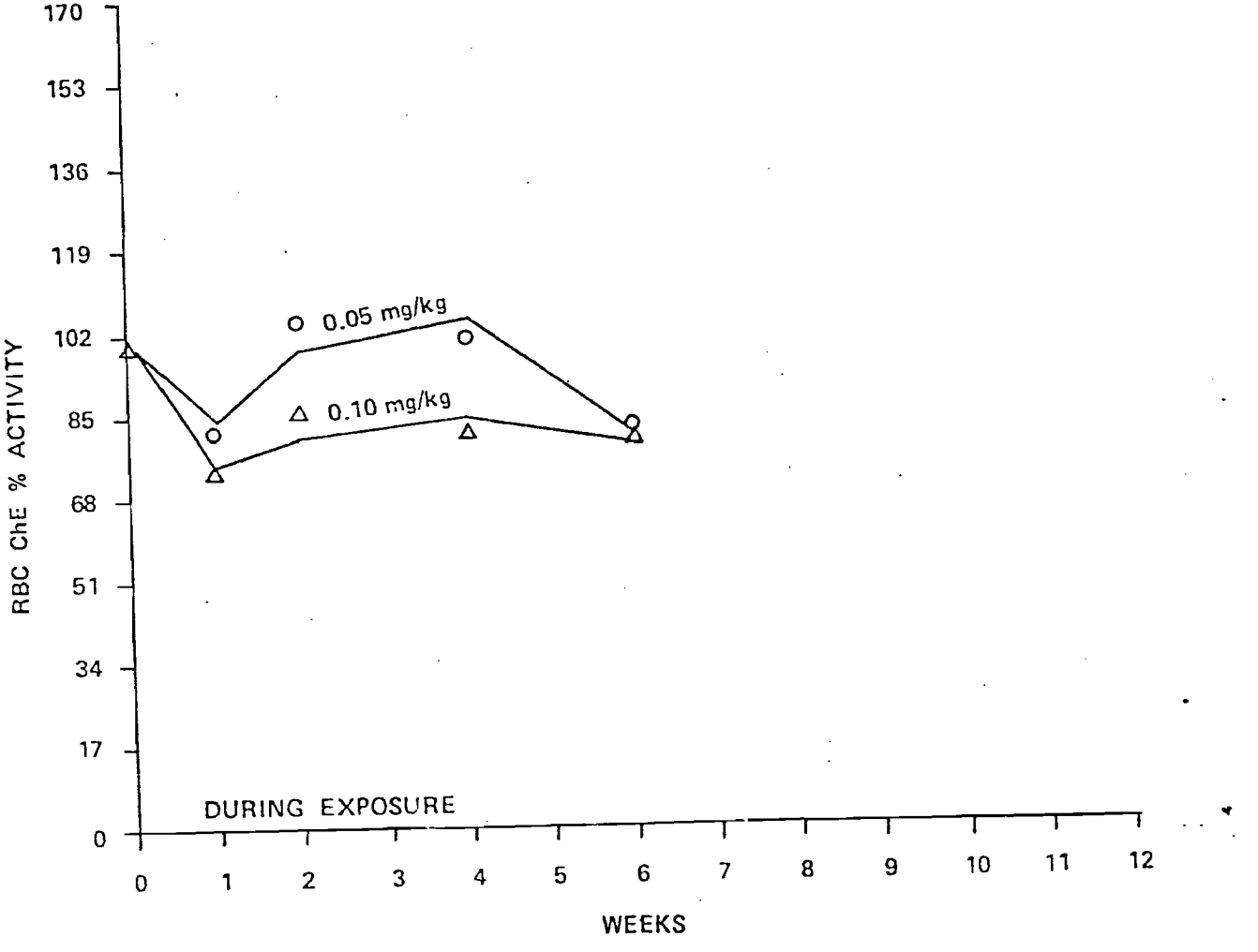


Figure 36. RESIDUAL PLASMA ChE ACTIVITY IN DOGS EXPOSED ORALLY TO ETHYL PARATHION

