THE PHARMACOKINETICS OF METHSUXIMIDE AND A MAJOR METABOLITE IN THE DOG

BY

MICHAEL R. DOBRINSKA

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Michael R. Dobrinska

(Under the supervision of Associate Professor Peter G. Welling)

Methsuximide is an agent useful in the treatment of petit mal epilepsy and is marketed as Celontin^{R} 150 or 300 mg oral capsules. One of its major biotransformation products identified in blood is the N-demethylated compound, 2-methyl-2-phenylsuccinimide. This metabolite is pharmacologically active and potentially toxic. Methsuximide induces its own metabolism by stimulating the activity of drug metabolizing enzymes. Little information exists on the pharmacokinetic behavior of this drug in humans or experimental animals. The present studies were undertaken to elucidate the pharmacokinetics of methsuximide after single intravenous doses.

The dog was used as an experimental model since intravenous doses of methsuximide or metabolite were required to best define distribution volumes. It was found that methsuximide obeys the two compartment open model while the metabolite, after intravenous dosing, was best described by the one compartment open model. The metabolite plasma level profile after methsuximide dosing was described by a triexponential equation showing the influence of the methsuximide biexponential and its own monoexponential equations. The blood level data were fit to these equations with the aid of

a digital computer. Parameters reflecting the distribution and elimination characteristics of parent drug and metabolite were obtained. The metabolite's biological half-life was found to exceed that of the parent drug by a factor of about 15. The N-demethylation metabolic step accounted for approximately 40% of the overall elimination of methsuximide.

APPROVED Peter Welling

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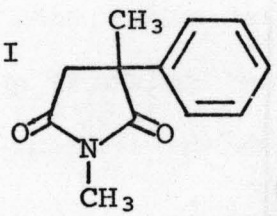
TABLE OF CONTENTS

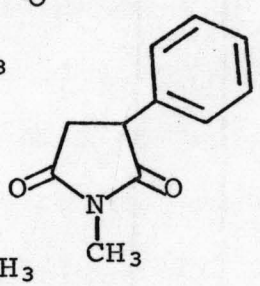
INTRODUCTION

Succinimide derivatives potentially useful in the treatment of petit mal epilepsy were first introduced by Miller and Long in 1951 (1). The anticonvulsant activity of the α-phenylsuccinimides was confirmed by Chen *et al.* in 1951 (2). It was found that the α-phenyl, 2-methyl and N-methyl groups on the succinimide ring increased anticonvulsant activity while an increase in length of the N-alkyl side chain decreased activity. Another derivative, devoid of the α-phenyl group, proved also to be highly efficacious in preliminary clinical studies (3, 4). Those succinimides currently in use in the United States are:

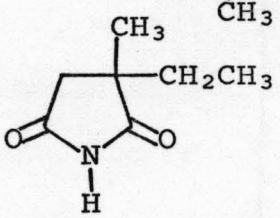
(±)-N,2-dimethyl-2-phenylsuccinimide (methsuximide, Celontin®)[a] I



(±)-N-methyl-2-phenylsuccinimide (phensuximide, Milontin®) II



(±)-2-ethyl-2-methylsuccinimide (ethosuximide, Zarontin®) III



There is little quantitative information on the pharmacokinetics of the succinimides in experimental animals or

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[a]Celontin, Milontin and Zarontin are registered trademarks of Parke-Davis and Company. In all drug studies referred to, or studied in this thesis, the racemic modification was used.

man. Methsuximide possesses many interesting properties which affect its pharmacokinetic profile and was chosen as the drug used in the present studies.

Glazko and Dill (5) have reported methsuximide plasma levels in twelve normal adult males at two dose levels of 0.6 g and 1.2 g in a cross-over design study. Mean peak plasma levels of 3.1 $\pm$ 0.5 and 6.8 $\pm$ 0.6 (standard error) $\mu g\ ml^{-1}$ occurred at one hour after dosing 0.6 and 1.2 g respectively. Thus, in this dosage range the plasma level was found to be roughly proportional to dose. The mean plasma half-life, $t_{1/2}$, with both doses was 2.6 hours over the 1-12 hour period. The experiments were repeated weekly for four weeks. It was found that the plasma $t_{1/2}$'s during the first week were approximately 75% greater than during the fourth week. This was interpreted in terms of induction of hepatic drug metabolizing enzymes. Recent evidence confirmed this interpretation since administration of I, II or III for three days to the rat resulted in increased oxidation of hexobarbitone, hydroxylation of aniline, liver:body weight ratio, hepatic microsomal cytochrome P-450, hepatic δ-amino-laevulinic acid synthetase and a reduction in hexobarbitone-induced hypnosis (6). These investigators also noted a decreased anticonvulsant activity after three days of methsuximide administration to the rat.

In 1971 Nicholls and Orton (7) reported on the absorption, distribution, metabolism and excretion (ADME) of N-$^{14}CH_3$ labeled methsuximide in the rat. After oral dosing

they found significant levels of radioactivity in the brain, liver, kidney, heart, adrenals, spleen, testes, lungs, salivary glands, eyes, fat and skeletal muscle indicating rapid and extensive drug distribution. Levels in body fat tended to be higher than those in other tissues. About 29% of the administered dose appeared as $^{14}CO_2$ in expired air within 24 hours after dosing. This suggested that there may be extensive N-demethylation of the parent drug to 2-methyl-2-phenylsuccinimide. Rats which received oral 100 mg kg^{-1} methsuximide doses exhibited anti-leptazol activity for up to six hours after dosing yet there was little parent drug in the brain at this time. It was suggested that since the metabolite also possesses anti-leptazol activity (2, 7, 8) it may have been responsible for the extended pharmacological activity. This is not uncommon among antiepileptic drugs as a similar phenomenon exists after mephobarbital, metharbital, mesantoin, trimethadione or paramethadione administration (9).

Few studies on the metabolism of methsuximide have appeared in the literature. Horning and coworkers (10) found N,2-dimethyl-2-(3,4-dihydroxy-1,5-cyclohexadien-1-yl)-succinimide, N,2-dimethyl-2-(4-hydroxyphenyl)-succinimide, N,2-dimethyl-2-(3-hydroxyphenyl)-succinimide, N-methyl-2-hydroxymethyl-2-phenylsuccinimide, two isomeric N,2-dimethyl-3-hydroxy-2-phenylsuccinimides and a diol presumed to be N,2-dimethyl-2-(4-hydroxyphenyl)-3-hydroxysuccinimide as well as small amounts of parent drug in the urine of the rat, guinea pig and man after oral methsuximide administration.

Assignment of metabolite structures was based on gas chromatography-mass spectrometry (GC-MS) after methylation and trimethylsilylation without pure metabolite reference standards. Dudley et al. (11) studied the metabolism of methsuximide in the dog and identified metabolites in 48 hour urine by melting point determination, mass spectroscopy, IR and UV absorption spectroscopy and NMR using pure synthesized metabolites as reference standards. After dosing one or two grams of methsuximide, roughly 7-20% of the dose was recovered as 2-(p-hydroxyphenyl)-2-methylsuccinimide and N-methyl-2-(p-hydroxyphenyl)-2-methylsuccinimide. The former derivative was the primary para-hydroxylated metabolite. Only a small amount of the N-demethylated metabolite was recovered as was the case after 2-methyl-2-phenylsuccinimide itself was administered. There was no evidence of metabolites formed by opening of the succinimide ring. No unchanged methsuximide was recovered and the authors stated that the N-demethylation reaction is probably the primary biotransformation route for methsuximide.

Nicholls and Orton (8) discussed methsuximide ADME in quantitative terms. The absorption half-life after oral doses in the rat was 17.4 minutes while distribution characteristics were similar to those previously found (7). The 2-methyl-2-phenylsuccinimide metabolite was identified in the urine of the rat, guinea pig (12) and man after oral methsuximide administration. Although the anticonvulsant activity of the N-demethyl metabolite is about half that of

the parent drug it has been found to be active for up to six hours after oral metabolite administration to the rat (2). The metabolite has been identified in rabbit plasma by GC-MS after oral methsuximide dosing (13). The parent drug was rapidly metabolized and within 30 minutes the concentration of the metabolite was much higher than that of the drug.

The plasma of 17 patients on chronic methsuximide therapy was analyzed for methsuximide and 2-methyl-2-phenyl-succinimide using the sensitive quadrupole mass fragmentography method (14). The metabolite level was found to be 700 times that of the parent drug. Metabolite levels of less than 10 $\mu g\ ml^{-1}$ were ineffective in seizure control while levels in excess of 40 $\mu g\ ml^{-1}$ were toxic. This metabolite is very lipophilic and has a pK_a of 8.52 (8). Since only 2.7% of the methsuximide dose was excreted into the 24 hour rat urine as the metabolite, while 29% was exhaled as $^{14}CO_2$ in the same time period (8), a long metabolite biological $t_{1/2}$ may be expected. Hence, the metabolite is not only rapidly formed, pharmacologically active and potentially toxic, but also may be persistent in the body. The clinical implications of this situation are obvious.

In 1973 Karch reported an overdose of methsuximide by an 18 year old female patient who ingested about 10 g of the drug (15). Sixteen hours post-ingestion plasma levels of drug and metabolite were 18 and 44 $\mu g\ ml^{-1}$, respectively. At 64 hours post-ingestion methsuximide levels had declined to 2 $\mu g\ ml^{-1}$ whereas metabolite levels were only slightly

lowered at 38 μg ml^{-1}. The clinical course was biphasic and consisted of initial lethargy, from which the patient could be easily aroused, a period of improvement followed by a long period of profound coma. Since the $t_{1/2}$ of methsuximide is less than 3 hours the coma could not have been due to parent drug and was attributed to the 2-methyl-2-phenylsuccinimide metabolite. The biphasic toxicity experienced with this drug is potentially dangerous and requires close scrutiny in the treatment of overdose victims. This case report emphasizes the need for pharmacokinetic information not only on the parent drug but also on the metabolite. This information would also be invaluable in seeking solutions to problems associated with a drug which exhibits auto-induction of hepatic metabolizing enzymes and forms active and potentially toxic metabolites.

The present studies were designed to elucidate the pharmacokinetics of both methsuximide and 2-methyl-2-phenylsuccinimide after intravenous administration of these compounds to male beagle dogs.

Intravenous dosing was employed in order to best define the distribution and elimination characteristics of these agents in the absence of complications due to absorption rates or variability in bioavailability.

The use of beagle dogs may be rationalized in terms of the following: (1) dogs are often useful models in predicting the pharmacokinetic characteristics of a drug in humans (16); (2) intravenous methsuximide and

2-methyl-2-phenylsuccinimide are not officially recognized dosage forms for human use; (3) multiple blood samples over prolonged time periods were required to adequately define the pharmacokinetic profiles.

It is hoped that this thesis will provide some of the basic information necessary to improve methsuximide drug therapy in patients suffering from petit mal epilepsy.

EXPERIMENTAL

A. Materials

Pure 5 gram samples of methsuximide and phensuximide were obtained from the manufacturer[a] while 3 grams of pure 2-methyl-2-phenylsuccinimide were obtained commercially[b]. Two male beagle dogs[c] were used; dog A weighed 14 kg and dog B 17.5 kg. The dogs had free access to water at all times but food was withheld a minimum of 12 hours prior to an experiment.

B. Experimental Procedure

The dog was prepared for each experiment by placing it in a restraining apparatus which consisted of a strong sheet which supported its body and through which its limbs protruded. The limbs were held secure by pediatric limb restraints tied to the shell of the restraining apparatus as in Figure 1. The dog was made as comfortable as possible and was held in restraints only during the initial period of the experiment, usually 1-2 hours, when frequent blood samples were obtained.

Two vein infusion sets[d] were positioned, one in a front

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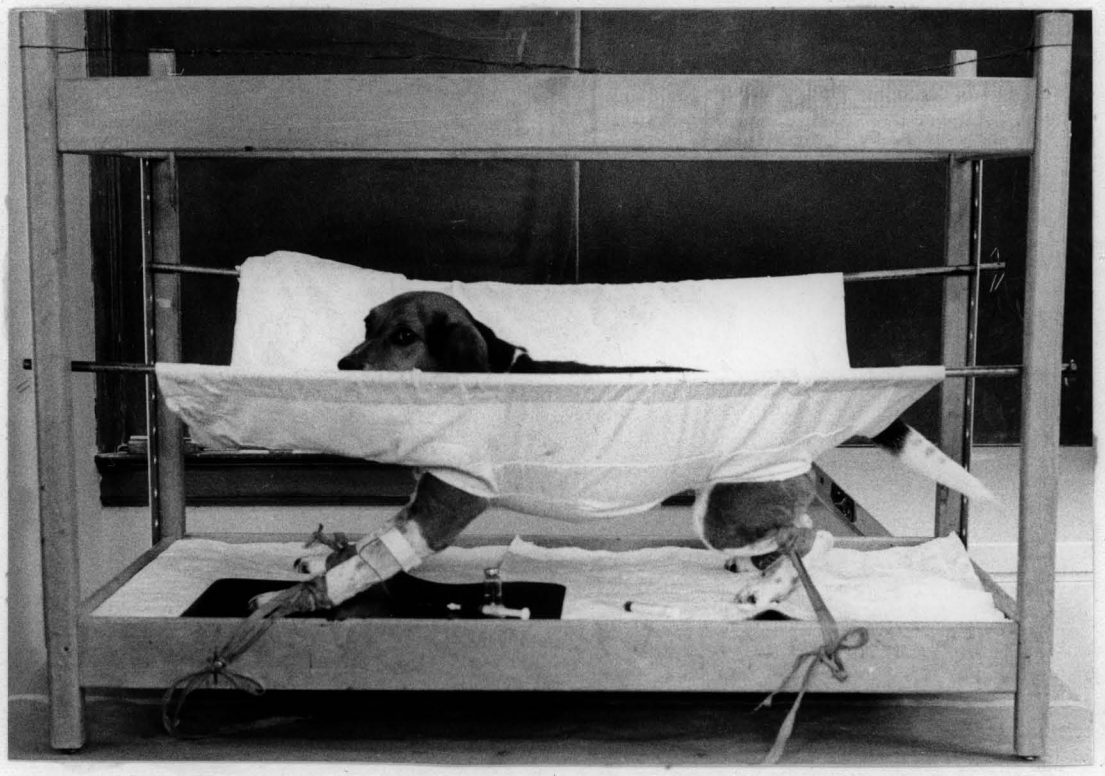
[a] Parke-Davis and Company, Detroit, Michigan.

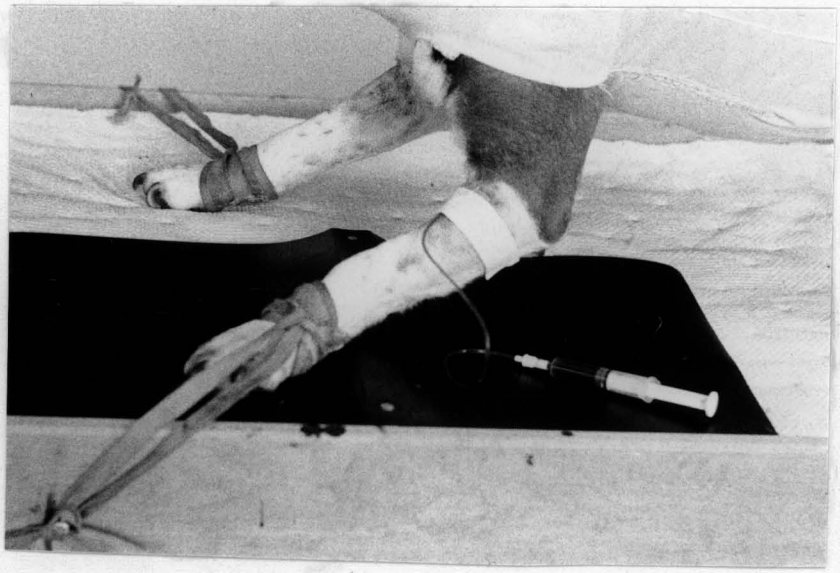
[b] Custom synthesis, Aldrich Chemical Company, Milwaukee, Wisconsin.

[c] Animal Care Unit, the University of Wisconsin, Madison, Wisconsin.

[d] Miniset[R] Vein Infusion Set, Travenol Labs, Deerfield, Illinois.

Figure 1. Dog restraining apparatus (upper) showing limb restraints and vein infusion set placement (lower).





Photographs by Shabbir T. Anik.

limb vein, the other in the other front or a hind limb vein. The sets had 19 gauge X 7/8" needles with 30 cm of flexible plastic tubing attached which could contain about 0.6 ml of fluid. The infusion sets were kept free of blood clots by infusion of about 2 ml of sodium heparin solution[a] (10 units ml^{-1}) into them approximately every hour they were in position. One set was used to rapidly administer the drug solution while the other was used to collect blood samples. Infusion sets were found to be necessary to assure intravenous dosing and to facilitate rapid collection of several blood samples in the first hour of the experiments without multiple venipunctures.

The water solubility of methsuximide is 2.8 mg ml^{-1} at pH 7.0 and 25° C (5). A dose of 250 mg of either methsuximide or the metabolite was selected since this represents a low therapeutic dose in children. One assumption in the pharmacokinetic analysis was that the injection was accomplished instantaneously. The volume of drug solution which could be injected had therefore to be minimized and this precluded the use of an aqueous drug solution. The following co-solvent system was developed which yielded a visually clear solution of methsuximide or metabolite at 25° C:

methsuximide or, 2-methyl-2-phenylsuccinimide	300 mg
propylene glycol, USP	4.5 ml
water for injection, USP qs ad.	6.0 ml

[a]Saline diluted Lipo-Heparin[R] 5000 u ml^{-1}, Riker Labs, Northridge, California.

Injection of 5.0 ml of this solution provided 250 mg of drug. The drug solution was prepared within 2 hours of use and stored in a 10 ml sterile multi-dose vial. Before injecting, the solution was warmed to about 37° C to prevent chills and consequent local vasoconstriction (17). The 5 ml injection was accomplished in approximately 120 seconds. A faster injection led to drug precipitation and formation of a local hematoma. The infusion set was immediately flushed with 10 ml of normal saline solution. The set was removed and analysis of water flushings indicated no methsuximide or metabolite remained in the set.

Blood samples (5 ml) were then collected via the other infusion set at 0, 2-5, 10, 15, 30, 45, 60 and 120 minutes. Collection of blood at 3, 4, 5, 6, 8, 10, 12, 18, 24, 36 and 48 hours was done by direct venipuncture in most cases. Alterations in times occurred depending on the experiment. Before each blood sample was drawn 5 ml of "residual fluid" was withdrawn to avoid the 0.6 ml of heparin solution contained in the set from diluting the blood sample. The 5 ml blood sample was then drawn and replaced by a 5 ml injection of normal saline solution. The residual fluid was re-injected followed by 1-2 ml of heparin solution 5 units ml^{-1}. Direct venipunctures were done on any leg. Blood samples were placed in 10 ml heparinized vacutainers[a] and

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[a]Green stopper Vacutainer® evacuated glass tubes coated with 143 units sodium heparin, Becton-Dickinson, Rutherford, New Jersey.

centrifuged[a]. The plasma, about 2 ml, was deep frozen until analyzed, usually within 2 weeks. Some experiments required 90-100 ml of blood; however, visual inspection of the centrifuged blood indicated no decrease in the hematocrit during the sampling period.

The minimum time between experiments on the same dog was one month. This reduced the danger of changes in pharmacokinetic parameters due to prior drug exposure, i.e. enzyme induction or residual drug related materials in the body, and allowed for complete healing of the venipuncture sites.

C. Assay Procedure

The assay was a modification of that of Kinkel et al. (5). One ml of plasma or 1 ml of standard aqueous methsuximide and metabolite standard in blank plasma was pipetted into 13 ml glass stoppered centrifuge tubes and acidified with 0.5 ml of 0.5 N HCl. Five mls of $CHCl_3$[b] was added and the tubes were horizontally shaken on a flat-bed shaker for 15 minutes. The tubes were centrifuged at 2300 rpm for 15 minutes or until clean phase separation was accomplished. Since emulsification was a frequent problem 4.0 ml aliquots of the clear $CHCl_3$ drug containing layer were pipetted off and placed in dry clean tubes. One ml of phensuximide $CHCl_3$ solution, 6 $\mu g\ ml^{-1}$, was added to the $CHCl_3$ aliquot as an

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[a] 2300 rpm's for 15 minutes with the Dynac centrifuge, Clay Adams, Parsippany, New Jersey.

[b] $CHCl_3$, A.R., Mallinckrodt, as supplied.

external standard. The $CHCl_3$ was carefully evaporated to dryness in a 40° C water bath under a gentle stream of N_2. The residue was immediately redissolved in about 100 µl of CS_2[a] and the samples were analyzed on the same day by GC.

The GC[b] used for quantification was a programmable dual column gas chromatograph equipped with dual flame ionization detectors (FID). A six foot two mm (ID) U shaped glass column packed with 3% OV-17 on Gas Chrome Q 100/120 mesh[c] was used. The carrier gas was N_2 flowing at 20 ml min^{-1} while the flame gases were H_2 and compressed air flowing at 20 and 200 ml min^{-1}, respectively. The solid state electrometer was set at a range of 10^{-11} amperes and the attenuator at 8-64 so that a recorder[d] full scale pen deflection occurred with an input signal of 8-64 X 10^{-11} amperes. The GC was operated in the single column mode at an isothermal column temperature of 175° C with FID bath at 200° C and injection block at 210° C. Sample volume introduced by the on column injection technique was 3 µl and chart speed was 15 inches hr^{-1}. The column was initially conditioned for 48 hours at 200° C and overnight after each series of plasma sample extracts were run. In order to prevent compound adsorption at active sites and to maintain column integrity

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[a]Carbon disulfide, A.R., Mallinckrodt, as supplied.

[b]Nuclear Chicago Selectra System 5000.

[c]Applied Science Laboratories, State College, Pennsylvania.

[d]Barber-Colman Chromocorder Dual Pen X-Y Recorder, Rockford, Illinois.

20 µl of Silyl-8[a] was injected onto the column after approximately every six hours of column use.

D. Summary of Experiments

The experiments conducted may be summarized as follows:

Experiment	Dog	Dose
A	A	Methsuximide 250 mg
B	B	Methsuximide 250 mg
C	B	Methsuximide 250 mg
D	B	2-Methyl-2-phenylsuccinimide 250 mg
E	B	2-Methyl-2-phenylsuccinimide 250 mg

[a]Pierce Chemical Company, Rockford, Illinois.

RESULTS

A. Assay

1. Plasma Sample Workup

The plasma sample workup was repeatedly changed in an effort to gain maximum extraction efficiency and cleaner samples for GC analysis. Drug recovery trials were done when $CHCl_3$ was the final GC solvent. Triplicate runs of blank dog plasma containing methsuximide and metabolite at concentrations of 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 10.0, 15.0, 20.0, 30.0, 35.0 and 40.0 $\mu g\ ml^{-1}$, representing the range in expected plasma levels, were done. The recovery of methsuximide was $92 \pm 3\%$ while that of 2-methyl-2-phenylsuccinimide was 88 ± 5 (S.D.)%. It has been reported (5) that evaporation of the $CHCl_3$ layer to dryness may result in drug losses. However, improved quantitation of drug and metabolite peaks resulted from changing the final GC solvent from $CHCl_3$ to CS_2 which gives a negligible solvent peak. This change resulted in no significant differences in recoveries of either compound. All aqueous or $CHCl_3$ reference solutions used in the recovery trials were refrigerated and found to remain stable for periods in excess of 3 months. Derivatization of drug samples was found not to be necessary for the GC analysis.

2. Gas Chromatography

Gas chromatography can be extremely sensitive and

reproducible if the operating parameters are carefully selected (19). The H_2/air flame gas flow ratio should be 1:10 to obtain a good flame but the individual flows can be altered to obtain maximum sensitivity of the FID to the compounds. Figure 2 is a plot of area under the drug peaks, determined by disc integration, versus H_2 flow rate. The selection of flame gas flow rates of 20 and 200 ml min^{-1}, yielded the maximum sensitivity of the FID to both compounds.

The optimum carrier gas (N_2) flow rate was determined through use of the experimentally obtained Van Deemter plot (18, 19). A GC column may be considered as a series of "theoretical plates" which are of a thickness such that equilibrium is reached between solution leaving the plate and the average concentration of solute in the stationary phase (OV-17) throughout the plate (18). The thickness of the plate is referred to as the height equivalent of a theoretical plate (HETP) and is obtained through equations 1-3,

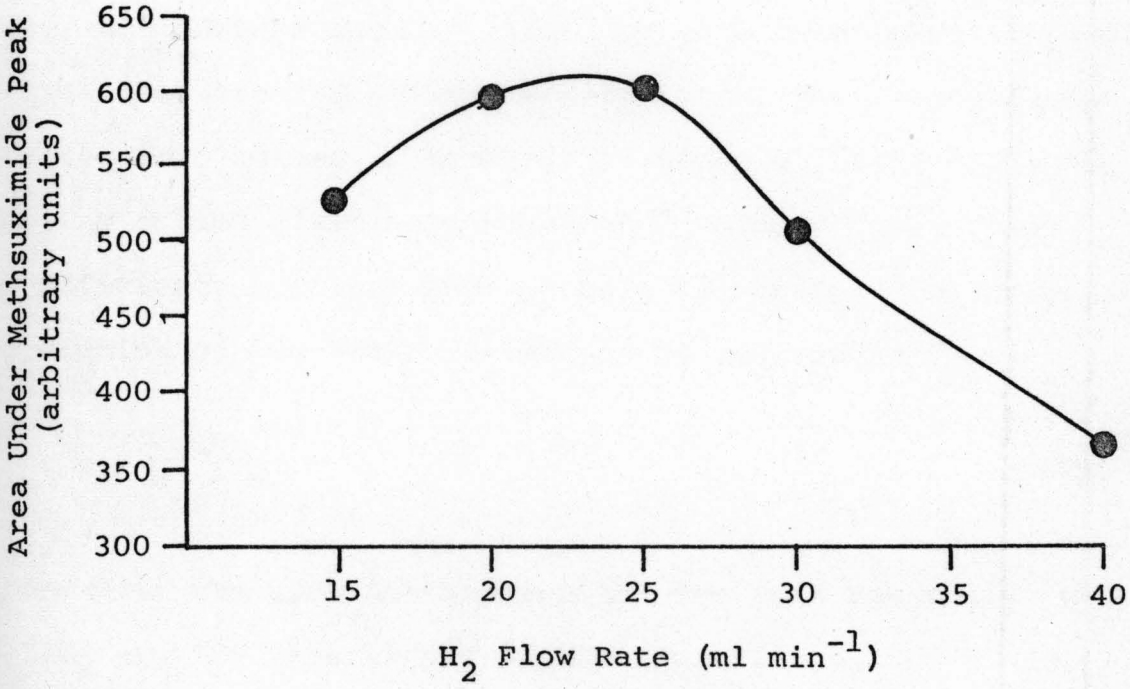
$$N = 16\left(\frac{t_{corr}}{W}\right)^2 \qquad \text{Eq. 1}$$

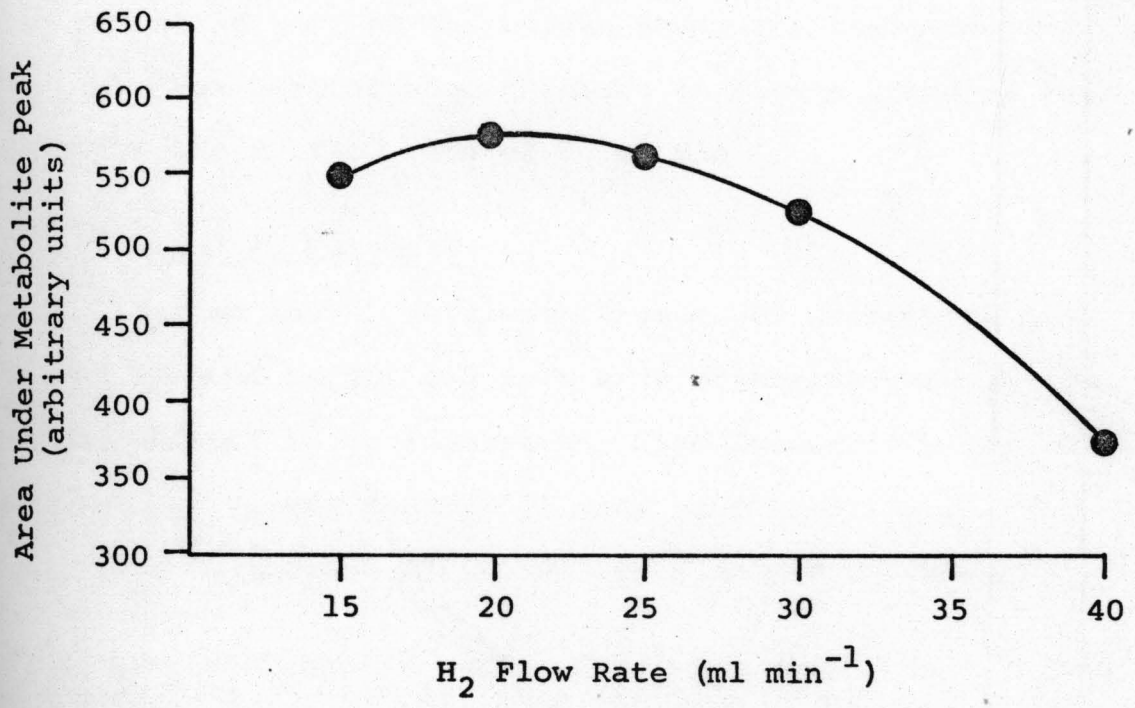
$$\overline{N} = \frac{N}{L} \qquad \text{Eq. 2}$$

$$HETP = \frac{l}{\overline{N}} \qquad \text{Eq. 3}$$

where N is the number of theoretical plates, t_{corr} is the

Figure 2. Area under drug (upper) and metabolite (lower) GC peaks determined by disc integration versus H_2 flow rate. Air flow was 10 X the H_2 flow rate and column temperature 175° C with N_2 flow at 20 ml min^{-1}. The points were experimentally determined and lines were hand drawn.


Area Under Methsuximide Peak
(arbitrary units)
650
600
550
500
450
400
350
300
15
20
25
30
35
40
H2 Flow Rate (ml min-1)


Area Under Metabolite Peak
(arbitrary units)
650
600
550
500
450
400
350
300
15
20
25
30
35
40
H2 Flow Rate (ml min-1)

time between the air peak[a] and the compound's peak apex, W is the baseline width of the triangulated peak, t_{corr} and W have the same units, $\overline{N}$ is N divided by column length in feet, L. HETP is usually expressed in centimeters. A larger $\overline{N}$ indicates greater column efficiency for the compounds on the specific column. Reference 19 gives a rating scale for judging column efficiency based on $\overline{N}$ values. Regardless of efficiency a column must be able to separate the compounds. Resolution of two peaks is defined by equation 4

$$R = \frac{2D}{W_1 + W_2} \qquad \text{Eq. 4}$$

where D is the distance between the two peak apexes and W_1 and W_2 are the base widths of the two triangulated peaks. Generally, when two ideal peaks have an R = 1.5 they overlap to the extent of about 0.3%. Table I indicates the resolution and efficiency of the column under the conditions of use. The Van Deemter plot is shown in Figure 3 and is the basis for the N_2 flow rate of 20 ml min^{-1}.

3. Standard Curves

During the GC development over 300 peaks were quantitated by peak height and peak area determinations. Areas were calculated by triangulation, disc integration and planimetry. It was found that peak height ratios of drug or metabolite to phensuximide external standard were more

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[a]Under the experimental conditions the time of the air peak was considered to be zero, the injection point.

Table I

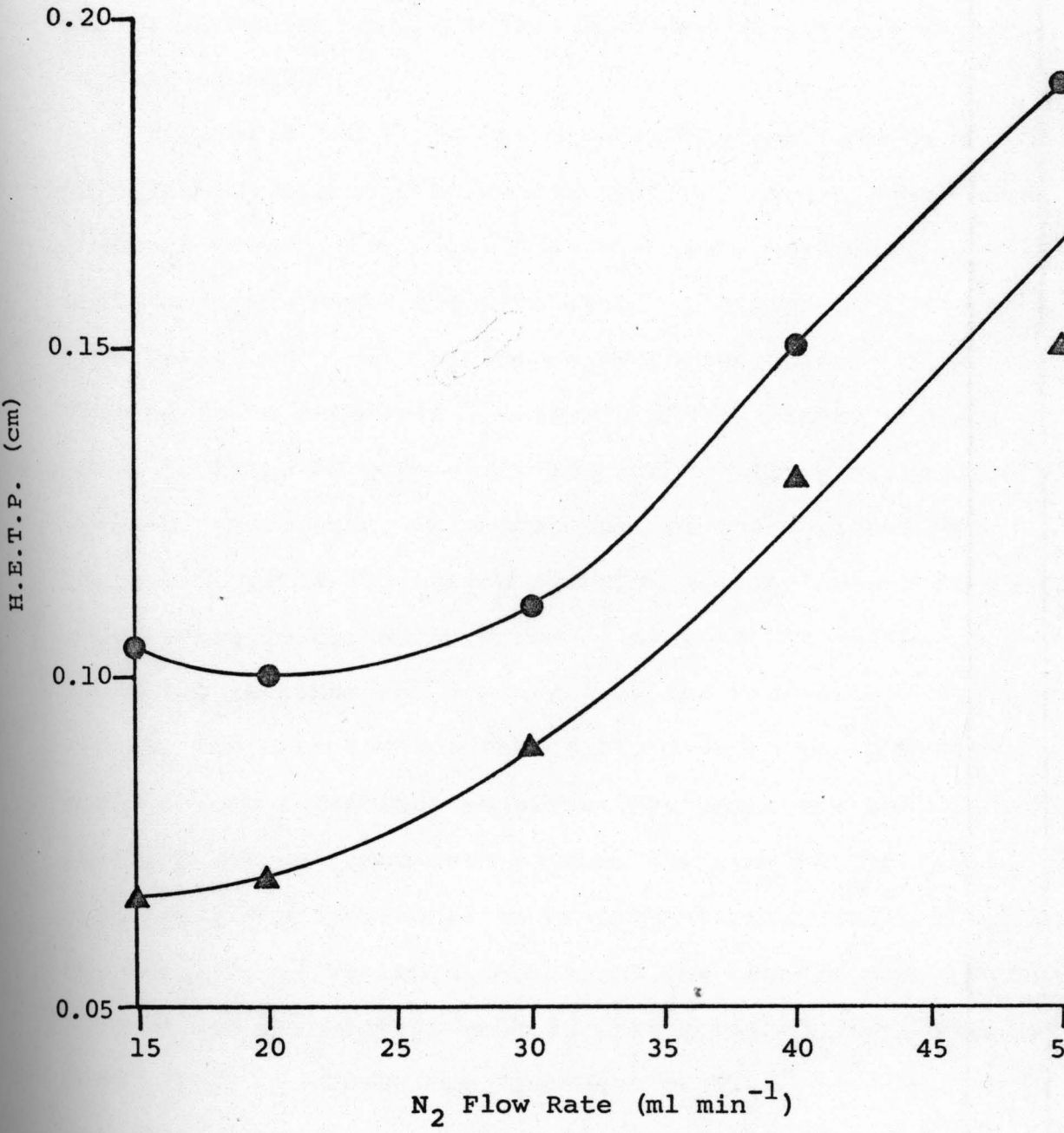
GC Column Efficiency Parameter Values

	methsuximide	2-methyl-2-phenylsuccinimide
HETP (cm)	0.095	0.070
$\overline{N}$ (ft^{-1})	321	435
R[a]	1.4	1.0
Rating[b]	good	good

[a]Resolution is with respect to the nearest peak, phensuximide.

[b]See reference 19.

Figure 3. The Van Deemter plot; HETP (cm) vs N_2 flow rate (ml min^{-1}). Points were experimentally determined, methsuximide (●) and metabolite (▲), while lines were hand drawn.


0.20
0.15
0.10
0.05
H.E.T.P. (cm)
15
20
25
30
35
40
45
5
N2 Flow Rate (ml min-1)

reproducible than peak area ratios. Efforts were made to obtain sharp narrow peaks so that peak heights would be a reliable quantitative method. Area determination of thin peaks leads to considerable error by any method other than digital computation since the thickness of the pen tracing becomes significant.

Figures 4 and 5 are the standard curves used to quantitate unknown plasma drug concentrations. Seven drug concentrations ranging from 0.5-15 $\mu g\ ml^{-1}$ were used. Triplicate runs were made using the same stock solutions so that three data points were obtained at each concentration. This allowed for a statistical analysis of the linear regression model in terms of pure error and lack of fit variance contributions. Pure error is a component of the variance not explained by the regression equation and includes errors of replication, i.e., assay errors. Lack of fit is the remaining variance not explained by the regression equation and can indicate lack of fit of the data to the proposed model. Both regression equation intercepts are not significantly different from zero so that the peak height ratios are directly proportional to concentrations. Table II gives the analysis of variance (ANOVA) of the regressions. Nomenclature and calculation methods were obtained from Draper and Smith (20). Although the "goodness of fit"[a], R^2, and correlation coefficient, r, are excellent, Table II indicates that

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[a]Coefficient of determination, R^2, is $\frac{\sum obs.^2 - \sum dev.^2}{\sum obs.^2}$.

Figure 4. Methsuximide standard curve, peak height ratio (methsuximide:phensuximide) versus plasma concentration ($\mu g\ ml^{-1}$). Regression line is $y = 0.16\ (\pm\ 0.01)X + 0.00\ (\pm\ 0.08)$ where quantities in parenthesis are the 95% confidence limits. $R^2 = 0.9795$ and $r = 0.9995$. Open circles indicate one determination, half-filled circles and filled circles indicate two and three equivalent determinations, respectively.

Peak Height Ratio methsuximide/phensuximide
2.5
2.0
1.5
1.0
0.5
0
5
10
15
c (µG ml^{-1})

Figure 5. 2-Methyl-2-phenylsuccinimide standard curve, peak height ratio (metabolite:phensuximide) versus plasma concentration ($\mu g\ ml^{-1}$). Regression line is $y = 0.11\ (\pm\ 0.004)X - 0.02\ (\pm\ 0.029)$ where quantities in parenthesis are 95% confidence limits. $R^2 = 0.9949$ and $r = 0.9985$. Symbols are as in Figure 4.

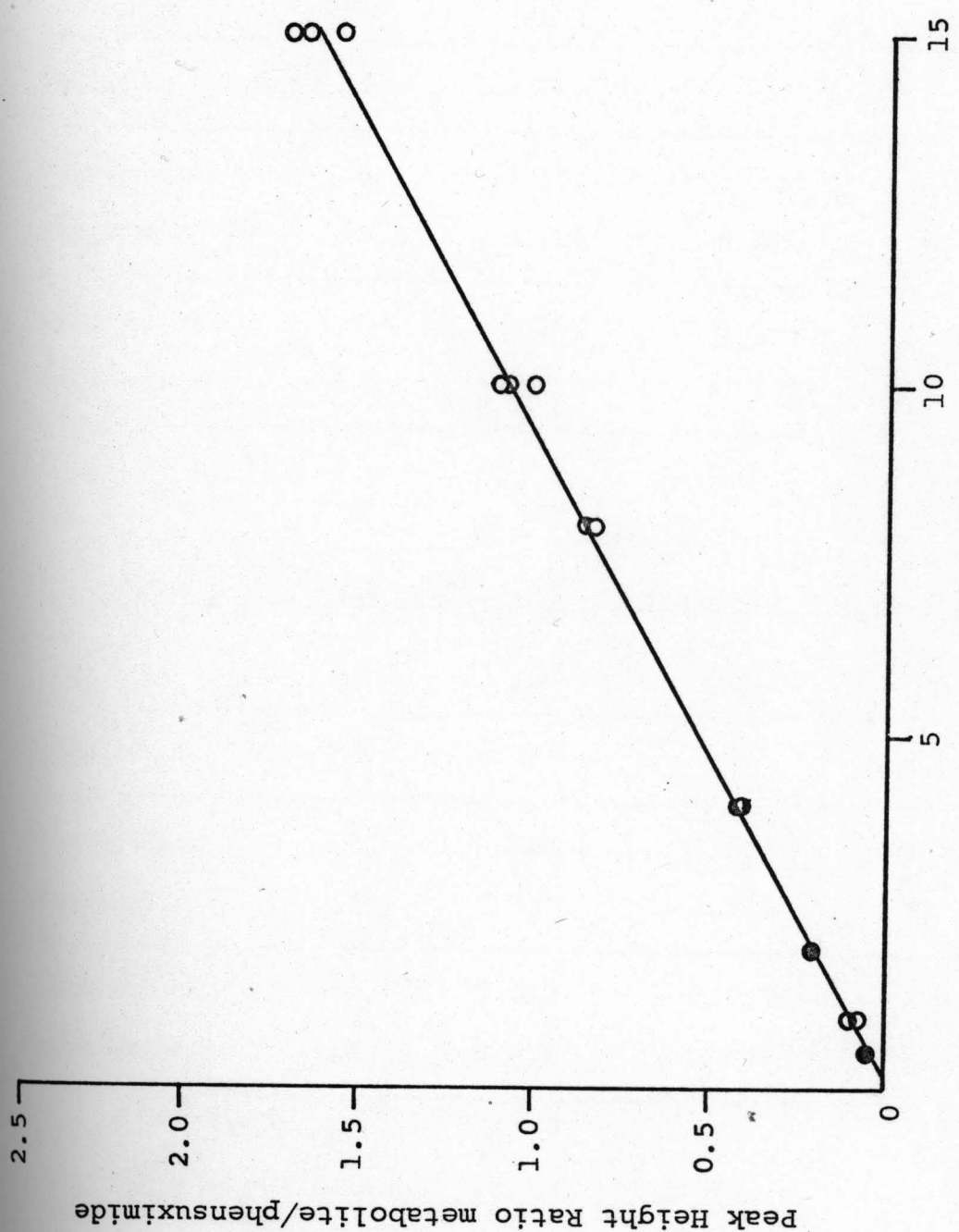

Peak Height Ratio metabolite/phensuximide
2.5
2.0
1.5
1.0
0.5
0
5
10
15
c (µg ml⁻¹)

Table II

ANOVA for Methsuximide Standard Curve

Source	df	SS	MS	F ratio
Total	20	14.068		
Regression	1	13.780	13.780	1005.8
Residual	19	0.288	0.014	($P < 0.01$)
Lack of fit	5	0.276	0.055	55
Pure error	14	0.012	0.001	($P < 0.01$)

ANOVA for 2-Methyl-2-phenylsuccinimide Standard Curve

Source	df	SS	MS	F ratio
Total	20	6.318		
Regression	1	6.285	6.285	3142
Residual	19	0.033	0.002	($P < 0.01$)
Lack of fit	5	0.017	0.003	3 borderline
Pure error	14	0.016	0.001	($P = 0.05$)

the methsuximide linear model suffers from a significant lack of fit. This problem was not investigated further as the linear model was judged sufficient to meet the demands of these experiments. Caution was exercised in extrapolations of the regression equation beyond 15 $\mu g\ ml^{-1}$. In cases where plasma levels exceeded 15 $\mu g\ ml^{-1}$ the linear model was checked by spiking blank plasma at the higher concentrations. Deviations from the concentrations predicted by the linear model did not exceed $\pm$ 5%.

4. Representative GC Chart

Representative GC charts with $CHCl_3$ and CS_2 as solvents are given in Figure 6. Retention times were methsuximide 191 sec, phensuximide external standard 239 sec and metabolite 281 sec with the CS_2 system.

B. Intravenous Drug and Metabolite Plasma Level-Time Data

Plasma levels of drug and metabolite after i.v. doses of methsuximide are given in Tables III-V and graphically in Figures 7-9. Plasma levels of metabolite after dosing this compound are described in Tables VI and VII and Figures 10 and 11. The solid lines in the figures are best computer fits as described in the text.

Figure 6. Representative GC chart. Solvent peaks in I and II are $CHCl_3$ and CS_2 respectively. Peaks a, b and c are methsuximide, phensuximide and 2-methyl-2-phenylsuccinimide, respectively.

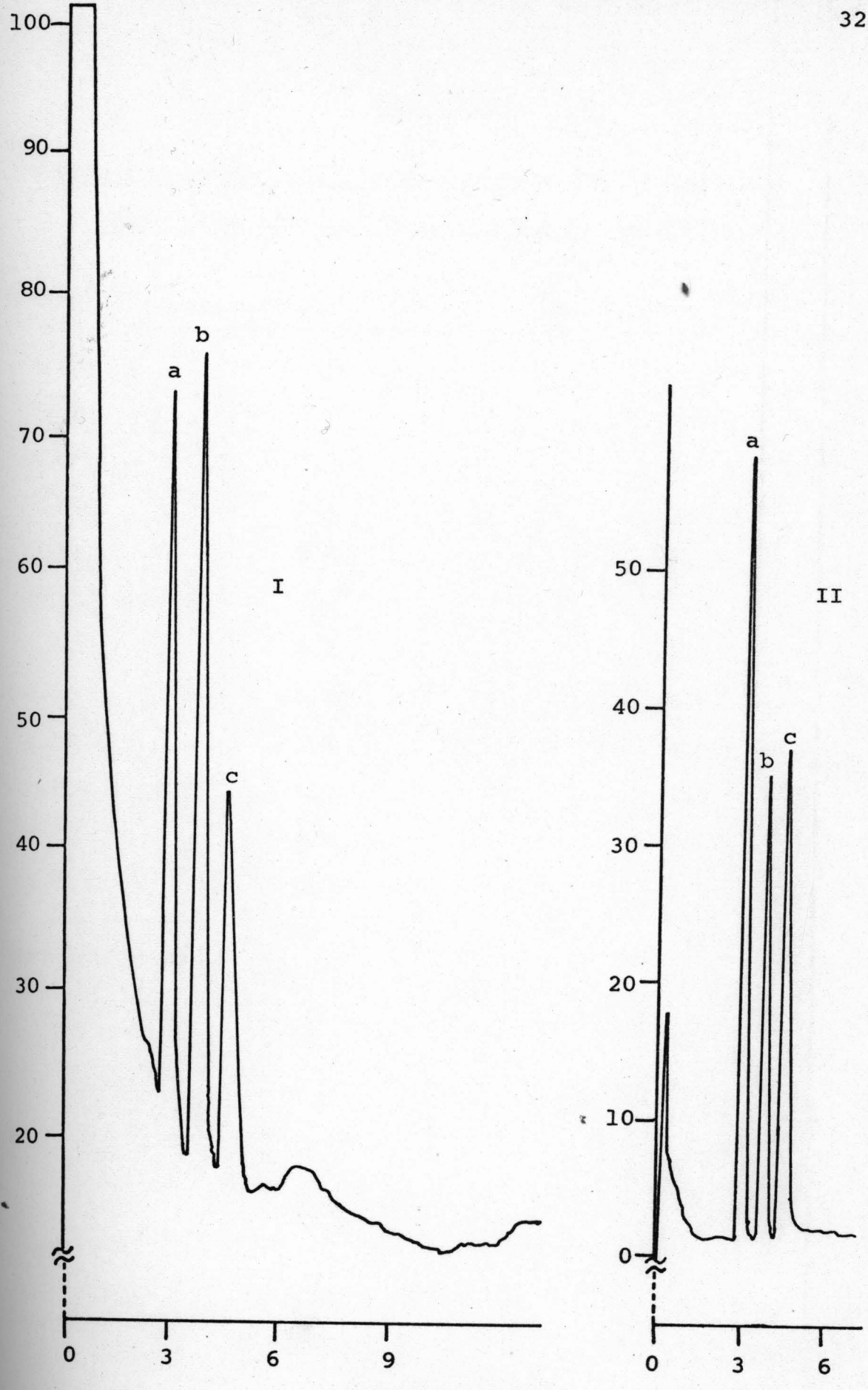

100
90
80
70
60
50
40
30
20
a
b
c
I
0
3
6
9
50
40
30
20
10
0
a
b
c
II
0
3
6
TIME (minutes)

Table III

Drug and Metabolite Plasma Levels after Intravenous Methsuximide Administration to Dog A, Experiment A

t (hrs)	$C_{methsuximide}$ ($\mu g\ ml^{-1}$)	$C_{metabolite}$ ($\mu g\ ml^{-1}$)
0.16	13.6	3.5
0.27	12.2	4.3
0.50	7.2	5.0
0.75	5.6	5.5
1.00	5.6	5.5
2.25	---[a]	7.0
3.00	4.4	7.0
4.00	3.4	6.5
6.00	1.6	6.5
8.00	1.3	5.5
10.00	0.9	5.0
12.00	0.7	4.5

[a]Not determined.