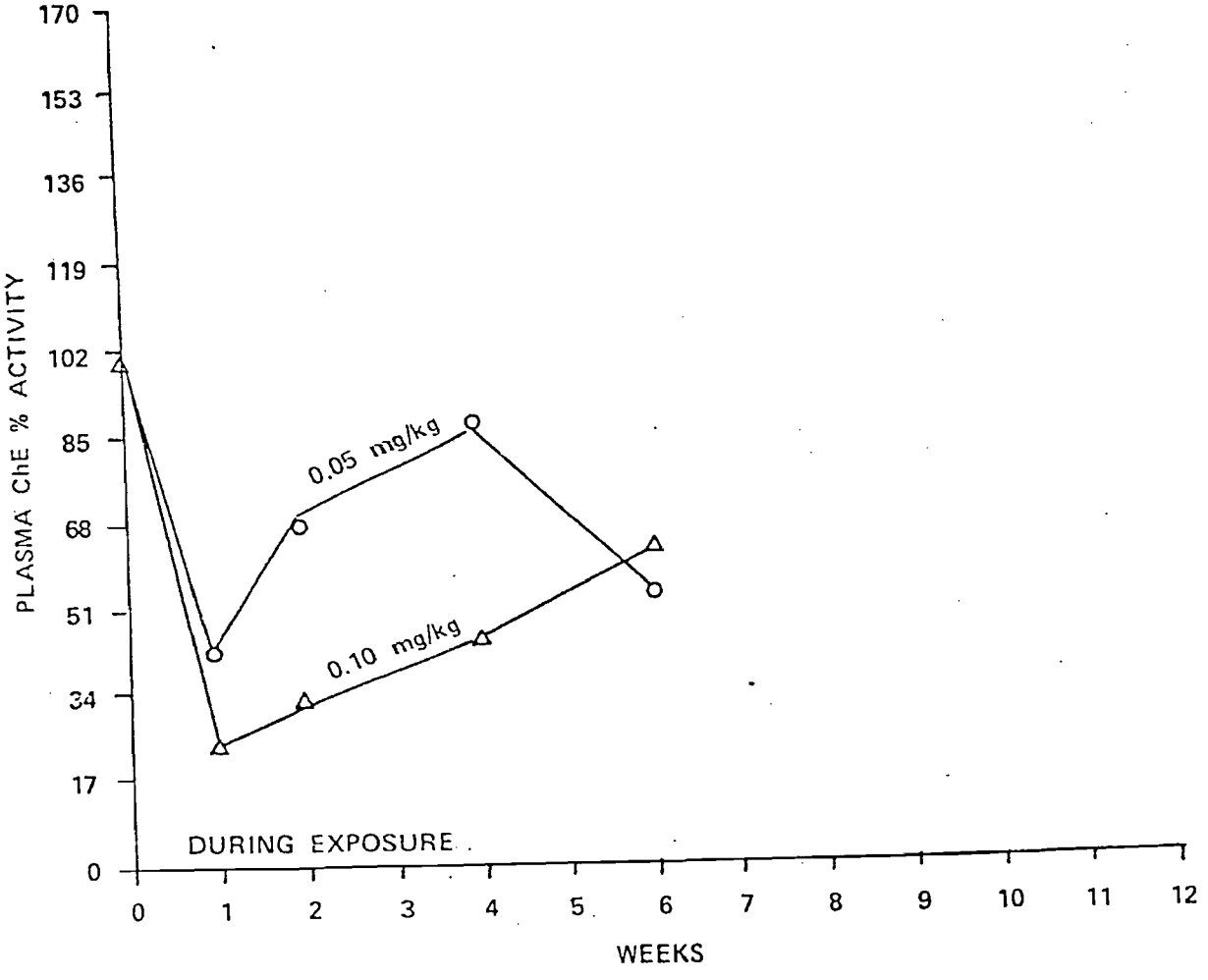


Figure 37. RECOVERY RATE OF RBC ChE ACTIVITY IN DOGS FOLLOWING ORAL EXPOSURE TO ETHYL PARATHION

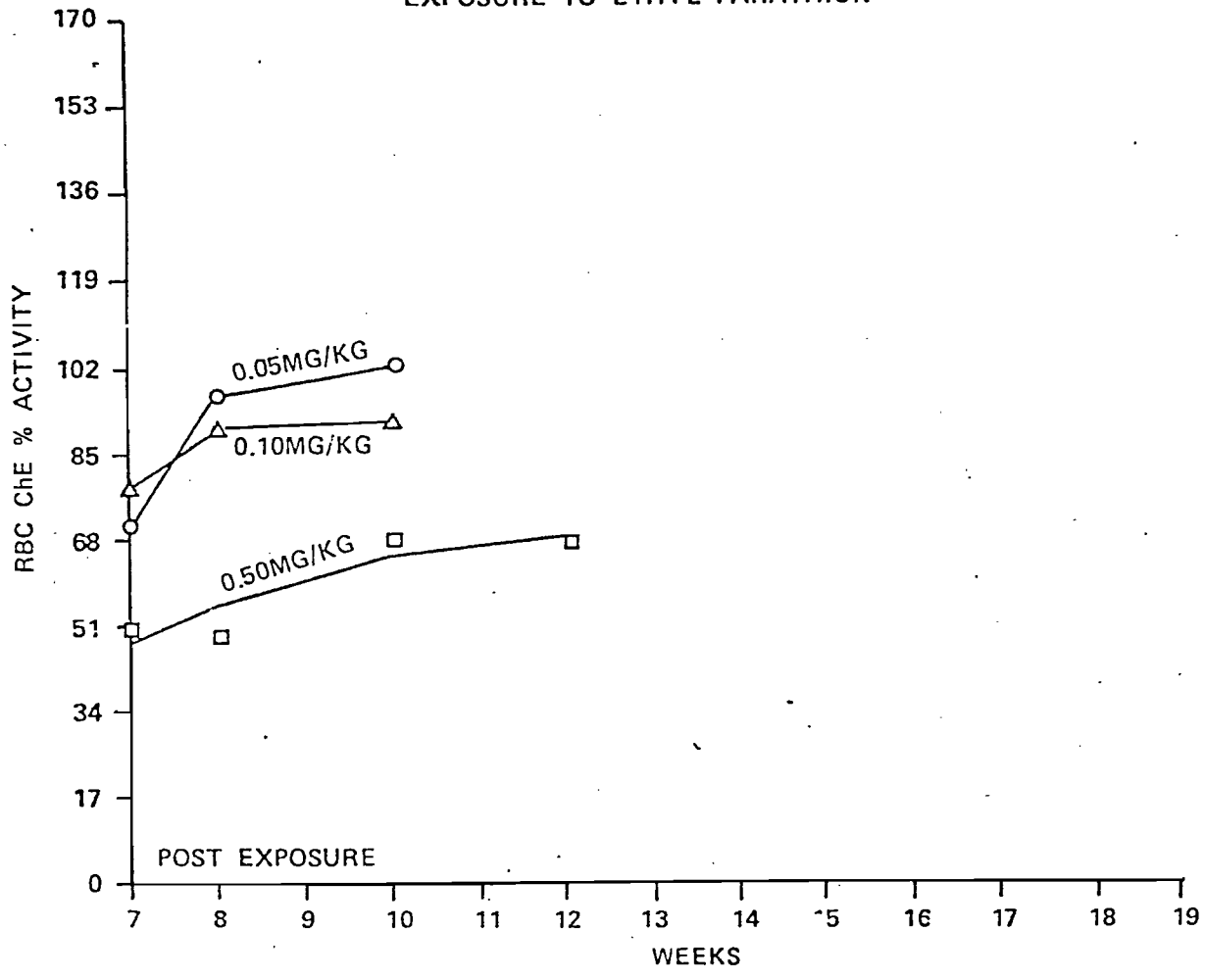