Table IV

Drug and Metabolite Plasma Levels after Intravenous Methsuximide Administration to Dog B, Experiment B

t (hrs)	$C_{methsuximide}$ ($\mu g\ ml^{-1}$)	$C_{metabolite}$ ($\mu g\ ml^{-1}$)
0.08	12.6	---[a]
0.17	9.1	---
0.25	6.9	1.8
0.50	5.7	3.3
0.75	4.0	4.5
1.00	3.0	4.9
2.00	1.6	6.1
3.00	0.8	6.2
4.00	0.5	5.9
6.00	---[a]	5.2
8.00	---	4.9
10.00	---	4.8
12.00	---	4.9
14.00	---	4.7
16.00	---	3.9
18.00	---	3.7

[a] Below limits of detection.

Table V

Drug and Metabolite Plasma Levels after Intravenous Methsuximide Administration to Dog B, Experiment C

t (hrs)	$C_{methsuximide}$ ($\mu g\ ml^{-1}$)	$C_{metabolite}$ ($\mu g\ ml^{-1}$)
0.03	10.7	---[a]
0.08	8.6	0.6
0.25	6.7	1.4
0.50	5.3	2.0
0.75	4.7	2.9
1.00	3.9	2.6
1.50	2.9	3.4
2.00	1.8	3.3
3.00	1.3	4.4
4.00	0.9	4.5
5.00	0.6	4.2
6.00	0.4	4.5
8.00	---[a]	4.3
10.00	---	4.4
12.00	---	4.4
24.00	---	2.4
36.00	---	1.3
48.00	---	0.5

[a]Below limits of detection.

Table VI

Metabolite Plasma Levels after Intravenous 2-Methyl-2-phenylsuccinimide Administration to Dog B, Experiment D

t (hrs)	$C_{metabolite}$ ($\mu g\ ml^{-1}$)
0.09	19.8
0.17	15.0
0.25	18.0
0.50	16.4
0.75	14.8
1.00	16.5
2.00	13.2
3.20	14.1
4.00	16.1
6.00	12.2
8.00	12.6
10.00	11.4
12.00	9.1
18.00	7.8
24.00	5.7
36.00	3.4
48.00	1.6

Table VII

Metabolite Plasma Levels after Intravenous 2-Methyl-2-phenylsuccinimide Administration to Dog B, Experiment E

t (hrs)	$C_{metabolite}$ ($\mu g\ ml^{-1}$)
0.08	24.0
0.17	21.3
0.25	19.0
0.50	19.2
1.00	17.9
2.00	17.5
3.80	17.9
6.00	17.4
8.00	14.5
11.00	11.7
13.00	12.2
18.00	10.4
24.00	7.5
36.00	4.3
48.00	1.9

Figure 7. Methsuximide and 2-methyl-2-phenylsuccinimide plasma level vs time profiles after a 250 mg intravenous injection of methsuximide, experiment A. The methsuximide profile (●) was drawn using the computer determined equation $C_1 = 16.7e^{-4.71t} + 6.6e^{-0.20t}$ while the metabolite profile (▲) was hand drawn.

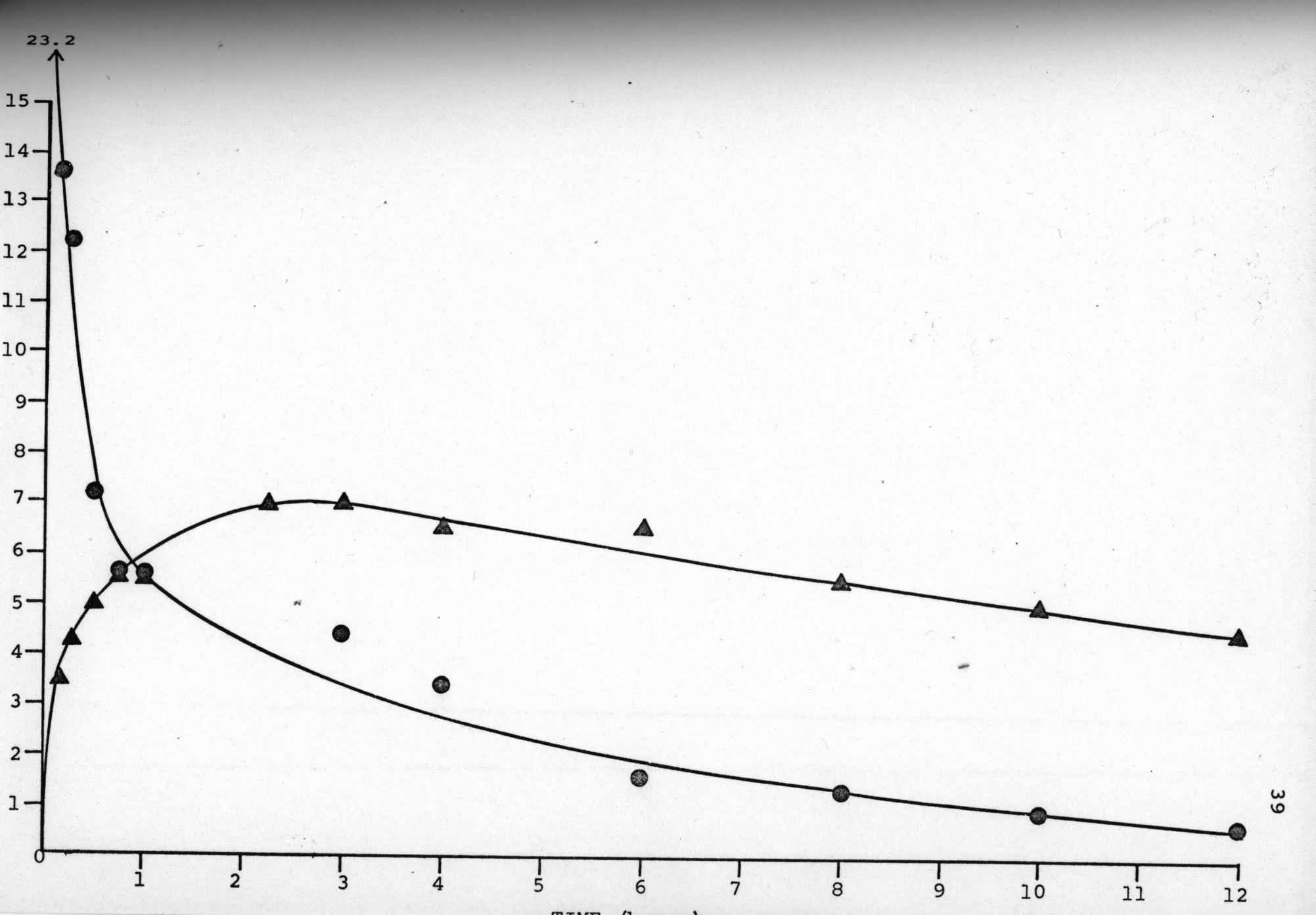

23.2
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
1
2
3
4
5
6
7
8
9
10
11
12

Figure 8. Methsuximide and 2-methyl-2-phenylsuccinimide plasma level vs time profiles after a 250 mg intravenous injection of methsuximide, experiment B. Computer determined equations are methsuximide (●)

$$C_l = 11.6e^{-8.64t} + 7.2e^{-0.78t}$$

and metabolite (▲)

$$C_{M_b} = -1.0e^{-8.64t} - 7.1e^{-0.78t} + 8.1e^{-0.047t}.$$

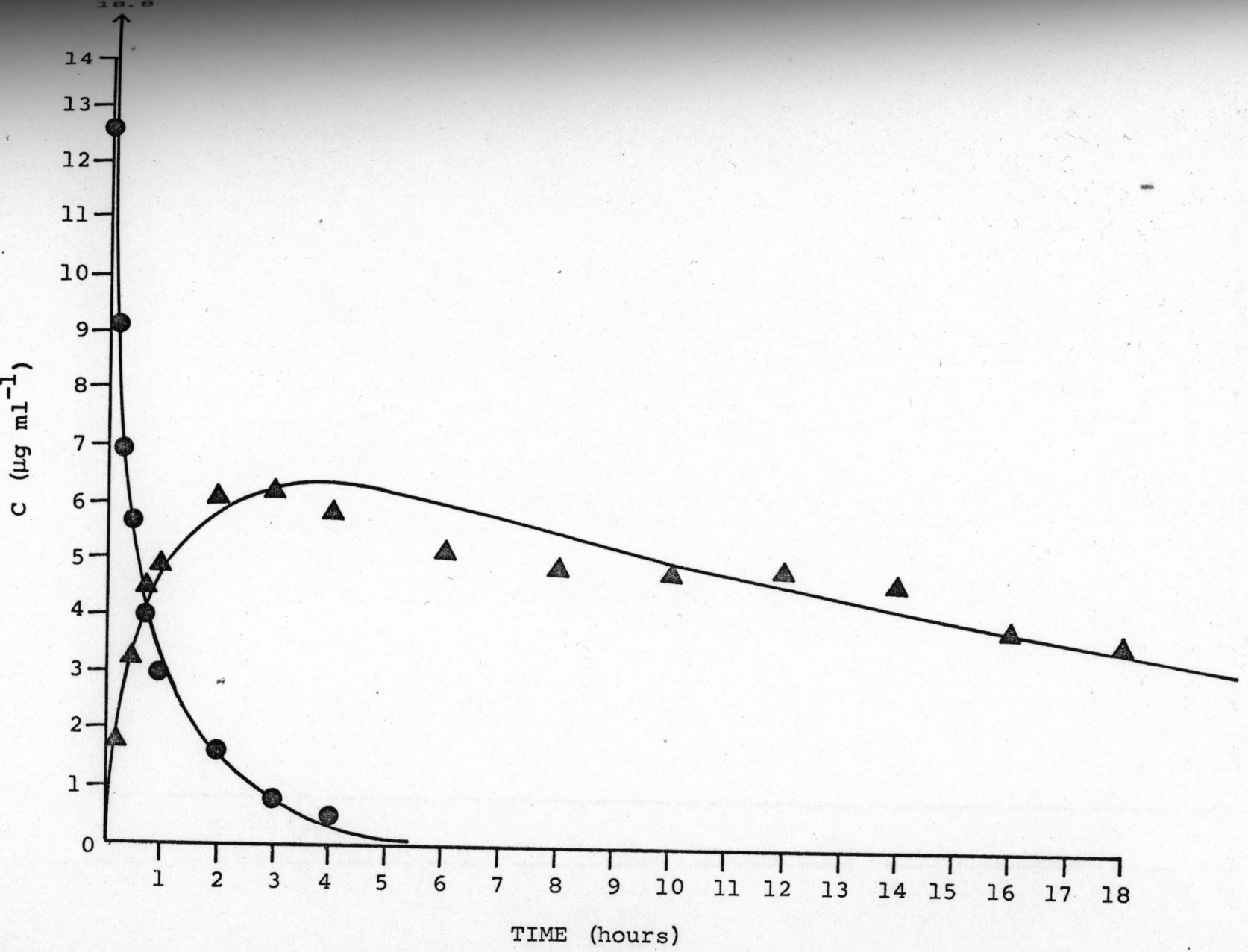

c (μg ml⁻¹)
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
TIME (hours)

Figure 9. Methsuximide and 2-methyl-2-phenylsuccinimide plasma level *vs* time profiles after a 250 mg intravenous injection of methsuximide, experiment C. Computer determined equations are methsuximide (●)

$$C_l = 6.2e^{-2.24t} + 4.2e^{-0.40t}$$

and metabolite (▲)

$$C_{M_b} = -1.4e^{-2.24t} - 5.6e^{-0.40t} + 7.0e^{-0.047t}.$$

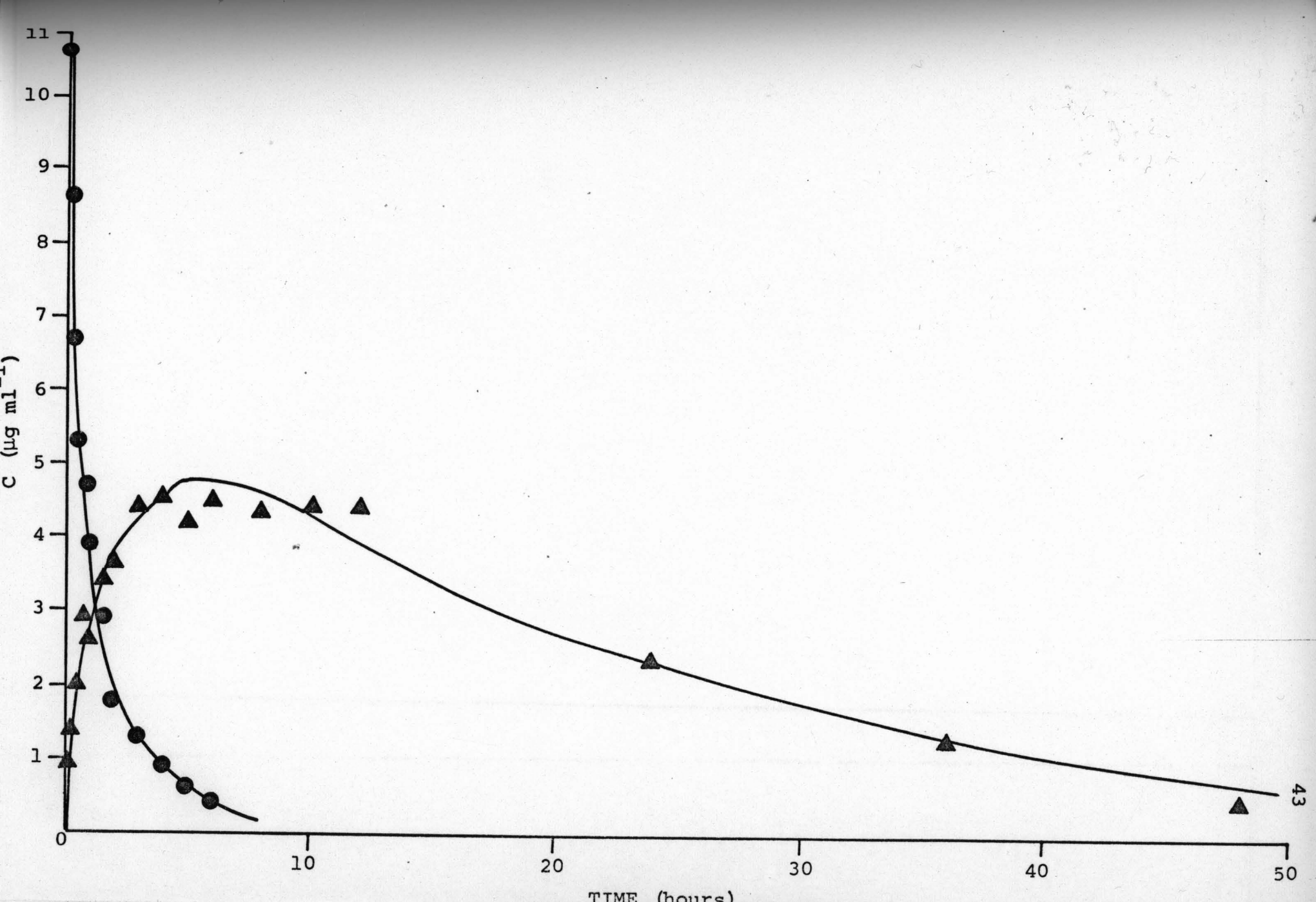

11
10
9
8
7
6
5
4
3
2
1
0
C (µg ml⁻¹)
10
20
30
40
50
TIME (hours)

Figure 10. 2-Methyl-2-phenylsuccinimide plasma level vs time profile after a 250 mg injection of this metabolite, experiment D. The equation describing the profile is $C_{M_b} = 17.1e^{-0.047t}$.

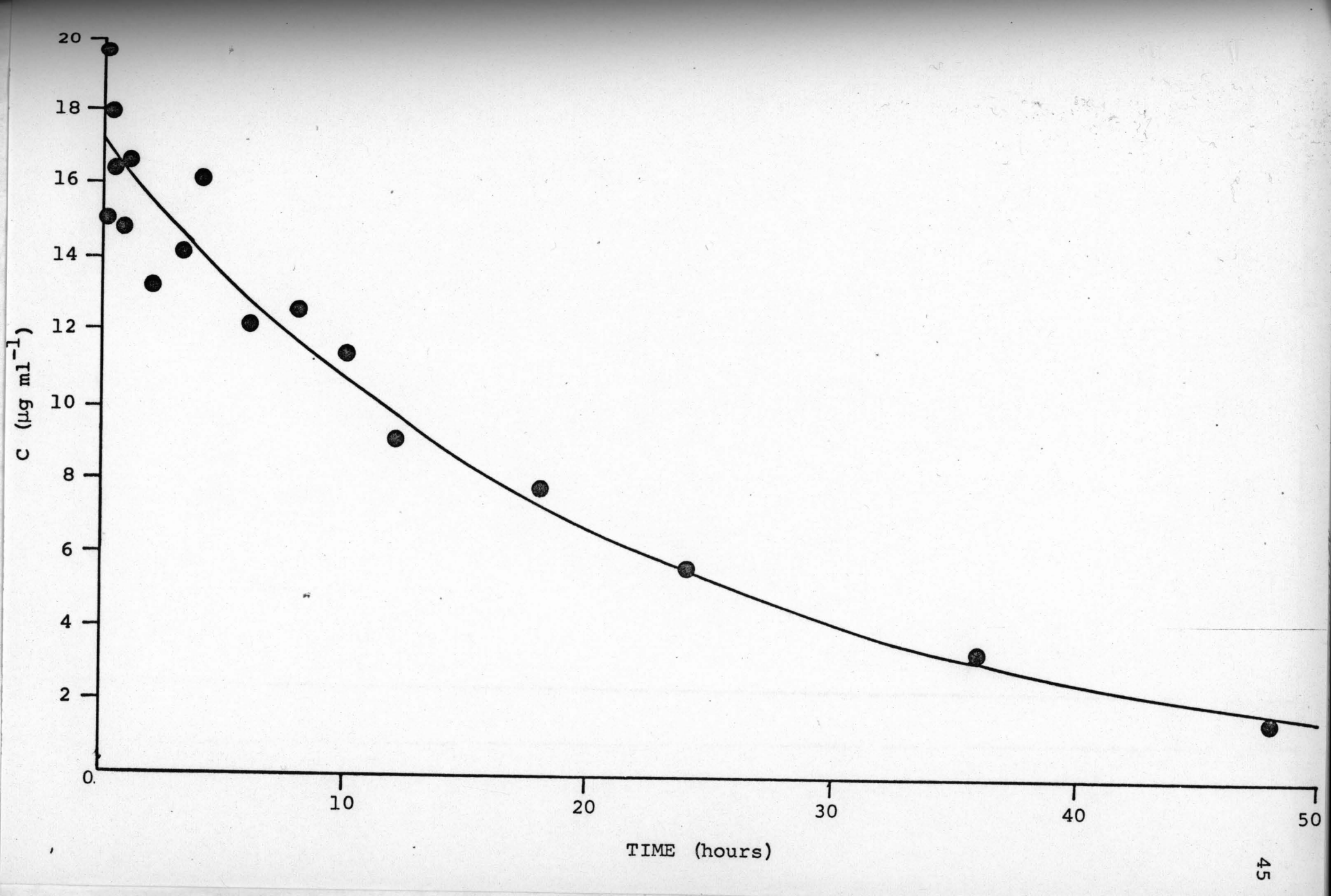
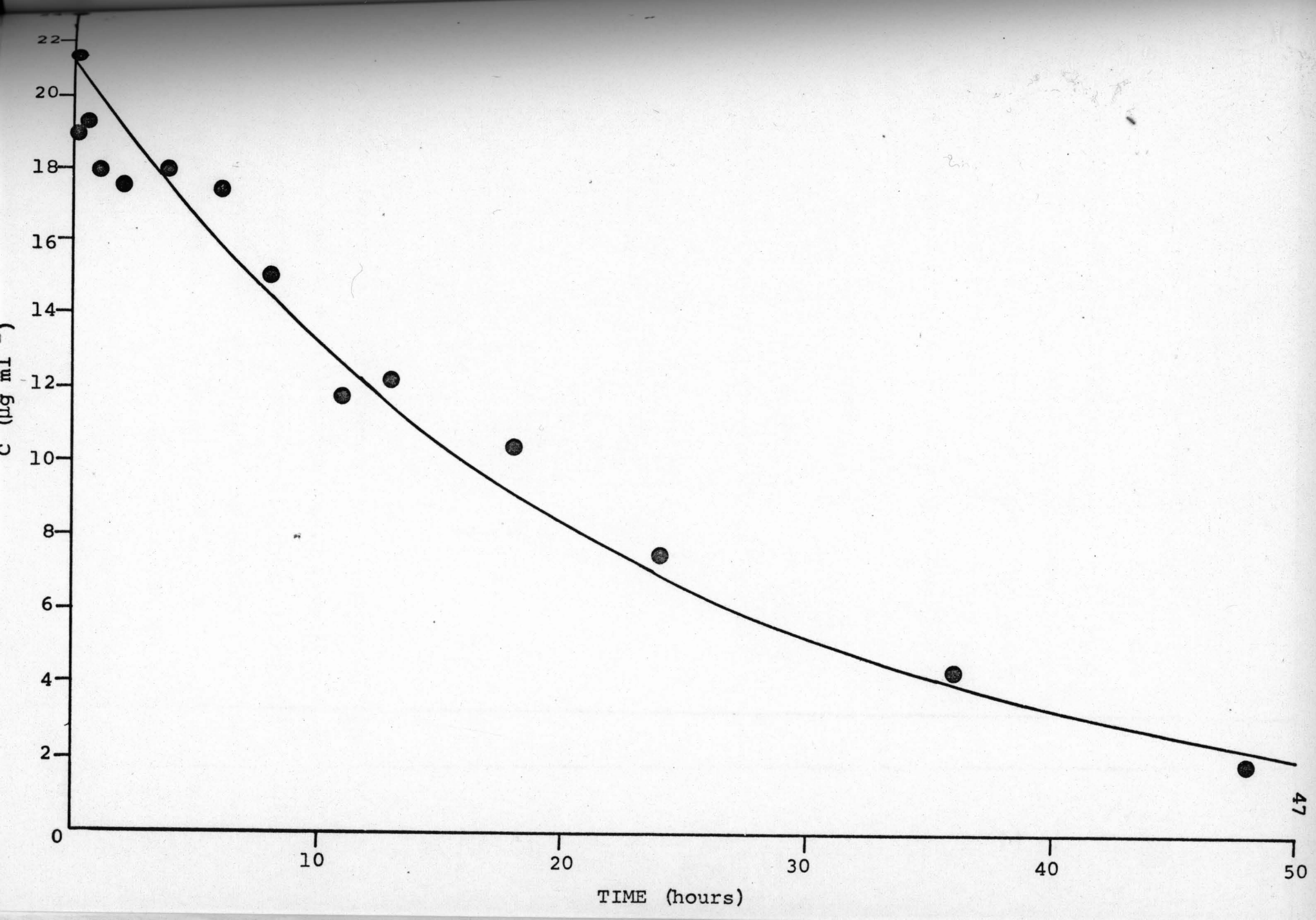

20
18
16
14
12
10
8
6
4
2
0
C (μg ml⁻¹)
10
20
30
40
50
TIME (hours)

Figure 11. 2-Methyl-2-phenylsuccinimide plasma level vs time profile after a 250 mg injection of this metabolite, experiment E. The equation describing the profile is $C_{M_b} = 21.1e^{-0.047t}$.


22
20
18
16
14
12
10
8
6
4
2
0
C (μg ml⁻¹)
10
20
30
40
50
TIME (hours)

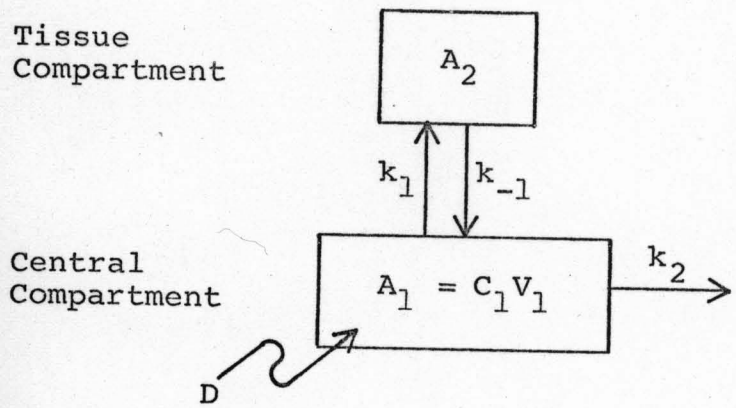
DISCUSSION

A. Methsuximide Pharmacokinetics

The methsuximide concentration vs time profiles are given in Figures 12-14 on a semilogarithmic scale. The figures indicate that the plasma level versus time profile after intravenous methsuximide is biexponential and may be analyzed in terms of the two compartment open pharmacokinetic model (20) depicted in Scheme I.

Scheme I

Two Compartment Open Model with Intravenous Injection



The model describes the instantaneous introduction of an intravenous dose of drug D into a rapidly accessible central or plasma compartment of apparent distribution volume V_1 and equilibration between the central compartment and a less readily accessible tissue compartment A_2. The quantities A_1 and A_2 refer to amounts of unchanged drug in the central and tissue compartments respectively. The disposition first

Figure 12. Semilogarithmic plot of drug concentration-time data of Table III showing biexponential decline in methsuximide plasma level. Equations are computer fits to Scheme I model using unweighted data (- - -) and data weighted by 1/C (———). The equations are $C_1 = 15.4e^{-4.01t} + 6.2e^{-0.18t}$ and $C_1 = 16.7e^{-4.71t} + 6.6e^{-0.20t}$ respectively.

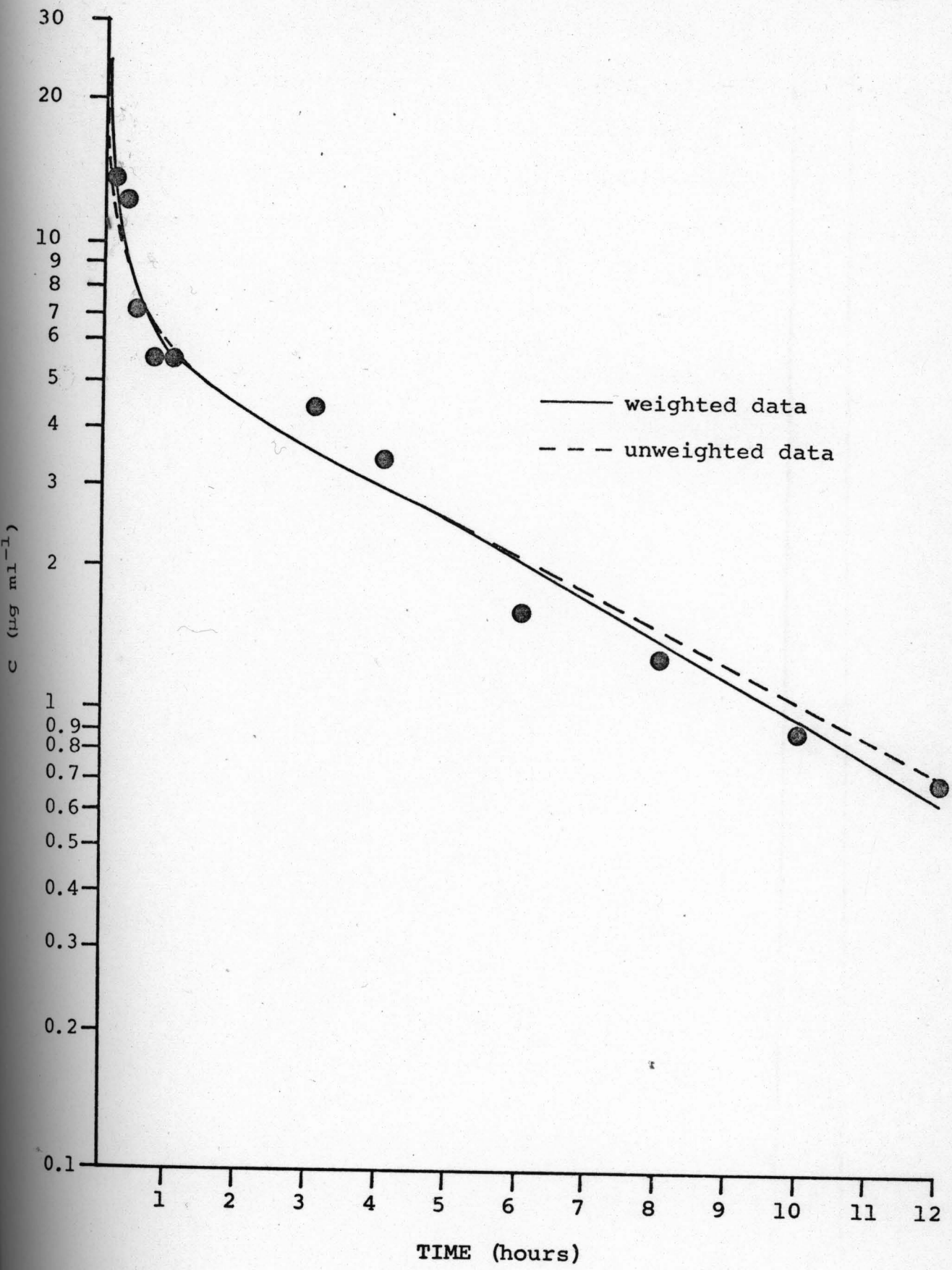

30
20
10
9
8
7
6
5
4
3
2
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
C (μg ml⁻¹)
weighted data
unweighted data
1
2
3
4
5
6
7
8
9
10
11
12
TIME (hours)

Figure 13. Semilogarithmic plot of drug concentration-time data of Table IV showing biexponential decline in methsuximide plasma level. Equations are computer fits to Scheme I model using unweighted data (- - -) and data weighted by 1/C (———). The equations are $C_1 = 12.1e^{-9.95t} + 7.7e^{-0.81t}$ and $C_1 = 11.7e^{-8.03t} + 6.8e^{-0.71t}$ respectively.

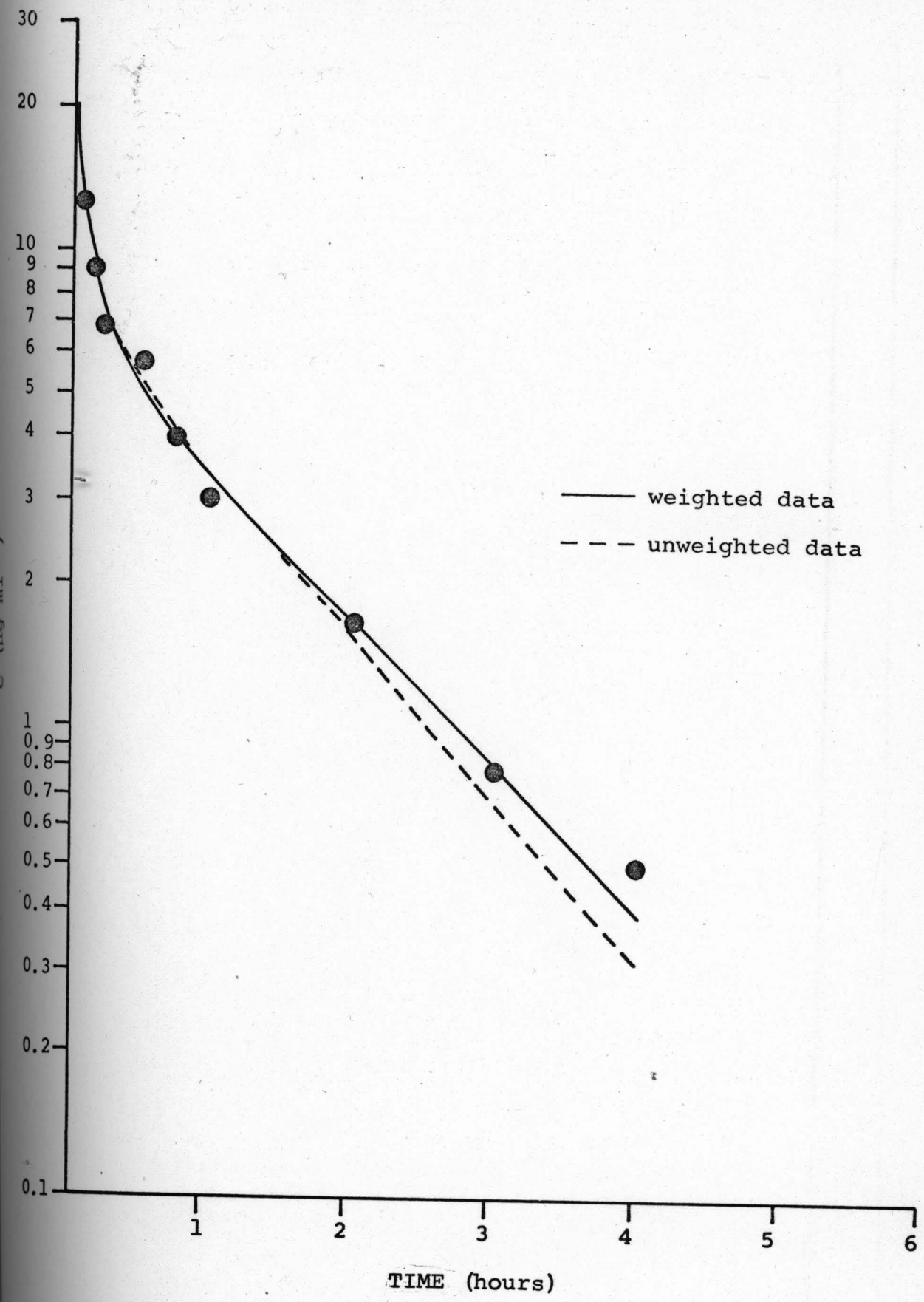
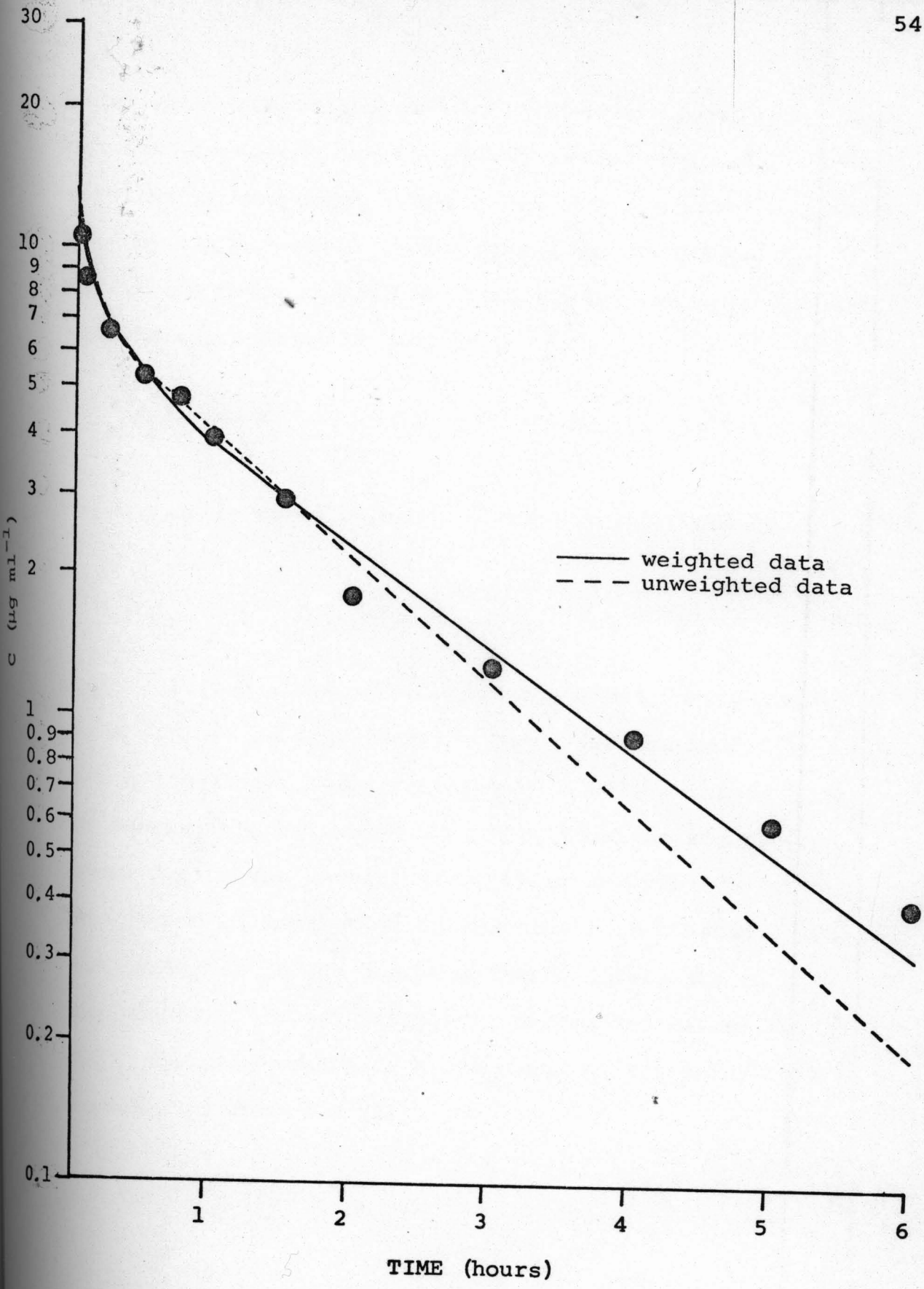

30
20
10
9
8
7
6
5
4
3
2
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
1
2
3
4
5
6
TIME (hours)
weighted data
unweighted data

Figure 14. Semilogarithmic plot of drug concentration-time data of Table V showing biexponential decline in methsuximide plasma level. Equations are computer fits to Scheme I model using unweighted data (- - -) and data weighted by 1/C (———). The equations are $C_1 = 5.3e^{-14.26t} + 7.3e^{-0.61t}$ and $C_1 = 4.9e^{-5.48t} + 6.2e^{-0.50t}$ respectively.


30
20
10
9
8
7
6
5
4
3
2
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
C (μg ml⁻¹)
weighted data
unweighted data
1
2
3
4
5
6
TIME (hours)

order rate constants k_1 and k_{-1} govern the transfer of drug between the compartments while k_2 is the first order rate constant representing loss of drug from the central compartment by all processes, i.e., excretion and metabolism. Equation 5 describes the drug plasma concentration vs time profile appropriate to this model (21).

$$C_1 = \frac{D}{V_1(\alpha - \beta)}[(\alpha - k_{-1})e^{-\alpha t} + (k_{-1} - \beta)e^{-\beta t}] \qquad \text{Eq. 5}$$

The composite rate constants α and β are defined by

$$\begin{matrix}\alpha \\ \beta\end{matrix} = \frac{1}{2}[(k_1 + k_{-1} + k_2) \pm \sqrt{(k_1 + k_{-1} + k_2)^2 - 4k_{-1}k_2}] \qquad \text{Eq. 6}$$

where β is the slope of the post-distributive log-linear phase of loss of drug from the body, divided by 2.303, and α is the log-linear slope, divided by 2.303, obtained from subtracting the extrapolated β line from the actual data points during the initial curvilinear distributive phase. This method of separating exponential rate constants has been described in the pharmacokinetic literature as 'feathering', 'curve stripping', or 'method of residuals' (21). The rate constants k_1, k_{-1} and k_2 are determined through equations 7-9 (21).

$$k_{-1} = \frac{A\beta + B\alpha}{A + B} \qquad \text{Eq. 7}$$

$$k_2 = \frac{\alpha\beta}{k_{-1}} \qquad \text{Eq. 8}$$

$$k_1 = \alpha + \beta - k_{-1} - k_2 \qquad \text{Eq. 9}$$

where A and B are the intercepts on the concentration axis of the α and β extrapolated lines, respectively. The apparent volume of distribution V_1 is determined with intravenous data by,

$$V_1 = \frac{D}{A + B} \qquad \text{Eq. 10}$$

The biological half-life $t_{1/2}$ is determined by equation 11 while T/P, the ratio of amount of drug in the tissue compartment to that in the central compartment at equilibrium, is determined by equation 12 (21).

$$t_{1/2} = \frac{0.693}{\beta} \qquad \text{Eq. 11}$$

$$T/P = \frac{k_1}{k_{-1} - \beta} \qquad \text{Eq. 12}$$

Subsequent to graphical analysis, improved estimates of all parameters together with confidence limits, correlation coefficients and coefficients of determination were obtained using the iterative nonlinear regression program NREG[a] on a digital computer[b]. Input into the computer consisted of graphical estimates of parameters together with the relevant

---

[a] With user supplied subroutine - see Appendix A for a typical NREG output.

[b] Univac 1110 digital computer, Madison Academic Computing Center, the University of Wisconsin, Madison.

equations contained in the user supplied subroutine. Table VIII gives the pharmacokinetic parameters describing the methsuximide kinetics after intravenous administration based on the computer estimates. The dashed lines in Figures 12-14 are based on these values. Computer fits of the terminal data were poor and this is especially evident in experiment C. Since NREG is a least squares fitting routine a small relative error in the higher concentration range will contribute more to the sums of squares than an equivalent error in the lower concentration range. In order to make all data points contribute equally to the sums of squares, concentrations were individually weighted by the factor 1/C. The computer estimated parameters with weighted data are given in Table IX while the computer fits are the solid lines in Figures 12-14. The fits resulting from the weighted data were judged better than those from the unweighted data on the basis of the overall statistical computer outputs (sums of squares, correlation matrix, confidence limits on linear hypothesis, exploration, graph of residuals, R^2, r, etc. - see Appendix A). Table IX indicates that the distribution characteristics of methsuximide, k_1, k_{-1}, α, V_1 and T/P, differed between the two dogs although they were similar orders of magnitude. There was more rapid equilibration of drug between the two compartments in Dog B (α, k_1, k_{-1}) while Dog A had a greater amount of drug in the tissue compartment at equilibrium than Dog B (T/P). The elimination characteristics, k_2, β and $t_{1/2}$, also differed between the two dogs. Dog A eliminated

Table VIII

Methsuximide Computer Estimated Pharmacokinetic Parameters Using Unweighted Data

	Experiment A, Dog A	Experiment B, Dog B	Experiment C, Dog B
D mg	250	250	250
V_1 l	11.6	12.6	19.8
D/V_1 mg l^{-1}	21.5 (15.0-28.1)[a]	19.8 (15.0-24.5)	12.6 (11.2-14.1)
A $\mu g\ ml^{-1}$	15.4	12.2	5.3
B $\mu g\ ml^{-1}$	6.2	7.7	7.4
α hr^{-1}	4.01	9.95	14.26
β hr^{-1}	0.18	0.81	0.61
$t_{1/2}$ hrs	3.85	0.85	1.14
k_1 hr^{-1}	2.34(0.64-4.05)	4.55 (1.53-7.57)	5.29 (1.96-8.63)
k_{-1} hr^{-1}	1.28 (0.43-2.13)	4.35 (2.08-6.62)	8.55 (4.70-12.40)
k_2 hr^{-1}	0.56 (0.33-0.79)	1.86 (1.30-2.42)	1.02 (0.87-1.17)
T/P	2.13	1.28	0.67
R^2	0.9935	0.9980	0.9987
r	0.9919	0.9975	0.9985

[a] 95% confidence intervals.

Table IX

Methsuximide Computer Estimated Pharmacokinetic Parameters

Where Each Concentration was Weighted by 1/Concentration

	Experiment A, Dog A	Experiment B, Dog B	Experiment C, Dog B
D mg	250	250	250
V_1 l	10.7	13.5	22.5
D/V_1 mg l^{-1}	23.3 (12.9-33.7)	18.5 (13.4-23.6)	11.1 (9.6-12.6)
A $\mu g\ ml^{-1}$	16.7	11.7	4.9
B $\mu g\ ml^{-1}$	6.6	6.8	6.2
α hr^{-1}	4.71	8.03	5.48
β hr^{-1}	0.20	0.71	0.50
$t_{1/2}$ hrs	3.47	0.98	1.39
k_1 hr^{-1}	2.80 (0.32-5.29)	3.67 (1.02-6.32)	1.86 (0.074-3.65)
k_{-1} hr^{-1}	1.47 (0.69-2.26)	3.40 (1.89-4.91)	3.28 (0.73-5.82)
k_2 hr^{-1}	0.63 (0.35-0.91)	1.67 (1.21-2.13)	0.84 (0.70-0.97)
T/P	2.20	1.36	0.67
R^2	0.9930	0.9977	0.9972
r	0.9913	0.9970	0.9964

and/or metabolized methsuximide more slowly. Differences were observed in parameters from experiments B and C in the same dog. This was not unexpected since the time period between experiments exceeded two months. For this reason each experiment was considered separately.

The rate constant k_2 reflects excretion of unchanged methsuximide by any route and biotransformation to any metabolite. Since the 2-methyl-2-phenylsuccinimide was specifically quantitated in all methsuximide experiments it was possible to separate k_2 into components representing 1) formation of 2-methyl-2-phenylsuccinimide and 2) elimination of unchanged methsuximide and formation of any other metabolites. A previous report (11) indicated that no unchanged methsuximide was found in 48 hour dog urine so that k_2 primarily reflects biotransformation of methsuximide. Elimination by routes other than into urine (saliva, bile, etc.) is also possible. Before the 2-methyl-2-phenylsuccinimide data could be incorporated into Scheme I its apparent distribution volume V_3 and individual pharmacokinetic model had to be obtained. This was accomplished by intravenous dosing of pure 2-methyl-2-phenylsuccinimide.