Figure 38. RECOVERY RATE OF PLASMA ChE ACTIVITY IN DOGS FOLLOWING ORAL EXPOSURE TO ETHYL PARATHION

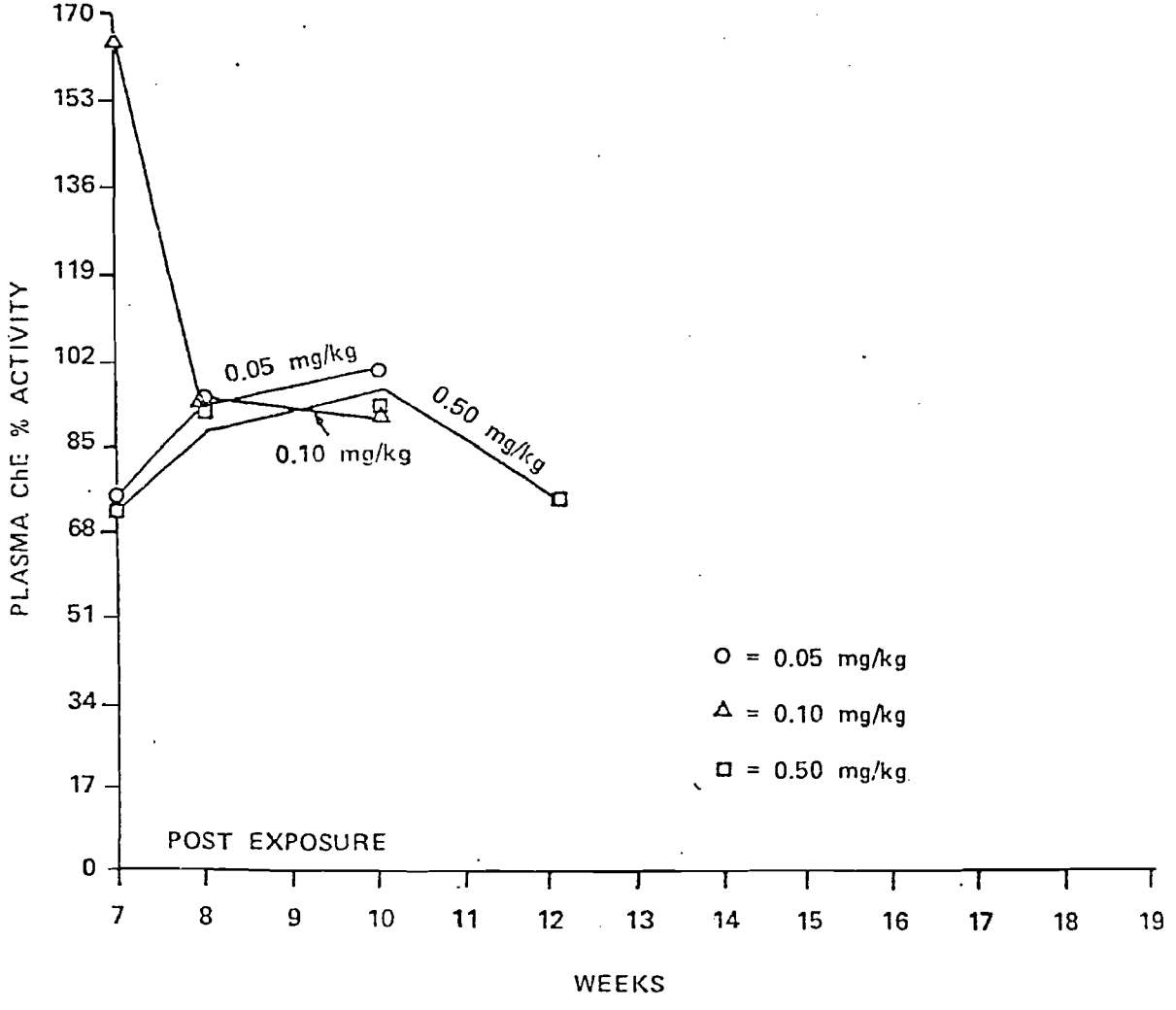


Figure 39. GROWTH CURVE OF SUB–ACUTE DOGS EXPOSED TO ETHYL PARATHION FOR SIX WEEKS BY THE ORAL ROUTE (DOSES= 0.5, 0.1 AND 0.05 MG/KG)