B. 2-Methyl-2-phenylsuccinimide (Metabolite) Pharmacokinetics

Figures 15 and 16 are semilogarithmic plots of data sets D and E (Tables VI-VII) obtained from intravenous metabolite experiments in Dog B on two separate occasions. Multiple blood samples during the first hour were necessary to

Figure 15. Semilogarithmic plot of metabolite concentration-time data of Table VI showing monoexponential decline in metabolite plasma level in dog B after dosing this compound. The linear regression equation including the 95% confidence limits on the slope and intercept is $\log C = -0.0205 (\pm 0.0015)t + 1.2326 (\pm 0.0261)$.

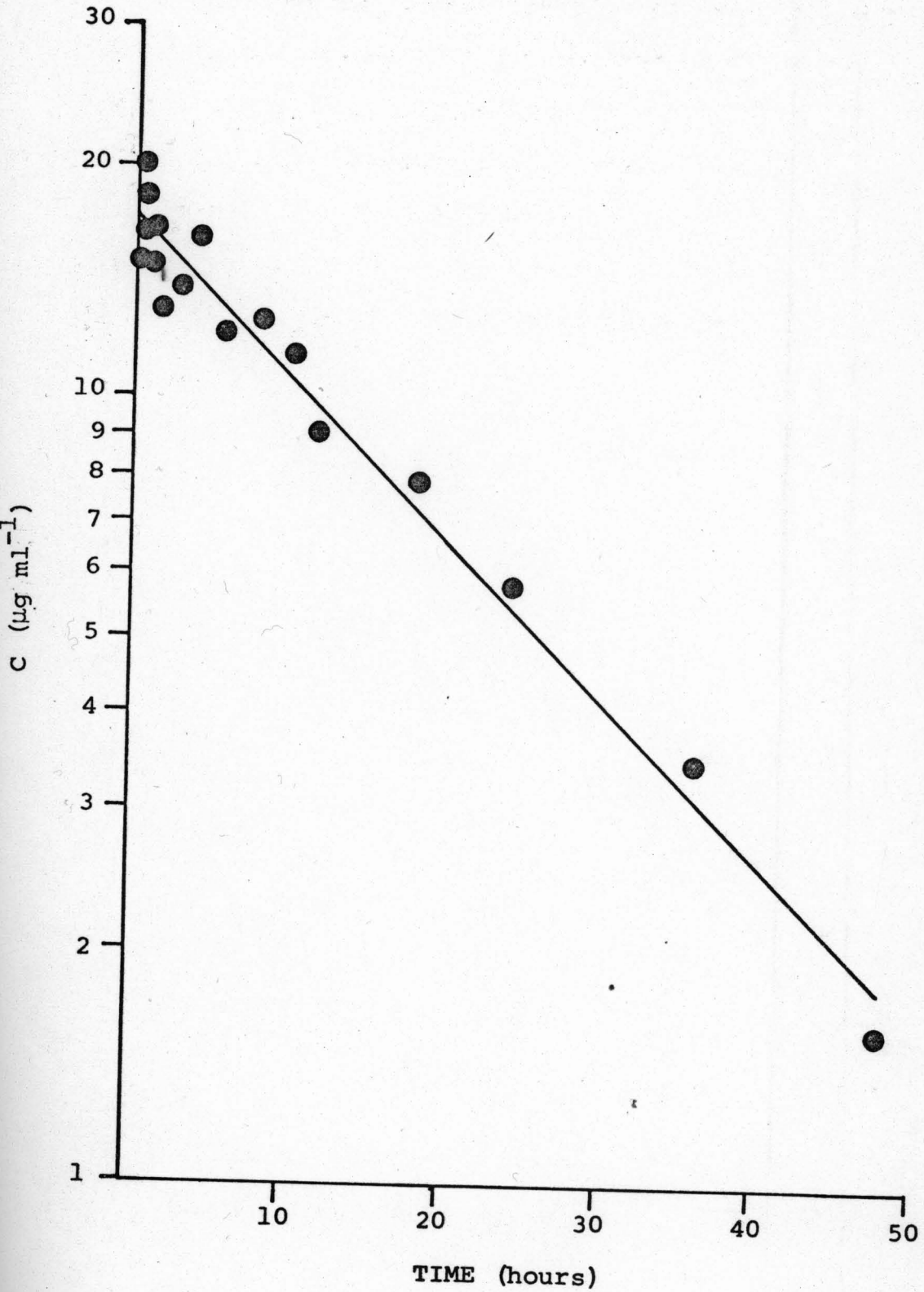
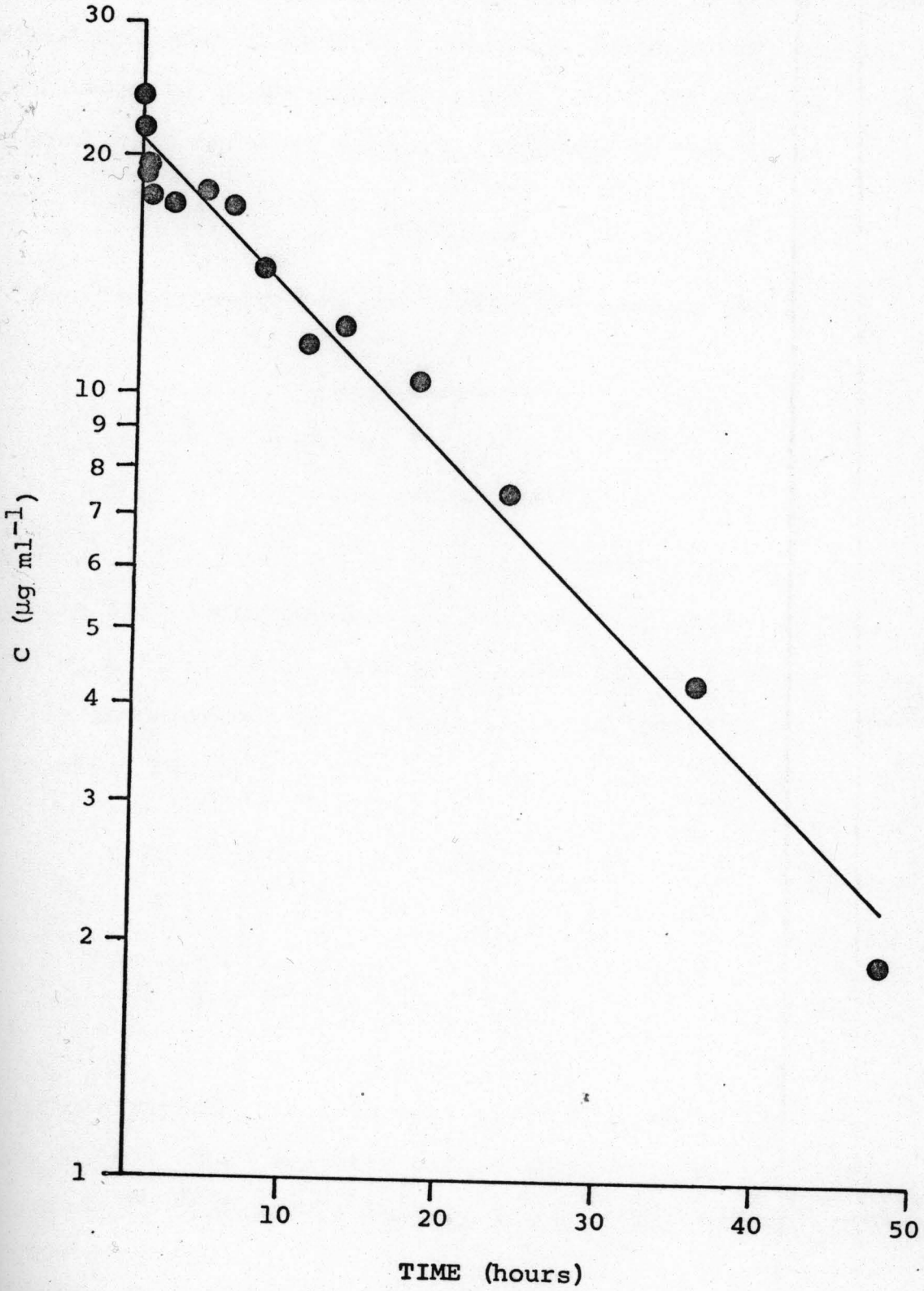

30
20
10
9
8
7
6
5
4
3
2
1
c (μg ml⁻¹)
10
20
30
40
50
TIME (hours)

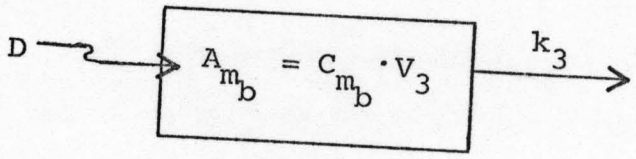
Figure 16. Semilogarithmic plot of metabolite concentration-time data of Table VII showing monoexponential decline in metabolite plasma level in dog B after dosing this compound. The linear regression equation including the 95% confidence limits on the slope and intercept is log C = $-0.0203 (\pm 0.0017)t + 1.3245 (\pm 0.0314)$.


30
20
10
9
8
7
6
5
4
3
2
1
C (μg ml⁻¹)
10
20
30
40
50
TIME (hours)

ascertain whether the metabolite obeyed one-, two-, or multi-compartment model kinetics. There was insufficient initial curvilinearity in the data to justify more than the one compartment open model as depicted in Scheme II (21).

Scheme II

One Compartment Open Model with Intravenous Injection



The dose D of metabolite is instantaneously injected into an apparent distribution volume V_3 and excreted and/or metabolized by a first order process k_3. The plasma level *vs* time profile is described by equation 13 or in logarithmic form by equation 14 (21).

$$C_{m_b} = \frac{D}{V_3} e^{-k_3 t} \qquad \text{Eq. 13}$$

$$\log C_{m_b} = \log \frac{D}{V_3} - \frac{k_3}{2.303} t \qquad \text{Eq. 14}$$

The concentration axis intercept gives D/V_3 while the slope is $-k_3/2.303$. The parameter values obtained from the linear regressions[a], included in Figures 15-16, are summarized in

[a] Performed on a Compucorp 344 Statistician Micro-Computer, Computer Design Corp., Los Angeles, California.

Table X and regression ANOVA data are summarized in Table XI.

As was expected, the biological half-life, equation 15, was long

$$t_{1/2} = \frac{0.693}{k_3} \qquad \text{Eq. 15}$$

and was identical in the two experiments. The apparent distribution volumes were similar.

Since the appropriate pharmacokinetic models were thus established for both the methsuximide and metabolite data independently the drug and metabolite data from experiments A, B and C were analyzed as described below.

C. Methsuximide Pharmacokinetics Including Formation of the Metabolite, 2-Methyl-2-phenylsuccinimide

1. Development of the Model

Scheme III depicts the model representing intravenous administration of methsuximide with subsequent formation of the metabolite 2-methyl-2-phenylsuccinimide, where D is the amount of methsuximide intravenously administered, k_1 and k_{-1} are as previously defined, k_2 is the first order rate constant describing excretion and metabolism, other than to 2-methyl-2-phenylsuccinimide, k_f is the first order rate constant describing formation of the metabolite and k_3 is the first order rate constant representing excretion and/or further metabolism of 2-methyl-2-phenylsuccinimide.

The differential equations 16-18 describe the rate of

Table X

2-Methyl-2-phenylsuccinimide Pharmacokinetic Parameters

	D/V_3 (mg/l)	V_3 (l)	k_3 (hr^{-1})	$t_{1/2}$ (hr)
Experiment D	17.08	14.63	0.047	14.68
Experiment E	21.11	11.84	0.047	14.68

Table XI

ANOVA for Metabolite Linear Regressions

Experiment D

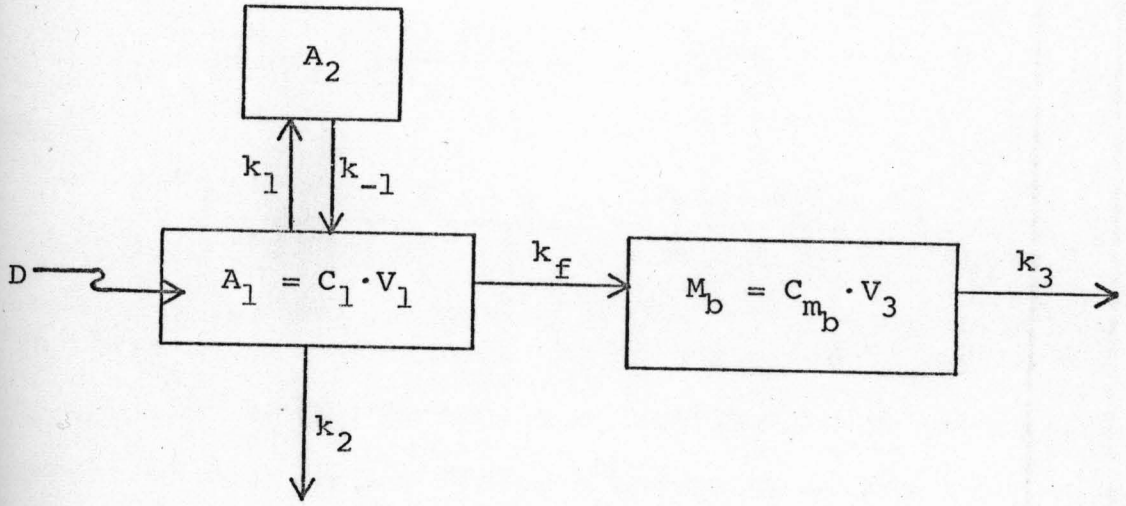
Source	SS	df	MS
regression	1.2993	1	1.2993
residual	0.0244	15	0.0016
total	1.3237	16	

Experiment E

Source	SS	df	MS
regression	1.2121	1	1.2121
residual	0.0247	13	0.0019
total	1.2368	14	

Scheme III

Model for a Drug Which Obeys Two Compartment Kinetics With a Metabolite Obeying One Compartment Kinetics



change of drug amounts in the various compartments as a function of time.

$$\frac{dA_1}{dt} = k_{-1}A_2 - (k_1 + k_f + k_2)A_1 \qquad \text{Eq. 16}$$

$$\frac{dA_2}{dt} = k_1A_1 - k_{-1}A_2 \qquad \text{Eq. 17}$$

$$\frac{dM_b}{dt} = k_fA_1 - k_3M_b \qquad \text{Eq. 18}$$

The differential equations were integrated using Laplace transformations and matrix algebra, as described in Appendix B, to yield equations 19-21.

$$A_1 = \frac{D}{(\alpha - \beta)} \left\{ (k_{-1} - \beta)e^{-\beta t} - (k_{-1} - \alpha)e^{-\alpha t} \right\} \quad \text{Eq. 19}$$

$$A_2 = \frac{Dk_1}{(\alpha - \beta)} (e^{-\beta t} - e^{-\alpha t}) \quad \text{Eq. 20}$$

$$M_b = \frac{189}{203} Dk_f \left\{ \left[\frac{k_{-1} - \alpha}{(k_3 - \alpha)(\beta - \alpha)} \right] e^{-\alpha t} + \right. \quad \text{Eq. 21}$$

$$\left. \left[\frac{k_{-1} - \beta}{(k_3 - \beta)(\alpha - \beta)} \right] e^{-\beta t} + \left[\frac{k_{-1} - k_3}{(\beta - k_3)(\alpha - k_3)} \right] e^{-k_3 t} \right\}$$

In these equations amounts can be converted to concentrations by dividing by the appropriate distribution volumes. The amount of drug in the tissue compartment at any time (equation 20) can only be calculated in this study since drug concentrations were determined only from the central compartment. Since the D in equation 21 is the dose of methsuximide then the factor 189/203, which is the ratio of molecular weights of metabolite:methsuximide, was necessary to convert μg of methsuximide to μg of metabolite. The composite rate constants α and β are defined by equation 22 which is analogous to equation 6.

$$\begin{matrix} \alpha \\ \beta \end{matrix} = \frac{1}{2} \left\{ (k_1 + k_f + k_2 + k_{-1}) \pm \right.$$

$$\left. \sqrt{(k_1 + k_f + k_2 + k_{-1})^2 - 4(k_{-1}k_f + k_2k_{-1})} \right\} \quad \text{Eq. 22}$$

Equation 19 is identical to equation 5 with the k_2 of Scheme I explicitly separated into $k_2 + k_f$ in Scheme III. The

equation describing the concentration of metabolite in the body, equation 21, is triexponential indicating its dependence on the methsuximide biexponential process, equation 5, and its own monoexponential process, equation 13.

The stripping of triexponential curves is known to be an inaccurate procedure (22). In the case of the metabolite plasma levels vs time profiles, experiments A, B and C, however, initial estimates of some parameter values were provided by the final computer estimates from the methsuximide analysis, Table IX. Initial estimates of the rate constants α, β and k_{-1} were obtained in this fashion. There are two ways to obtain estimates of k_3. First, k_3 can be estimated from the independent metabolite experiments or second, from the log-linear portion of equation 21. Since, in equation 21, $\alpha > \beta > k_3$ there existed a time such that $e^{-\alpha t}$ and $e^{-\beta t}$ were insignificant relative to $e^{-k_3 t}$ so that after this time equation 21 became log-linear with slope equal to $-k_3/2.303$. The volume V_3 was estimated using the average V_3's from experiments D and E. Initial estimates of k_f were obtained by comparison of areas under the metabolite and methsuximide plasma level profiles from each methsuximide experiment. The area under the C_1 curve was obtained by integration of equation 19 as

$$\text{area } C_1 = \int_0^\infty C_1 dt \qquad \text{Eq. 23}$$

resulting in equation 24 (20).

$$\text{area } C_1 = \frac{Dk_{-1}}{V_1 \alpha\beta} \qquad \text{Eq. 24}$$

The area under the metabolite curve was similarly given by equations 25 and 26 (see Appendix C).

$$\text{area } C_{m_b} = \int_0^{\infty} C_{m_b} dt \qquad \text{Eq. 25}$$

$$= \frac{189 k_f k_{-1} D}{203 V_3 k_3 \alpha\beta} \qquad \text{Eq. 26}$$

so that

$$k_f = \frac{203 V_3 k_3}{189 V_1} \cdot \frac{\text{area } C_{m_b}}{\text{area } C_1} \qquad \text{Eq. 27}$$

These areas are from t_0 to t_∞ so that the area under the curve from the time of the final data point C_f to infinity had to be calculated. If the C_f's are at long enough times, t_f, such that equations 19 or 21 have become essentially monoexponential, then the concentrations after time t_f are given by:

$$C_1 = C_f' e^{-\beta t}$$

and

$$C_{m_b} = C_f'' e^{-k_3 t} \qquad \text{Eq. 28}$$

where C_f' and C_f'' represent the terminal data points for unchanged drug and metabolite, respectively. Integration from t_f to t_∞ then yields:

$$\text{terminal methsuximide areas} = \frac{C_f'}{\beta}$$

$$\text{Terminal metabolite areas} = \frac{C_f''}{k_3} \qquad \text{Eq. 29}$$

The areas from time zero to t_f were determined by the trapezoidal rule. The remaining parameter k_2 was estimated using equation 30

$$k_2 = \frac{\alpha\beta - k_{-1}k_f}{k_{-1}} \qquad \text{Eq. 30}$$

which is obtained from the product of α and β (equation 22).

The methsuximide and metabolite data, experiments A, B and C, were simultaneously fitted, using the program NREG, to equations 19 and 21. Initial estimates of parameters are given in Table XII.

2. NREG Computer Results

When all seven parameter values (Table XII) were allowed to float in the program wide confidence intervals were obtained for k_2, k_f and D/V_3. High correlations ($r > 0.80$) existed between these parameters. Since the independent metabolite experiments (Table XI) and curve stripping of metabolite data from experiments B and C yielded nearly

Table XII

Initial Estimates of Scheme III Parameters

Parameter[a]	Experiment A	Experiment B	Experiment C	Source
k_1	2.80	3.67	1.86	Table IX
k_{-1}	1.47	3.40	3.28	Table IX
k_2	0.38	0.96	0.55	Eq. 30
k_f	0.26	0.72	0.29	Eq. 27
k_3	0.047	0.047	0.047	Table XI[b]
D/V_1	23.3	18.5	11.1	Table IX
D/V_3	18.9	18.9	18.9	Table XI

[a] Units of all rate constants = hr^{-1}; units of D/V = $\mu g\ ml^{-1}$.

[b] For experiments B and C the terminal log linear form of eq. 21 yielded k_3 values of 0.047 and 0.050 hr^{-1} respectively.

identical values of k_3, and since the value of D/V_3 was accurately determined from experiments D and E these parameters were fixed during the computer analysis. This procedure significantly reduced the 95% confidence intervals while causing only slight changes in the values of the remaining parameters.

The computer was unable to satisfactorily fit the metabolite data from data set A regardless of whether parameters were fixed or not. The primary reason for this failure was that this experiment was terminated at 12 hours. The values of α, β and k_3 were such that equation 21 never became monoexponential. The rate constant k_3 could not therefore be computer determined and k_f, calculated with equation 27, was in error because equation 29 was not applicable. Another reason for this failure is that the initial estimate of D/V_3 was based on experiments in Dog B whereas data set A was from Dog A. Since the Table IX parameters show variability between data sets the assumption that V_3 was the same in both dogs was tenuous.

The final computer estimates of experiment B and C parameters are listed in Table XIII with relevant statistics and derived pharmacokinetic parameters. The solid lines in Figures 7-9 are the computer fits to the plasma level vs time equations as specified with the exception of the Figure 7 metabolite profile which is hand drawn. All data was weighted by the factor 1/C.

It is noteworthy that the incorporation of the

Table XIII

Summary of Pharmacokinetic Computer Estimated Scheme III Parameters

Parameter	Data Set B	Data Set C
k_1 (hr^{-1})	3.84 (0.52-7.17)[a]	0.71 (0.20-1.23)
k_{-1} (hr^{-1})	3.80 (1.92-5.68)	1.14 (0.26-2.02)
k_2 (hr^{-1})	1.01 (0.69-1.33)	0.50 (0.42-0.58)
k_f (hr^{-1})	0.77 (0.54-1.00)	0.28 (0.24-0.31)
k_3 (F)[b] (hr^{-1})	0.047	0.047
D/V_1 ($\mu g\ ml^{-1}$)	18.9 (12.8-25.0)	10.4 (9.3-11.5)
D/V_3 (F)[b] ($\mu g\ ml^{-1}$)	18.9	18.9
V_1 (l)	13.2	24.0
V_3 (l)	13.2	13.2
α (hr^{-1})	8.64	2.24
β (hr^{-1})	0.78	0.40
$t_{1/2}$ (methsuximide)	0.89	1.73
$t_{1/2}$ (metabolite)	14.74	14.74
Initial sums of squares	0.86	1.13
Final sums of squares	0.78	1.01

Table XIII (continued)

Parameter	Data Set B	Data Set C
R^2 (methsuximide)	0.9979	0.9937
r (methsuximide)	0.9951	0.9931
R^2 (metabolite)	0.9919	0.9914
r (metabolite)	0.9933	0.9928
R^2 (overall)	0.9950	0.9928

[a]95% confidence interval.

[b]Indicates parameter was fixed.

metabolite equation in the computer program did not significantly alter the methsuximide parameters (cf. Table IX). Of particular interest is the relative importance of the rate of biotransformation of methsuximide to the pharmacologically active and potentially toxic 2-methyl-2-phenylsuccinimide, k_f, compared to the overall elimination and metabolism rate constants, $k_f + k_2$. This metabolic step accounted for 43 and 36% of the overall elimination of methsuximide in the two experiments. The large value of k_f together with the small k_3 (long half-life) leads to a metabolite plasma level profile after a single intravenous dose of methsuximide which mirrors a prolonged sustained release type profile. Figures 7-9 indicate that the metabolite appeared in the dog's plasma in less than five minutes after intravenous methsuximide dosing. Since methsuximide is orally administered on a daily basis to petit mal patients there may be significant accumulation of the metabolite in the body with multiple dosing regimens.

Methsuximide administration results in induction of hepatic drug metabolizing enzymes (5, 6). It has been observed in patients on chronic methsuximide therapy that this 'auto-induction' process is so marked that 2-methyl-2-phenylsuccinimide is the only drug related compound detected in blood after repeated oral methsuximide administration, even shortly after dosing (23). The possibility exists that the metabolite may be partially or totally responsible for the enzyme induction. If this were the case, then both rate

constants, k_f and k_3, may increase after repeated exposure to methsuximide. If k_3 were to increase then accumulation of metabolite in the body would be reduced. The above problem could be elucidated pharmacokinetically through multiple dosing experiments with methsuximide and 2-methyl-2-phenylsuccinimide. However, since several other metabolites have been found in dog plasma (11) a complete pharmacokinetic analysis would require administration of each metabolite individually. This is the approach for which further experiments should be designed.

APPENDIX A

Example of Computer Output Using the Program NREG

```
1234567890123456789012345678901234567890123456789012345678901234567890123456789012345678901234567890**SEQ NO. 01
1234567890123456789012345678901234567890123456789012345678901234567890123456789012345678901234567890**SEQ NO. 01
1234567890123456789012345678901234567890123456789012345678901234567890123456789012345678901234567890**SEQ NO. 01
1234567890123456789012345678901234567890123456789012345678901234567890123456789012345678901234567890**SEQ NO. 01
 *     *     *     *     *     *  UNIVAC 1110 TIME/SHARING EXEC --- MULTI-PROCESSOR SYSTEM --- VER.  MACC 31.48  SITE *  @ MACC     *     *     *     *     *     *
     RUNID * B15365      FILE NAME * PR@000B15365      PART NUMBER *  00     DATE * 073075       DEVICE NAME *  PR2

@RUN,/R DOBRINSKA,41000,3895003204,5M,200/50
@FOR,SI      ,MAIN
FORTRAN-MACC 1.145-07/30/75-13:27:17            MAIN
00101     1.          PARAMETER
00101     2.         1NEXPD = 50,
00101     3.         2NVAR = 1,
00101     4.         3NPD = 7,
00101     5.         4NROBS = NEXPD,
00101     6.         5NRPRD = NEXPD,
00101     7.         6NS=(17+NEXPD*NVAR)*NPD+2*NRPRD*NVAR+2*(NPD+1)*(NPD+2)+1
00102     8.          REAL THINT(NPD),THFIN(NPD),YOBS(NROBS,NVAR),YPRD(NROBS,NVAR),S(NS)
00102     9.         1,TOL(4),T(NEXPD),BNDLO(NPD),BNDHI(NPD),NAMES(NPD),DIFF(NPD),FIX(NP
00102    10.         2D),WTS(NROBS,NVAR)
00103    11.          INTEGER ITEMS(12),INFO(7),IDENT(13),NEXP,NP
00104    12.          COMMON T
00105    13.          COMMON/LIM/NEXP1,NEXP2,K,AL,BE
00106    14.          DATA FIX/4*1.0,1*0.0,1*1.0,1*0.0/
00110    15.          DATA DIFF/7*0.001/
00112    16.          DATA BNDLO/7*1.0E-4/
00114    17.          DATA BNDHI/7*1.0E4/
00116    18.          DATA NAMES/6HK1    ,6HK-1   ,6HK2    ,6HKE    ,6HK3    ,6HDV1   ,6
00116    19.         1DV3    /
00120    20.          DATA TOL/1.5E-6,1.0E-9,0.0,1.0E-16/
00122    21.          DATA INFO/1,10,5*1/
00124    22.          DATA ITEMS/
00124    23.         11,NVAR,1,NROBS,NRPRD,NROBS,'MARQ','ALL','NREG','CENT','REL',50/
00126    24.          READ(5,110) (IDENT(I), I=1,13)
00134    25.      110 FORMAT(13A6)
00135    26.          READ (5,120) NEXP1,NEXP2,NP
00142    27.      120 FORMAT(2X,I3,2X,I3,3X,I2)
00143    28.          NEXP = NEXP1 + NEXP2
00144    29.          ITEMS(1) = NEXP
00145    30.          ITEMS(3)=NP
00146    31.          READ(5,100)( THINT(I), I=1,NP )
00154    32.          READ (5,100) (YOBS(I,1),I=1,NEXP1)
00162    33.          READ(5,100)  (WTS(I,1),I=1,NEXP1)
00170    34.          READ (5,100) (T(I), I = 1,NEXP1)
00176    35.          K = NEXP1+ 1
00177    36.          IF (K.GE.NEXP) GO TO 66
00201    37.          READ (5,100) (YOBS(I,1),I=K,NEXP)
00207    38.          READ(5,100)  (WTS(I,1),I=K,NEXP)
00215    39.          READ (5,100) (T(I),I=K,NEXP)
00223    40.       66 CONTINUE
00224    41.      100 FORMAT(8F10.5)
00225    42.          EXTERNAL F,DERIV
00226    43.          CALL NREG(THINT,NAMES,BNDLO,BNDHI,FIX,DIFF,THFIN,YOBS,YPRD,
00226    44.         1WTS,F,'NONE',ITEMS,TOL,INFO,IDENT,S)
00227    45.          CALL OUTPUT(NEXP,NEXPD,THFIN,NVAR,NP,NRPRD,YPRD,YOBS)
00230    46.          END

     END OF COMPILATION:        NO DIAGNOSTICS.
@FOR,SI    , SUBF
FORTRAN-MACC 1.145-07/30/75-13:27:41            SUBF
00101     1.          SUBROUTINE F(TH,Y,NEXP,NVAR,NP,NRPRD)
```

```
00102     2.          DIMENSION TH(1),Y(NRPRD,1),T(1)
00103     3.          COMMON T
00104     4.          COMMON/LIM/NEXP1,NEXP2,K,AL,BE
00105     5.          TH1 = TH(1)
00106     6.          TH2 = TH(2)
00107     7.          TH3 = TH(3)
00110     8.          TH4 = TH(4)
00111     9.          TH5 = TH(5)
00112    10.          TH6 = TH(6)
00113    11.          TH7 = TH(7)
00114    12.          AL = 0.5*((TH1+TH4+TH3+TH2)+SQRT((TH1+TH4+TH3+TH2)**2-4*(TH2*TH4+T
00114    13.         1H3*TH2)))
00115    14.          BE = 0.5*((TH1+TH4+TH3+TH2)-SQRT((TH1+TH4+TH3+TH2)**2-4*(TH2*TH4+T
00115    15.         1H3*TH2)))
00116    16.          DO 10 I = 1,NEXP1
00121    17.       10 Y(I,1) = (TH6/(AL-BE))*((TH2-BE)*EXP(-BE*T(I))-(TH2-AL)*EXP(-AL*T
00121    18.         1(I)))
00123    19.          IF( K.EQ.NEXP ) GO TO 30
00125    20.           DO 20 I = K,NEXP
00130    21.       20 Y(I,1)=189./203.*TH7*TH4*(((TH2-AL)/((TH5-AL)*(BE-AL)))*EXP(-AL*T
00130    22.         1(I))+((TH2-BE)/((AL-BE)*(TH5-BE)))*EXP(-BE*T(I)))+((TH2-TH5)/((BE-
00130    23.         2TH5)*(AL-TH5)))*EXP(-TH5*T(I)))
00132    24.       30 CONTINUE
00133    25.          RETURN
00134    26.          END

      END OF COMPILATION:       NO  DIAGNOSTICS.
$FOR,SI      ,OTP
FORTRAN-MACC 1.14S-07/30/75-13:27:58                    OTP
00101     1.          SUBROUTINE OUTPUT(NEXP,NEXPD,THFIN,NVAR,NP,NRPRD,YPRD,YOBS)
00102     2.          DIMENSION T(1),YOBS(1),YPRD(1)
00103     3.          COMMON T
00104     4.          COMMON/LIM/NEXP1,NEXP2,K,AL,BE
00105     5.          K = 0
00106     6.       200 CONTINUE
00107     7.          SO2 = 0.0
00110     8.          SP2 = 0.0
00111     9.          SC = 0.0
00112    10.          SYOBS = 0.0
00113    11.          SDEV = 0.0
00114    12.          COR = 0.0
00115    13.          RS = 0.0
00116    14.          YOM = 0.0
00117    15.          YPM = 0.0
00120    16.          K = K + 1
00121    17.          IF (K.EQ.1) GO TO 210
00123    18.          LL = NEXP1 + 1
00124    19.          LU = NEXP
00125    20.          GO TO 250
00126    21.       210 LL = 1
00127    22.           LU = NEXP1
00130    23.       250 DO 10 I = LL,LU
00133    24.          SYOBS = SYOBS + YOBS(I)**2
00134    25.          SDEV = SDEV + (YOBS(I)-YPRD(I))**2
00135    26.          YOM=YOM+YOBS(I)
00136    27.          YPM=YPM+YPRD(I)
00137    28.       10 CONTINUE
```

```
00141     29.          RS = (SYOBS-SDEV)/SYOBS
00142     30.          YOM=YOM/NEXP
00143     31.          YPM=YPM/NEXP
00144     32.          DO 20 I=1,NEXP
00147     33.          SC = SC+(YOBS(I)-YOM)*(YPRD(I)-YPM)
00150     34.          SO2 = SO2 + (YOBS(I)-YOM)**2
00151     35.          SP2 = SP2 + (YPRD(I)-YPM)**2
00152     36.       20 CONTINUE
00154     37.          COR = SC/(SQRT(SO2)*SQRT(SP2))
00155     38.          WRITE(6,100) K,RS,K,COR
00163     39.      100 FORMAT(1HO,'R-SQUARED FOR FUNCTION',I1,' =',F6.4/1X,'COR FOR FUNCT
00163     40.         1ION',I1,' =',F6.4)
00164     41.          IF (NEXP2.EQ.0) GO TO 66
00166     42.          IF(K.GT.1) GO TO 300
00170     43.          SYOBS1 = SYOBS
00171     44.          SDEV1 = SDEV
00172     45.          GO TO 200
00173     46.      300 SYOBS = SYOBS + SYOBS1
00174     47.          SDEV = SDEV + SDEV1
00175     48.          RS = (SYOBS - SDEV)/SYOBS
00176     49.          WRITE(6,111) RS
00201     50.      111 FORMAT(1X,'OVER ALL R-SQUARED=',F6.4)
00202     51.       66 CONTINUE
00203     52.          WRITE (6,101) AL,BE
00207     53.      101 FORMAT(1X,'ALPHA = ',F10.5,10X,'BETA = ',F10.5)
00210     54.          CALL PRPL (NEXP,NEXPD,THFIN,NVAR,NP,NRPRD,YPRD,YOBS)
00211     55.          RETURN
00212     56.          END

    END OF COMPILATION:       NO  DIAGNOSTICS.
$FOR,SI      ,PRPL
FORTRAN-MACC 1.145-07/30/75-13:28:09          PRPL
00101      1.          SUBROUTINE PRPL (NEXP,NEXPD,THFIN,NVAR,NP,NRPRD,YPRD,YOBS)
00102      2.          DIMENSION T(1),YOBS(NRPRD,1),YPRD(NRPRD,1)
00103      3.          COMMON T
00104      4.          COMMON/LIM/NEXP1,NEXP2,K
00105      5.          MM = 0
00106      6.      200 CONTINUE
00107      7.          MM = MM + 1
00110      8.          IF(MM.EQ.1) GO TO 50
00112      9.          DO 140 I = 1,NEXP2
00115     10.          MN = NEXP1 + I
00116     11.          YOBS(I,1) = YOBS(MN,1)
00117     12.      140 T(I) = T(MN)
00121     13.          LU = NEXP2
00122     14.          GO TO 60
00123     15.       50 CONTINUE
00124     16.          LU = NEXP1
00125     17.       60 CONTINUE
00126     18.          YMAX = YOBS(1,1)
00127     19.          DO 10 I = 2,LU
00132     20.       10 YMAX = AMAX1(YMAX,YOBS(I,1))
00134     21.          IF( MM.EQ.2 ) GO TO 170
00136     22.          TMAX = T(1)
00137     23.          DO 15 I = 2,NEXP
00142     24.       15 TMAX = AMAX1(TMAX,T(I))
00144     25.          BMAX = TMAX/(NEXPD-NEXP1-NEXP2)
```

```
00145    26.          NM1 = NEXP1 + NEXP2 + 1
00146    27.          NM2 = NEXP1 + NEXP2 + 2
00147    28.          T(NM1) = 0.0
00150    29.          DO 30 I = NM2,NEXPD
00153    30.          J = I - 1
00154    31.       30 T(I) = T(J) + BMAX
00156    32.          IF ( MM.EQ.1 ) GO TO 160
00160    33.          GO TO 170
00161    34.      160 NEX1 = NEXP1
00162    35.          NEXP1 = NEXPD
00163    36.          K = NEXPD
00164    37.          GO TO 180
00165    38.      170 CONTINUE
00166    39.          NEXP1 = 1
00167    40.          K = 1
00170    41.          NEXP = NEXPD
00171    42.      180 CONTINUE
00172    43.          CALL F(THFIN,YPRD,NEXPD,NVAR,NP,NRPRD)
00173    44.          NEXP1 = NEX1
00174    45.          DO 20 I = 1,NEXPD
00177    46.       20 YMAX = AMAX1(YMAX,YPRD(I,1))
00201    47.          YSCLE = YMAX/8.8
00202    48.          TSCLE = TMAX/8.8
00203    49.          CALL GRPH2N(T,1HR,YPRD,1HR,-NEXPD,3H9X9,0,TSCLE,0,YSCLE,17HFUNCTIO
00203    50.         1N VALUES*.,6HTIME*.,48H PLOT OF OBSERVED,O'S, AND PREDICTED,*'S, V
00203    51.         2ALUES,1H*)
00204    52.          CALL GRPH2V(T,1HR,YOBS,1HR,-LU,4HSAME,1HQ)
00205    53.          CALL GRPHND
00206    54.          IF (NEXP2.EQ.0) GO TO 66
00210    55.          IF(MM.EQ.1) GO TO 200
00212    56.       66 CONTINUE
00213    57.          RETURN
00214    58.          END

     END OF COMPILATION:      NO  DIAGNOSTICS.
@MAP
MAP 017P-0773-13:28


ADDRESS LIMITS    001000 047633     050000 072543
STARTING ADDRESS  047411

WORDS DECIMAL      19868 IBANK        9572 DBANK


        SEGMENT $MAIN$          001000 047633     050000 072543

NEXP1$/NAGFORFUN10        1   001000 001047       0   050000 050000
UR3SRH/UWCC               1   001050 001126
UR2MSK/UWCC               1   001127 001260       0   050001 050026
```

			2	BLANK$COMMON
URITRI/UWCC01	1	001261 001446		
URSORT/NAGUTILITY02	1	001447 002266	0	050027 050166
NRIFMK/NAGNLINREG00	1	002267 002530	0	050167 050247
			2	BLANK$COMMON
NRIRD/NAGNLINREG00	1	002531 002632	0	050250 050323
			2	BLANK$COMMON
NRIWRT/NAGNLINREG00	1	002633 002753	0	050324 050401
			2	BLANK$COMMON
NRIDRM/NAGNLINREG00	1	002754 003033	0	050402 050417
ASINCOS$/NAGFORFUN10	1	003034 003257	0	050420 050445
NRILIT/NAGNLINREG01	1	003260 003430	0	050446 050477
	3	NRIBLK	2	BLANK$COMMON
NRISWP/NAGNLINREG00	1	003431 004054	0	050500 050545
			2	BLANK$COMMON
NRIWSQ/NAGNLINREG00	1	004055 004343	0	050546 050616
			2	BLANK$COMMON
NRIPTV/NAGNLINREG00	1	004344 004742	0	050617 050745
			2	BLANK$COMMON
NRISRT/NAGNLINREG00	1	004743 005172	0	050746 050777
			2	BLANK$COMMON
NRISVD/NAGNLINREG00	1	005173 007312	0	051000 051211
			2	BLANK$COMMON
NRITRS/NAGNLINREG00	1	007313 010147	0	051212 051346
			2	BLANK$COMMON
NRIDIF/NAGNLINREG04	1	010150 010744	0	051347 051443
NRICK/NAGNLINREG00	1	010745 010762	0	051444 051444
URPNID/UWCC	1	010763 010771	0	051445 051445
URDATE/NAGUTILITY00	1	010772 011010	0	051446 051447
URTIME/NAGUTILITY00	1	011011 011017	0	051450 051450
EOUT$/SYS	1	011020 012056	0	051451 051451
			2	051452 052034
NRIHO/NAGNLINREG04	1	012057 012622	0	052035 052557
NRIHC/NAGNLINREG06	1	012623 015362	0	052560 053447
NRINST/NAGNLINREG01	1	015363 017065	0	053450 054264
	3	NRIBLK	2	BLANK$COMMON
NRIFPV/NAGNLINREG00	1	017066 017273	0	054265 054372
			2	BLANK$COMMON
NRIBLK (COMMON BLOCK)				054373 054410
NRIWK/NAGNLINREG02	1	017274 021737	0	054411 054657
	3	NRIBLK	2	BLANK$COMMON
NRIHV/NAGNLINREG02	1	021740 022703	0	054660 055035
NRIPUT/NAGNLINREG00	1	022704 023037	0	055036 055061
			2	BLANK$COMMON
NRIBDS/NAGNLINREG01	1	023040 023123	0	055062 055113
NRIBDM/NAGNLINREG00	1	023124 023201	0	055114 055127
			2	BLANK$COMMON
NRILTN/NAGNLINREG00	1	023202 023277	0	055130 055160
			2	BLANK$COMMON
NRIBDA/NAGNLINREG00	1	023300 023351	0	055161 055206
			2	BLANK$COMMON
NRILTZ/NAGNLINREG00	1	023352 023436	0	055207 055231
			2	BLANK$COMMON
NRIGRD/NAGNLINREG01	1	023437 023577	0	055232 055265
			2	BLANK$COMMON
NRIPST/NAGNLINREG00	1	023600 024224	0	055266 055422
			2	BLANK$COMMON

```
 NRITMS/NAGNLINREGO1          1   024225 024311          0   055423 055436
                                                         2   BLANK$COMMON
 NISYM$/FORIO
 NEXP$%/NAGFORFUN11           1   024312 024407          2   055437 055443
 ALOG$/NAGFORFUN10            1   024410 024517          2   055444 055453
 GRPRNT/GRFPRNTUWO1           1   024520 024635          2   055454 055527
                              1   024636 025123          0   055530 055706
                              3   G12345                 2   BLANK$COMMON
 GRHDCN/GRFPRNTUWO1           1   025124 025133          0   055707 055710
                                                         2   055711 055716
 URSRCH/UWCCO1                1   025134 025426          0   055717 055717
 NFTCH$/FORIO                 1   025427 025730          2   055720 055755
 NRIEDS/NAGNLINREGO9          1   025731 031470          0   055756 057345
 URXITP$/NAGUTILITYO1         1   031471 031550          2   057346 057404
 ERU$
 NOTIN$/FORIO                 1   031551 032060          2   057405 057411
 FORIO32/FORIO                1   032061 034437          2   057412 062076
 NTAB$/FORIO                                             2   062077 062143
 NFFTI$/FORIO                 1   034440 035514          2   062144 062374
 NFFTO$/FORIO                 1   035515 036105          2   062375 062436
 NOSYM$/FORIO                 1   036106 036215          2   062437 062442
 UWERR$/NAGFORFUNO2           1   036216 037026          2   062443 063102
 CNTRHD/GRFPRNTUWO1           1   037027 037256          0   063103 063143
                                                         2   BLANK$COMMON
 GRAPHZ/NAGGRAPH202           1   037257 041435          0   063144 063516
                                                         2   G12345
 URNPAR/UWCC                  1   041436 041464          0   063517 063517
                                                         2   063520 063521
 FORIO$4/FORIO
 NREG/NAGNLINREGO2            1   041465 041764          2   063522 063543
 EXP$/NAGFORFUN10             1   041765 042110          0   063544 063556
 NORUF$/FORIO                 1   042111 042213          2   063557 063602
 SQRT$/NAGFORFUN10            1   042214 042271          2   063603 063603
 FORIO$1/FORIO                1   042272 042341          2   063604 063615
 G12345 (COMMON BLOCK)        1   042342 045534          2   063616 064715
 GRAPH2/GRFPRNTUWO2                                                064716 070056
                              1   045535 046265          0   070057 070271
                              3   G12345                 2   BLANK$COMMON
 LIM (COMMON BLOCK)                                            070272 070276
 BLANK$COMMON (COMMON BLOCK)                                   070277 070360
 PRPL.                        1   046266 046635          0   070361 070462
                              3   LIM                    2   BLANK$COMMON
 OTP                          1   046636 047142          0   070463 070561
                              3   LIM                    2   BLANK$COMMON
 SUBF                         1   047143 047410          0   070562 070633
                              3   LIM                    2   BLANK$COMMON
 MAIN                         1   047411 047633          0   070634 072543
                              3   LIM                    2   BLANK$COMMON

 SYS$*RLIB$. LEVEL 49^
 END OF COLLECTION - TIME 4.155 SECONDS

 @XQT
```

SUMMARY OF THE DATA

ITEMS

ITEMS(1): NEXP = 23	NUMBER OF EXPERIMENTS	
ITEMS(2): NVAR = 1	NUMBER OF VARIABLES	
ITEMS(3): NP = 7	NUMBER OF PARAMETERS	
ITEMS(4): NROBS = 23	ROW DIMENSION OF ARRAY YOBS	
ITEMS(5): NRPRD = 23	ROW DIMENSION OF ARRAY YPRD	
ITEMS(6): NRWTS = 23	ROW DIMENSION OF ARRAY WTS	
ITEMS(7): METHOD = 'MARQ'	MARQUARDT'S METHOD	
ITEMS(8): KWTS = 'ALL'	WEIGHTING BY OBSERVATION	
ITEMS(9): KDERIV = 'NREG'	NREG CALCULATED DERIVATIVES	
ITEMS(10): KSYM = 'CENT'	CENTRAL DIFFERENCES	
ITEMS(11): KDIFF = 'REL'	RELATIVE DIFFERENCES	
ITEMS(12): MAXIT = 50	LIMIT ON NUMBER OF ITERATIONS	

TOLERANCES

TOL(1) = 1.5000000-06	REL. CHANGE IN A PARAMETER	
TOL(2) = 1.0000000-09	REL. CHANGE IN SUM OF SQUARES	
TOL(3) = 0.0000000	RATIO TO INITIAL SUM OF SQUARES	
TOL(4) = 1.0000000-16	PIVOT TOLERANCE	

SUNDRIES

NUMBER OF ACTIVE PARAMETERS = 5
NUMBER OF CELLS OF SCRATCH REQUIRED = 471

PARAMETERS

	NO.	NAME	INITIAL VALUE	PROPORTION FOR DERIV. ESTIMATE	LOWER BOUND	UPPER BOUND
	1	K1	2.8000000+00	1.0000000-03	1.0000000-04	1.0000000+04
	2	K-1	1.4700000+00	1.0000000-03	1.0000000-04	1.0000000+04
	3	K2	3.8000000-01	1.0000000-03	1.0000000-04	1.0000000+04
	4	KF	2.6000000-01	1.0000000-03	1.0000000-04	1.0000000+04
F	5	K3	4.7000000-02	1.0000000-03	1.0000000-04	1.0000000+04
	6	DV1	2.3300000+01	1.0000000-03	1.0000000-04	1.0000000+04
F	7	DV3	1.8900000+01	1.0000000-03	1.0000000-04	1.0000000+04