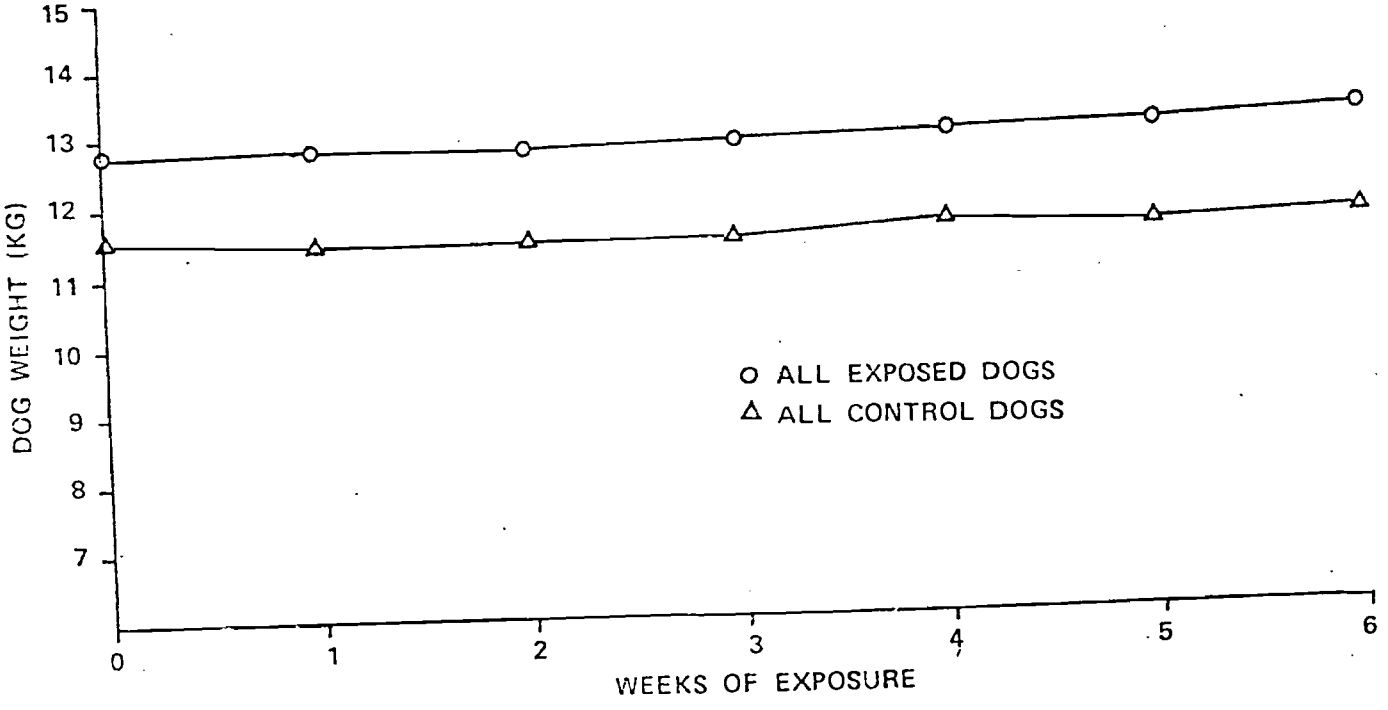


Figure 40. RECOVERY RATE OF ChE ACTIVITY IN RATS EXPOSED TO A SINGLE ORAL DOSE (2.80 MG/KG) OF ETHYL PARATHION