SINGULAR VALUES AND VECTORS AT INITIAL POINT

SING. VALUES			1.5209911+01	8.5806299+00	2.1133159+00	5.9846835-01	5.2752695-02
PAR.	1	K1	.0197258	-.0359773	.5912422	-.7742238	-.2220961
	2	K-1	-.0376984	.0558017	-.7968995	-.5984562	-.0476048
	3	K2	.0566902	-.9957878	-.0703364	-.0015207	-.0155990
	4	KF	-.9974665	-.0592821	.0372372	.0084663	-.0093723
F	5	K3	***	***	***	***	***
	6	DV1	-.0359773	.5912422	-.7742238	-.2220961	.0000000
F	7	DV3	***	***	***	***	***

SETUP TIME = .169 SECONDS

THE ITERATIONS

ITERATION NO. 1		BASE POINT		TEST POINT
SUM OF SQUARES		2.0451071+01		1.2642243+01
L		0		0
LAMBDA		0.0000000		0.0000000
GAMMA		1.0000000+00		1.0000000+00
ANGLE IN DEGREES		.0000		88.8377
MAX. PIVOT REDUCTION		1.0000000+00		1.4509598-01
PAR. 1 K1		2.8000000+00		4.1919542+00
2 K-1		1.4700000+00	S	1.5587288+00
3 K2		3.8000000-01		4.6122164-01
4 KF		2.6000000-01		5.1864593-01
5 K3	F	4.7000000-02	F	4.7000000-02
6 DV1		2.3300000+01		3.2726709+01
7 DV3	F	1.8900000+01	F	1.8900000+01

CUMULATIVE NO. OF FUNCTION CALLS = 2 ITERATION TIME = .170 SECONDS CUMULATIVE TIME = .339 SECONDS

ITERATION NO. 10		BASE POINT		TEST POINT
SUM OF SQUARES		3.3377039+00		3.3376852+00
L		0		0
LAMBDA		0.0000000		0.0000000
GAMMA		1.0000000+00		1.0000000+00
ANGLE IN DEGREES		89.5895		89.9846
MAX. PIVOT REDUCTION		1.8181388-01		1.0447983-01
PAR. 1 K1		1.6108894+01		1.6103229+01
2 K-1	S	4.9103313-01		4.9026747-01
3 K2		8.3745060+00		8.3835536+00
4 KF		8.2606049+00	S	8.2662183+00
5 K3	F	4.7000000-02	F	4.7000000-02
6 DV1		1.1337907+03		1.1361034+03
7 DV3	F	1.8900000+01	F	1.8900000+01

CUMULATIVE NO. OF FUNCTION CALLS = 14 ITERATION TIME = .071 SECONDS CUMULATIVE TIME = 1.096 SECONDS

THE LAST ITERATION

			BASE POINT		TEST POINT
ITERATION NO. 13					
SUM OF SQUARES			3.3376848+00		3.3376848+00
L			0		18
LAMBDA			0.0000000		7.6169012+01
GAMMA			1.0000000+00		5.0000000-01
ANGLE IN DEGREES			89.9838		11.8430
MAX. PIVOT REDUCTION			6.2900740-02		1.6006252+00
PAR.	1 K1		1.6102946+01		1.6102946+01
	2 K-1		4.9013491-01	S	4.9013453-01
	3 K2	S	8.3851470+00		8.3851470+00
	4 KF		8.2674358+00		8.2674358+00
	5 K3	F	4.7000000-02	F	4.7000000-02
	6 DV1		1.1365464+03		1.1365464+03
	7 DV3	F	1.8900000+01	F	1.8900000+01

CUMULATIVE NO. OF FUNCTION CALLS = 36 ITERATION TIME = .366 SECONDS CUMULATIVE TIME = 1.458 SECONDS

ITERATION TERMINATES;
MAX. RELATIVE CHANGE IN A PARAMETER .LT. TOL(1) = 1.5000000-06

FINAL PARAMETER VALUES

FINAL VALUE SUM OF SQUARES = 3.3376848+00

			FINAL VALUE
AR.	1	K1	1.6102946+01
	2	K-1	4.9013491-01
	3	K2	8.3851470+00
	4	KF	8.2674358+00
F	5	K3	4.7000000-02
	6	DV1	1.1365464+03
F	7	DV3	1.8900000+01

ITERATION SUMMARY

ITER NO.	SUM OF SQUARES	L	LAMBDA	GAMMA	ANGLE	NO. PIVOT FAILURES	NO. BOUNDS FAILURES	MAX. PIVOT REDUCTION	TIME IN SECONDS
0	2.0451071+01	0	0.0000000	1.0000000+00	.0000	0	0	1.0000000+00	.000
1	1.2642243+01	0	0.0000000	1.0000000+00	88.8377	0	0	1.4509598-01	.170
2	1.0717873+01	0	0.0000000	1.0000000+00	89.4822	0	0	3.8250508-02	.144
3	1.0602297+01	0	0.0000000	1.0000000+00	89.6044	0	0	2.4996527-02	.072
4	7.8291885+00	2	1.3070227-04	1.0000000+00	89.4272	0	0	2.1107513-01	.103
5	5.5815112+00	1	4.3552835-05	1.0000000+00	89.8060	0	0	2.6315963-01	.071
6	4.7656243+00	1	1.1200597-05	1.0000000+00	89.8864	0	0	2.3161651-01	.086
7	4.6961181+00	0	0.0000000	1.0000000+00	89.9623	0	0	1.7335901-01	.070
8	3.3492301+00	0	0.0000000	1.0000000+00	89.9659	0	0	1.1476095-01	.069
9	3.3377034+00	0	0.0000000	1.0000000+00	84.5895	0	0	1.8181388-01	.070
10	3.3376852+00	0	0.0000000	1.0000000+00	89.9846	0	0	1.0447983-01	.071
11	3.3376849+00	0	0.0000000	1.0000000+00	89.9827	0	0	8.0803708-02	.128
12	3.3376848+00	0	0.0000000	1.0000000+00	89.9838	0	0	6.2900740-02	.069
13	3.3376848+00	18	7.6169012+01	5.0000000-01	11.8430	0	0	1.4006252+00	.366

SINGULAR VALUES AND VECTORS AT TERMINAL POINT

SING. VALUES			1.1274202+01	8.3881985-01	5.6328676-01	2.7297219-01	9.8074986-04
PAR.	1	K1	.0116743	-.1127463	.1265469	-.9854616	.0017625
	2	K-1	-.9988489	.0269920	.0383708	-.0099934	.0001672
	3	K2	.0397849	.1125778	.9862397	.1142290	-.0051276
	4	KF	.0241137	.9868486	-.0991181	-.1253532	-.0032390
F	5	K3	•••	•••	•••	•••	•••
	6	DV1	-.1127463	.1265469	-.9854616	.0017625	-27836.8535156
F	7	DV3	•••	•••	•••	•••	•••

NORMALIZING ELEMENTS AND CORRELATION MATRIX

PARAMETER NO.			1	2	3	4	5	6
NORM. ELTS.			4.0411890+00	2.0960960-01	5.5311241+00	3.5402238+00	•••	1.0196076+03
PAR.	1	K1	1.0000000					
	2	K-1	.5306135	1.0000000				
	3	K2	-.4711510	-.6757723	1.0000000			
	4	KF	-.3127974	-.7015691	.8643170	1.0000000		
F	5	K3	•••	•••	•••	•••	•••	
	6	DV1	-.4447006	-.8134292	.9452399	.9328822	•••	1.0000000
F	7	DV3	•••	•••	•••	•••	•••	•••

PARAMETER NO.			7
NORM. ELTS.			•••
PAR. F	7	DV3	•••

CONFIDENCE LIMITS ON LINEAR HYPOTHESIS

			LOWER LIMIT	FINAL VALUE	UPPER LIMIT
PAR.	1	K1	1.2622575+01	1.6102946+01	1.9583317+01
	2	K-1	3.0961398-01	4.9013491-01	6.7065585-01
	3	K2	3.6216072+00	8.3851470+00	1.3148687+01
	4	KF	5.2185082+00	8.2674358+00	1.1316363+01
F	5	K3	***	4.7000000-02	***
	6	DV1	2.5843527+02	1.1365464+03	2.0146575+03
F	7	DV3	***	1.8900000+01	***

EXPLORATION

			LOWER TEST	SUM OF SQUARES	LINEAR EST. OF SUM OF SQUARES	UPPER TEST	SUM OF SQUARES	LINEAR EST. OF SUM OF SQUARES
PAR.	1	K1	1.5232853+01	3.4220665+00	3.4162008+00	1.6973038+01	3.4074404+00	3.4162008+00
	2	K-1	4.4500468-01	3.5944698+00	3.5959760+00	5.3526514-01	3.5777870+00	3.5959760+00
	3	K2	7.1942620+00	4.1854282+00	4.0747271+00	9.5760319+00	3.9781567+00	4.0747271+00
	4	KF	7.5052040+00	3.8148378+00	3.7812358+00	9.0296676+00	3.7438282+00	3.7812358+00
F	5	K3	4.7000000-02	***	***	4.7000000-02	***	***
	6	DV1	9.1701862+02	5.3668222+00	5.3667911+00	1.3560742+03	5.3667962+00	5.3667911+00
F	7	DV3	1.8900000+01	***	***	1.8900000+01	***	***

FINAL FUNCTION VALUES AND RESIDUALS

WEIGHTED ROOT MEAN SQUARE RESIDUAL = 4.3061227-01
THIS IS THE SCALE UNIT IN THE GRAPH OF THE WEIGHTED RESIDUALS. NO. DEGREES OF FREEDOM = 18

EXPT. NO.	VAR. NO.	PREDICTION	OBSERVATION	RESIDUAL	WEIGHTED RES.	GRAPH OF WEIGHTED RESIDUAL (-2 -1 0 +1 +2)
1	1	1.3844910+01	1.3600000+01	-2.4490988-01	-6.6622689-02	
2	1	8.0335118+00	1.2200000+01	4.1664882+00	1.1931006+00	
3	1	7.4453485+00	7.2000000+00	-2.4534851-01	-9.1472558-02	
4	1	6.9988267+00	5.6000000+00	-1.3988267+00	-5.9182108-01	
5	1	6.5791524+00	5.6000000+00	-9.7915244-01	-4.1426365-01	
6	1	4.0116921+00	4.4000000+00	3.8830787-01	1.8500741-01	
7	1	3.1326106+00	3.4000000+00	2.6738939-01	1.4498325-01	
8	1	1.9101350+00	1.6000000+00	-3.1013499-01	-2.4518324-01	
9	1	1.1647205+00	1.3000000+00	1.3527954-01	1.1863020-01	
10	1	7.1019784-01	9.0000000-01	1.8980215-01	2.0005903-01	
11	1	4.3304896-01	7.0000000-01	2.6695104-01	3.1911537-01	
12	1	4.4956108+00	3.5000000+00	-9.9561077-01	-5.3244235-01	
13	1	4.6062417+00	4.3000000+00	-3.0624175-01	-1.4782312-01	
14	1	4.7816197+00	5.0000000+00	2.1838027-01	9.7662626-02	
15	1	4.9554315+00	5.5000000+00	5.4456854-01	2.3232088-01	
16	1	5.1134411+00	5.5000000+00	3.8655895-01	1.6491168-01	
17	1	5.6997522+00	7.0000000+00	1.3002478+00	4.9169315-01	
18	1	5.9179990+00	7.0000000+00	1.0821010+00	4.0920020-01	
19	1	6.0901574+00	6.5000000+00	4.0984255-01	1.6083383-01	
20	1	6.1452383+00	6.5000000+00	3.5476172-01	1.3921855-01	
21	1	5.9606575+00	5.5000000+00	-4.6065748-01	-1.9652320-01	
22	1	5.6498145+00	5.0000000+00	-6.4981450-01	-2.9047171-01	
23	1	5.2790163+00	4.5000000+00	-7.7901626-01	-3.6704812-01	

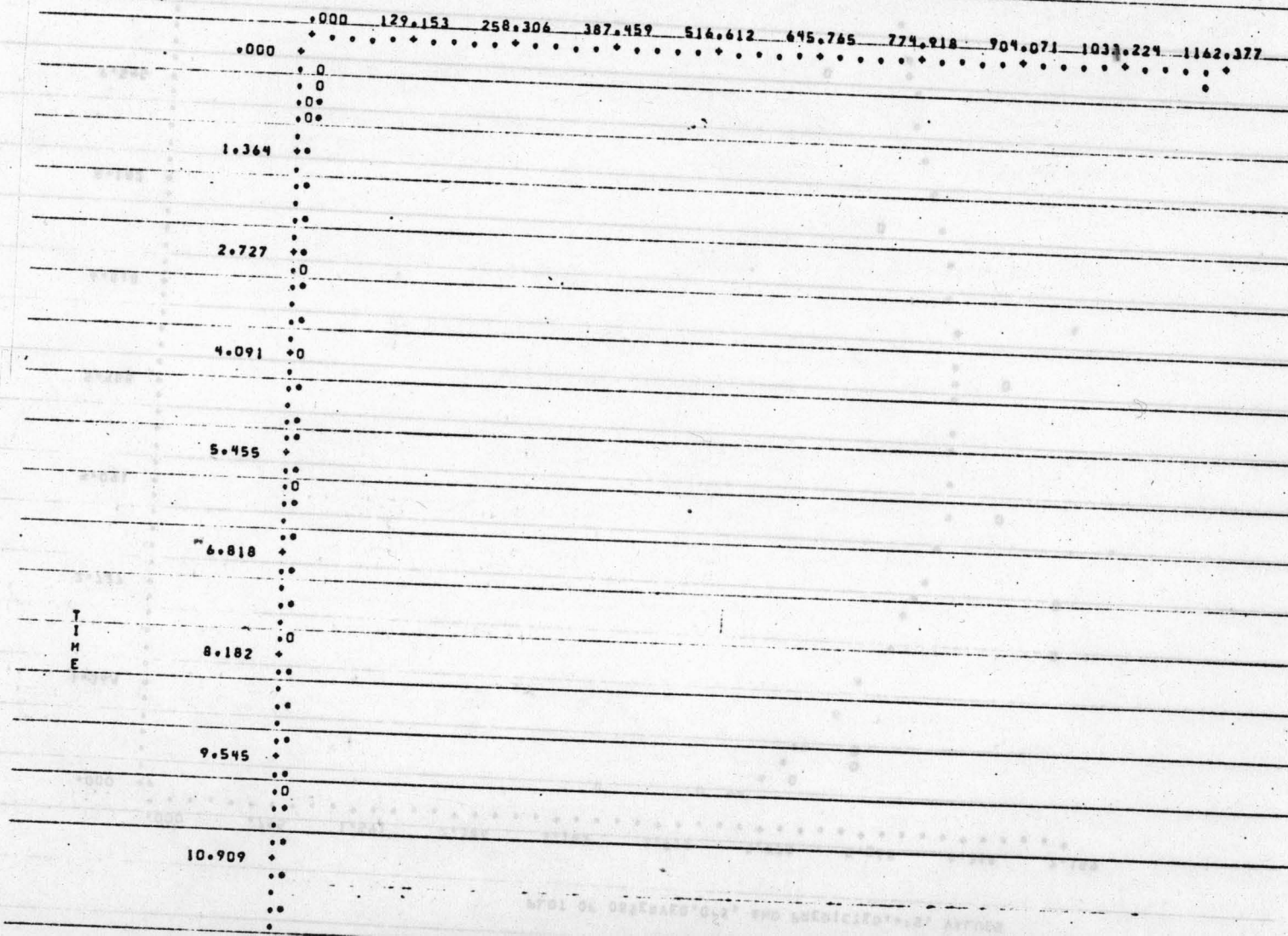
TIME SINCE END OF THE LAST ITERATION = .753 SECONDS TOTAL TIME = 2.411 SECONDS

R-SQUARED FOR FUNCTION1 = .9570
COR FOR FUNCTION1 = .9664

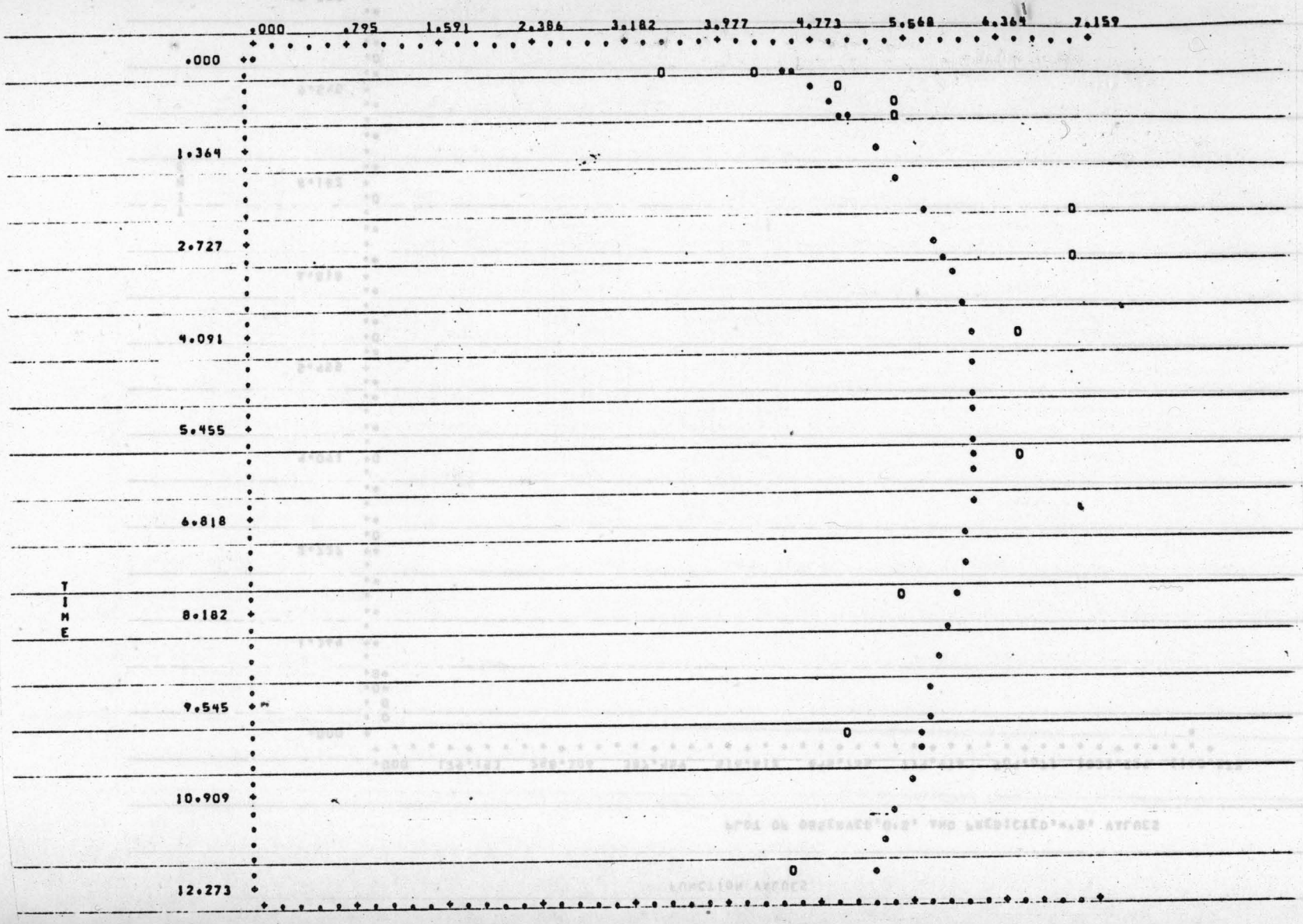
R-SQUARED FOR FUNCTION2 = .9840
COR FOR FUNCTION2 = .9615
OVER ALL R-SQUARED= .9688
ALPHA = 32.99832 BETA = .24735

FUNCTION VALUES

PLOT OF OBSERVED,O'S, AND PREDICTED,•'S, VALUES



PLOT OF OBSERVED,O'S, AND PREDICTED,•'S, VALUES



SUMMARY OF THE DATA

ITEMS

ITEMS(1): NEXP =	23	NUMBER OF EXPERIMENTS	
ITEMS(2): NVAR =	1	NUMBER OF VARIABLES	
ITEMS(3): NP =	7	NUMBER OF PARAMETERS	
ITEMS(4): NROBS =	23	ROW DIMENSION OF ARRAY YOBS	
ITEMS(5): NRPRD =	23	ROW DIMENSION OF ARRAY YPRD	
ITEMS(6): NRWTS =	23	ROW DIMENSION OF ARRAY WTS	
ITEMS(7): METHOD =	'MARQ'	MARQUARDT'S METHOD	
ITEMS(8): KWTS =	'ALL'	WEIGHTING BY OBSERVATION	
ITEMS(9): KDERIV =	'NREG'	NREG CALCULATED DERIVATIVES	
ITEMS(10): KSYM =	'CENT'	CENTRAL DIFFERENCES	
ITEMS(11): KDIFF =	'REL'	RELATIVE DIFFERENCES	
ITEMS(12): MAXIT =	50	LIMIT ON NUMBER OF ITERATIONS	

TOLERANCES

TOL(1) =	1.5000000-06	REL. CHANGE IN A PARAMETER
TOL(2) =	1.0000000-09	REL. CHANGE IN SUM OF SQUARES
TOL(3) =	0.0000000	RATIO TO INITIAL SUM OF SQUARES
TOL(4) =	1.0000000-16	PIVOT TOLERANCE

SUNDRIES

NUMBER OF ACTIVE PARAMETERS = 5

NUMBER OF CELLS OF SCRATCH REQUIRED = 471

PARAMETERS

	NO.	NAME	INITIAL VALUE	PROPORTION FOR DERIV. ESTIMATE	LOWER BOUND	UPPER BOUND
	1	K1	3.6700000+00	1.0000000-03	1.0000000-04	1.0000000+04
	2	K-1	3.4000000+00	1.0000000-03	1.0000000-04	1.0000000+04
	3	K2	9.5999999-01	1.0000000-03	1.0000000-04	1.0000000+04
F	4	KF	7.2000000-01	1.0000000-03	1.0000000-04	1.0000000+04
	5	K3	4.7000000-02	1.0000000-03	1.0000000-04	1.0000000+04
F	6	DV1	1.8500000+01	1.0000000-03	1.0000000-04	1.0000000+04
	7	DV3	1.8900000+01	1.0000000-03	1.0000000-04	1.0000000+04

SINGULAR VALUES AND VECTORS AT INITIAL POINT

SING. VALUES			8.1123259+00	3.9244547+00	8.8737120-01	2.7495076-01	6.6223234-02
PAR.	1	K1	.0202595	-.0062094	.7552687	-.4793550	-.4464738
	2	K-1	-.0170787	.0146188	-.5952069	-.7864457	-.1634846
	3	K2	.4118137	-.9094622	-.0368103	.0108664	-.0426010
	4	KF	-.9108685	-.4112596	.0097965	.0111735	-.0310367
F	5	K3	***	***	***	***	***
	6	DV1	-.0062094	.7652687	-.4793550	-.4464738	.0000000
F	7	DV3	***	***	***	***	***