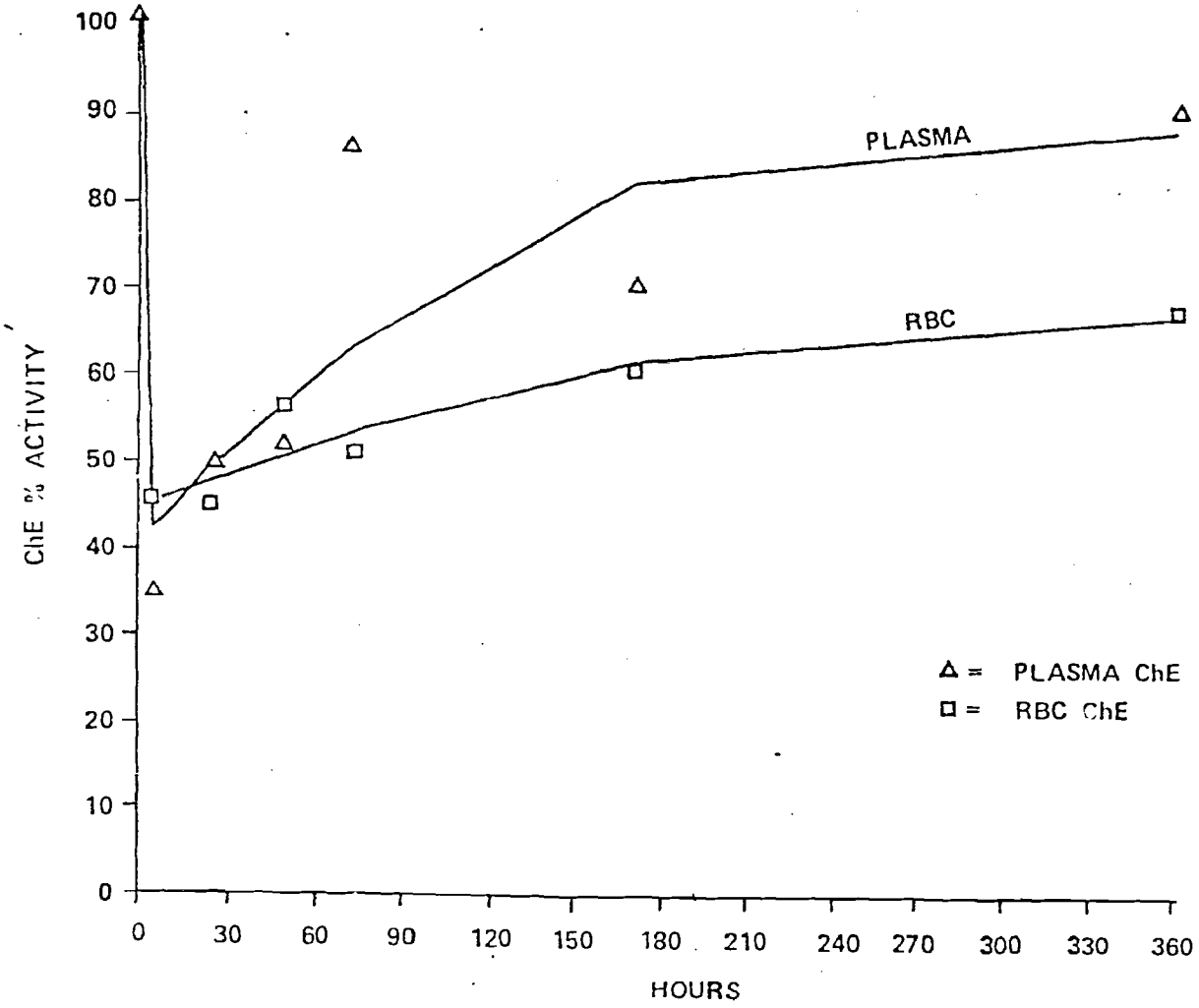


Figure 41. RECOVERY RATE OF ChE ACTIVITY IN DOGS EXPOSED TO A SINGLE ORAL DOSE (2.5 mg/kg) OF ETHYL PARATHION