SETUP TIME = .170 SECONDS

THE ITERATIONS

ITERATION NO. 1		BASE POINT		TEST POINT
SUM OF SQUARES		8.6335757-01		7.8152838-01
L		0		0
LAMBDA		0.0000000		0.0000000
GAMMA		1.0000000+00		1.0000000+00
ANGLE IN DEGREES		.0000		78.6903
MAX. PIVOT REDUCTION		1.0000000+00		4.1044156-02
PAR. 1 K1		3.6700000+00	S	3.6300795+00
2 K-1		3.4000000+00		3.6119662+00
3 K2		9.5999999-01		9.9044044-01
4 KF		7.2000000-01		7.5359801-01
5 K3	F	4.7000000-02	F	4.7000000-02
6 DV1		1.8500000+01		1.8624491+01
7 DV3	F	1.8900000+01	F	1.8900000+01

CUMULATIVE NO. OF FUNCTION CALLS = 2 ITERATION TIME = .172 SECONDS CUMULATIVE TIME = .342 SECONDS

ITERATION NO. 10		BASE POINT		TEST POINT		TEST POINT		TEST POINT		TEST POINT		TEST POINT	
SUM OF SQUARES		7.7950011-01		7.7950012-01		7.7950011-01		7.7950021-01		7.7950016-01		7.7950013-01	
L		4		3		4		5		6		7	
LAMBDA		6.5931633-02		2.9139575-02		6.7310817-02		1.5349266-01		3.3751212-01		7.1732096-01	
GAMMA		1.0000000+00		1.0000000+00		1.0000000+00		1.0000000+00		1.0000000+00		1.0000000+00	
ANGLE IN DEGREES		50.2801		55.7432		52.1122		49.8342		48.1216		46.4791	
MAX. PIVOT REDUCTION		4.5803053-01		3.2652597-01		4.6128381-01		5.7757851-01		6.5639806-01		7.0854040-01	
PAR. 1 K1		3.8449422+00		3.8450624+00		3.8450051+00		3.8449726+00		3.8449559+00		3.8449481+00	
2 K-1		3.8012480+00		3.8013619+00		3.8013208+00		3.8012902+00		3.8012710+00		3.8012602+00	
3 K2		1.0114211+00		1.0114284+00		1.0114246+00		1.0114229+00		1.0114222+00		1.0114218+00	
4 KF	S	7.6858285-01	S	7.6858737-01	S	7.6858463-01	S	7.6858351-01	S	7.6858310-01	S	7.6858294-01	
5 K3	F	4.7000000-02	F	4.7000000-02	F	4.7000000-02	F	4.7000000-02	F	4.7000000-02	F	4.7000000-02	
6 DV1		1.8926778+01		1.8926896+01		1.8926824+01		1.8926795+01		1.8926785+01		1.8926781+01	
7 DV3	F	1.8900000+01	F	1.8900000+01	F	1.8900000+01	F	1.8900000+01	F	1.8900000+01	F	1.8900000+01	

THE ITERATIONS

ITERATION NO. 10			TEST POINT		TEST POINT	
SUM OF SQUARES			7.7950013-01		7.7950004-01	
L			8		9	
LAMBDA			1.4953486+00		3.0809426+00	
GAMMA			1.0000000+00		1.0000000+00	
ANGLE IN DEGREES			44.7043		42.3377	
MAX. PIVOT REDUCTION			7.5328773-01		8.1068613-01	
PAR.	1	K1	3.8449447+00		3.8449433+00	
	2	K-1	3.8012543+00		3.8012512+00	
	3	K2	1.0114217+00		1.0114215+00	
	4	KF	S 7.6858287-01	S	7.6858284-01	
	5	K3	F 4.7000000-02	F	4.7000000-02	
	6	DV1	1.8926779+01		1.8926778+01	
	7	DV3	F 1.8900000+01	F	1.8900000+01	

CUMULATIVE NO. OF FUNCTION CALLS = 22 ITERATION TIME = .287 SECONDS CUMULATIVE TIME = 1.369 SECONDS

ITERATION TERMINATES:
MAX. RELATIVE CHANGE IN A PARAMETER .LT. TOL(1) = 1.5000000-06

FINAL PARAMETER VALUES

FINAL VALUE SUM OF SQUARES = 7.7950005-01

AR.	1	K1	3.8449433+00
	2	K-1	3.8012512+00
	3	K2	1.0114215+00
	4	KF	7.6858284-01
F	5	K3	4.7000000-02
	6	DV1	1.8926778+01
F	7	DV3	1.8900000+01

ITERATION SUMMARY

ITER NO.	SUM OF SQUARES	L	LAMBDA	GAMMA	ANGLE	NO. PIVOT FAILURES	NO. BOUNDS FAILURES	MAX. PIVOT REDUCTION	TIME IN SECONDS
0	8.6335757-01	0	0.0000000	1.0000000+00	.0000	0	0	1.0000000+00	.000
1	7.8152838-01	0	0.0000000	1.0000000+00	78.6903	0	0	4.1044156-02	.172
2	7.7968736-01	0	0.0000000	1.0000000+00	86.2780	0	0	3.8931925-02	.199
3	7.7953127-01	0	0.0000000	1.0000000+00	86.7937	0	0	3.9614417-02	.073
4	7.7950551-01	0	0.0000000	1.0000000+00	84.0117	0	0	3.8711498-02	.073
5	7.7950107-01	0	0.0000000	1.0000000+00	80.9840	0	0	6.1886707-02	.073
6	7.7950030-01	0	0.0000000	1.0000000+00	79.7461	0	0	6.1673263-02	.073
7	7.7950013-01	0	0.0000000	1.0000000+00	80.3224	0	0	6.1553260-02	.073
8	7.7950012-01	4	7.4519510-02	1.0000000+00	80.1019	0	0	6.0361309-01	.140
9	7.7950011-01	4	6.5931633-02	1.0000000+00	50.2801	0	0	4.5803053-01	.090
10	7.7950004-01	9	3.0809426+00	1.0000000+00	42.3377	0	0	8.1068613-01	.287

SINGULAR VALUES AND VECTORS AT TERMINAL POINT

SING. VALUES			7.7353038+00	3.7183796+00	8.1893100-01	2.4159880-01	5.9728217-02
PAR.	1	K1	.0198493	-.0080514	.7691636	.4412928	-.4617241
	2	K-1	-.0157299	.0159065	-.5674051	.8036389	-.1780882
	3	K2	.4201985	-.9054582	-.0397039	-.0114706	-.0432506
	4	KF	-.9070643	-.4195602	.0066415	-.0118357	-.0319262
F	5	K3	***	***	***	***	***
	6	DV1	-.0080514	.7691636	.4412928	-.4617241	**********
F	7	DV3	***	***	***	***	***

NORMALIZING ELEMENTS AND CORRELATION MATRIX.

PARAMETER NO.			1	2	3	4	5	6
NORM. ELTS.			7.9986128+00	4.5204853+00	7.6889910-01	5.6095008-01	***	1.4618660+01
PAR.	1	K1	1.0000000					
	2	K-1	.7875051	1.0000000				
	3	K2	.8887915	.5850706	1.0000000			
	4	KF	.9026839	.5619391	.9508169	1.0000000		
F	5	K3	***	***	***	***	***	
	6	DV1	.9313448	.5757798	.9436101	.9557852	***	1.0000000
F	7	DV3	***	***	***	***	***	***

PARAMETER NO.			7
NORM. ELTS.			***
PAR. F	7	DV3	***

CONFIDENCE LIMITS ON LINEAR HYPOTHESIS

			LOWER LIMIT	FINAL VALUE	UPPER LIMIT
PAR.	1	K1	5.1592264-01	3.8449433+00	7.1739638+00
	2	K-1	1.9198263+00	3.8012512+00	5.6826760+00
	3	K2	6.9140592-01	1.0114215+00	1.3314371+00
	4	KF	5.3511557-01	7.6858284-01	1.0020501+00
F	5	K3	***	4.7000000-02	***
	6	DV1	1.2842496+01	1.8926778+01	2.5011061+01
F	7	DV3	***	1.8900000+01	***

EXPLORATION

			LOWER TEST	SUM OF SQUARES	LINEAR EST. OF SUM OF SQUARES	UPPER TEST	SUM OF SQUARES	LINEAR EST. OF SUM OF SQUARES
PAR.	1	K1	3.0126881+00	1.1088721+00	1.0796678+00	4.6771984+00	1.0387525+00	1.0796678+00
	2	K-1	3.3308950+00	8.4464630-01	8.3968212-01	4.2716073+00	8.2846029-01	8.3968211-01
	3	K2	9.3141763-01	9.3067831-01	9.1968346-01	1.0914254+00	9.0820169-01	9.1968346-01
	4	KF	7.1021603-01	9.6126826-01	9.5550308-01	8.2694966-01	9.4384614-01	9.5550308-01
F	5	K3	4.7000000-02	***	***	4.7000000-02	***	***
	6	DV1	1.7405708+01	1.0638779+00	1.0638658+00	2.0447849+01	1.0638607+00	1.0638658+00
F	7	DV3	1.8900000+01	***	***	1.8900000+01	***	***

FINAL FUNCTION VALUES AND RESIDUALS

WEIGHTED ROOT MEAN SQUARE RESIDUAL = 2.0809987-01
THIS IS THE SCALE UNIT IN THE GRAPH OF THE WEIGHTED RESIDUALS.

NO. DEGREES OF FREEDOM = 18

EXPT. NO.	VAR. NO.	PREDICTION	OBSERVATION	RESIDUAL	WEIGHTED RES.	GRAPH OF WEIGHTED RESIDUAL (-2 -1 0 +1 +2)
1	1	1.2665892+01	1.2600000+01	-6.5891623-02	-1.8520118-02	
2	1	9.0445867+00	9.0999999+00	5.5413246-02	1.8378495-02	
3	1	7.3194330+00	6.9000000+00	-4.1943300-01	-1.5971533-01	
4	1	5.0685875+00	5.7000000+00	6.3141245-01	2.6413878-01	
5	1	4.0582172+00	4.0000000+00	-5.8217168-02	-2.9108584-02	
6	1	3.3242733+00	3.0000000+00	-3.2427326-01	-1.8712562-01	
7	1	1.5186298+00	1.6000000+00	8.1370160-02	6.4328760-02	
8	1	6.9418550-01	8.0000000-01	1.0581450-01	1.1830421-01	
9	1	3.1732131-01	5.0000000-01	1.8267869-01	2.8884037-01	
10	1	2.0182053+00	1.8000000+00	-2.1820536-01	-1.6270572-01	
11	1	3.0558603+00	3.3000000+00	2.4413964-01	1.3438773-01	
12	1	3.8238299+00	4.5000000+00	6.7617017-01	3.1859026-01	
13	1	4.4320368+00	4.9000000+00	4.6796322-01	2.1136195-01	
14	1	5.8320674+00	6.1000000+00	2.6793259-01	1.0850443-01	
15	1	6.2972161+00	6.2000000+00	-9.7216129-02	-3.9007782-02	
16	1	6.3431192+00	5.9000000+00	-4.4311923-01	-1.8216458-01	
17	1	5.9901493+00	5.2000000+00	-7.9014927-01	-3.4622606-01	
18	1	5.4978878+00	4.9000000+00	-5.9788781-01	-2.7004416-01	
19	1	5.0140685+00	4.8000000+00	-2.1406853-01	-9.7630272-02	
20	1	4.5661918+00	4.9000000+00	3.3380818-01	1.5076900-01	
21	1	4.1569376+00	4.7000000+00	5.4306239-01	2.5063374-01	
22	1	3.7840747+00	3.9000000+00	1.1592525-01	5.8654053-02	
23	1	3.4445960+00	3.7000000+00	2.5540397-01	1.3271179-01	

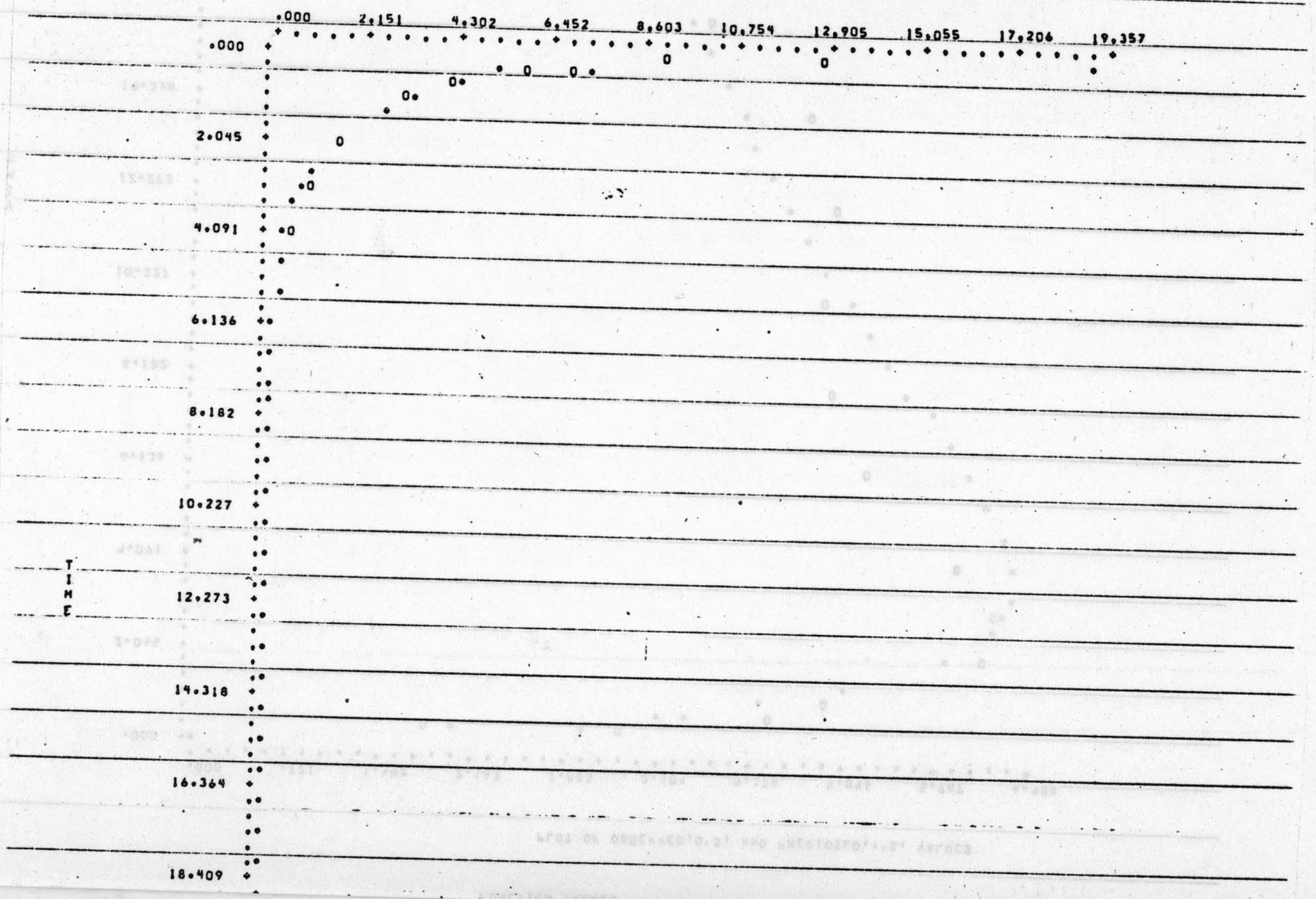
TIME SINCE END OF THE LAST ITERATION = .738 SECONDS TOTAL TIME = 2.107 SECONDS

R-SQUARED FOR FUNCTION1 = .9979
COR FOR FUNCTION1 = .9951

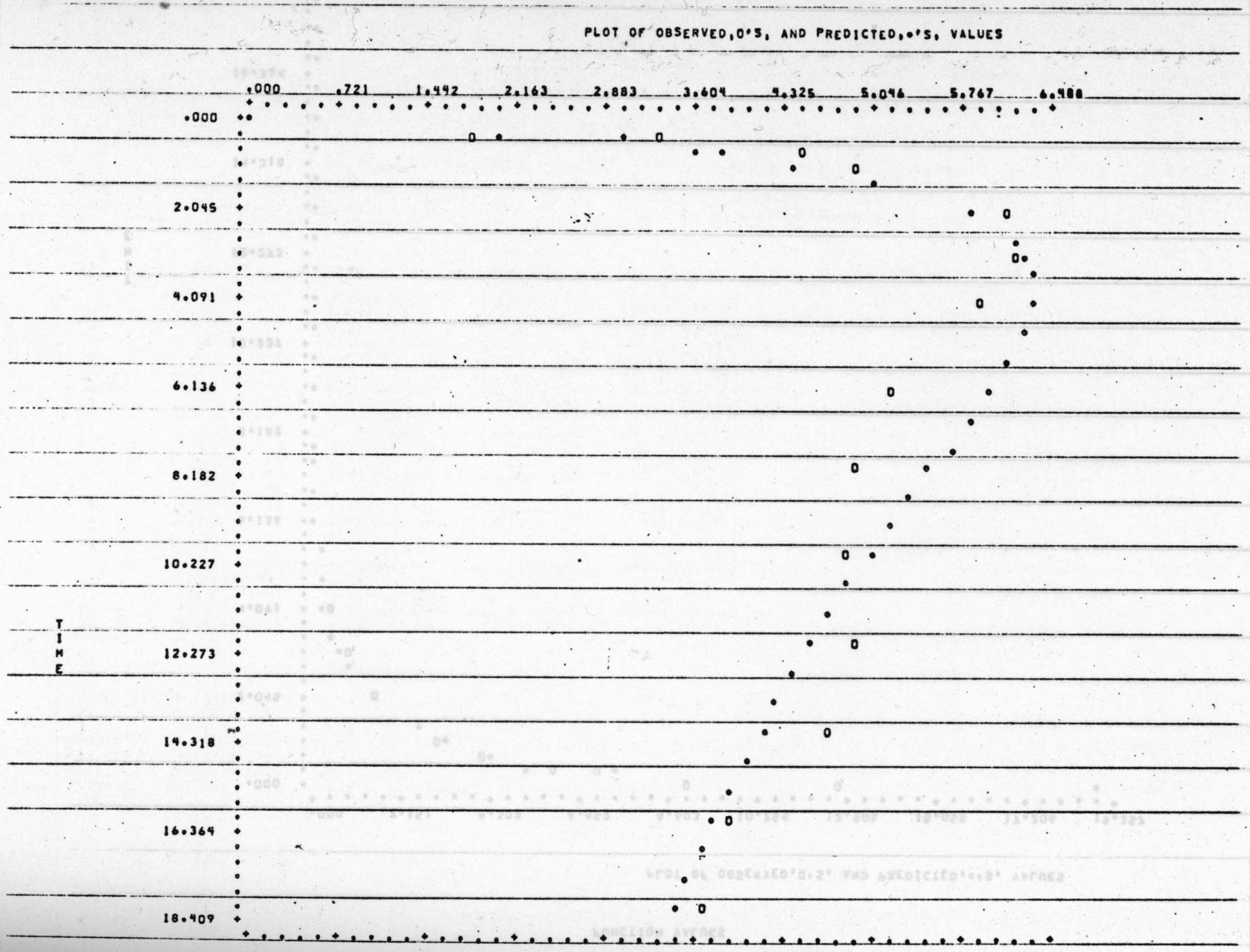
R-SQUARED FOR FUNCTION2 = .9919
COR FOR FUNCTION2 = .9933
OVER ALL R-SQUARED= .9950
ALPHA = 8.64337 BETA = .78282

FUNCTION VALUES

PLOT OF OBSERVED,O'S, AND PREDICTED,•'S, VALUES



FUNCTION VALUES



SUMMARY OF THE DATA

ITEMS

ITEMS(1):	NEXP =	29	NUMBER OF EXPERIMENTS	ITEMS(7): METHOD =	'MARQ'	MARQUARDT'S METHOD
ITEMS(2):	NVAR =	1	NUMBER OF VARIABLES	ITEMS(8): KWTS =	'ALL'	WEIGHTING BY OBSERVATION
ITEMS(3):	NP =	7	NUMBER OF PARAMETERS	ITEMS(9): KDERIV =	'NREG'	NREG CALCULATED DERIVATIVES
				ITEMS(10): KSYM =	'CENT'	CENTRAL DIFFERENCES
ITEMS(4):	NROBS =	29	ROW DIMENSION OF ARRAY Y_{OBS}	ITEMS(11): KDIFF =	'REL'	RELATIVE DIFFERENCES
ITEMS(5):	NRPRD =	29	ROW DIMENSION OF ARRAY YPRD			
ITEMS(6):	NRWTS =	29	ROW DIMENSION OF ARRAY WTS	ITEMS(12): MAXIT =	50	LIMIT ON NUMBER OF ITERATIONS

TOLERANCES

TOL(1) =	1.5000000-06	REL. CHANGE IN A PARAMETER
TOL(2) =	1.0000000-09	REL. CHANGE IN SUM OF SQUARES
TOL(3) =	0.0000000	RATIO TO INITIAL SUM OF SQUARES
TOL(4) =	1.0000000-16	PIVOT TOLERANCE

SUNDRIES

NUMBER OF ACTIVE PARAMETERS = 5
NUMBER OF CELLS OF SCRATCH REQUIRED = 525

PARAMETERS

	NO.	NAME	INITIAL VALUE	PROPORTION FOR DERIV. ESTIMATE	LOWER BOUND	UPPER BOUND
	1	K1	1.8600000+00	1.0000000-03	1.0000000-04	1.0000000+04
	2	K-1	3.2800000+00	1.0000000-03	1.0000000-04	1.0000000+04
	3	K2	5.5000000-01	1.0000000-03	1.0000000-04	1.0000000+04
	4	KF	2.9000000-01	1.0000000-03	1.0000000-04	1.0000000+04
F	5	K3	4.7000000-02	1.0000000-03	1.0000000-04	1.0000000+04
	6	DV1	1.1100000+01	1.0000000-03	1.0000000-04	1.0000000+04
F	7	DV3	1.8900000+01	1.0000000-03	1.0000000-04	1.0000000+04

SINGULAR VALUES AND VECTORS AT INITIAL POINT

SING. VALUES			1.9415062+01	7.3215140+00	1.0095845+00	3.0800784-01	1.1422449-01
PAR.	1	K1	.0175676	-.0062328	.8169992	-.1896727	.5442326
	2	K-1	-.0085460	-.0023702	-.3777079	.5368428	.7543592
	3	K2	.2480272	.9677010	-.0198410	-.0348487	.0207162
	4	KF	-.9685480	.2475249	.0112948	-.0204525	.0100155
F	5	K3	***	***	***	***	***
	6	DV1	-.0062328	.8169992	-.1896727	.5442326	.0000000
F	7	DV3	***	***	***	***	***

SETUP TIME = .169 SECONDS

THE ITERATIONS

ITERATION NO. 1		BASE POINT		TEST POINT
SUM OF SQUARES		1.1365013+00		1.0637526+00
L		0		0
LAMBDA		0.0000000		0.0000000
GAMMA		1.0000000+00		1.0000000+00
ANGLE IN DEGREES		.0000		88.6463
MAX. PIVOT REDUCTION		1.0000000+00		5.2269500-02
PAR. 1 K1		1.8600000+00	S	1.3704715+00
2 K-1		3.2800000+00		2.2616952+00
3 K2		5.5000000-01		5.5430590-01
4 KF		2.9000000-01		2.9586697-01
5 K3	F	4.7000000-02	F	4.7000000-02
6 DV1		1.1100000+01		1.1101266+01
7 DV3	F	1.8900000+01	F	1.8900000+01

CUMULATIVE NO. OF FUNCTION CALLS = 2 ITERATION TIME = .188 SECONDS CUMULATIVE TIME = .357 SECONDS

ITERATION NO. 10		BASE POINT		TEST POINT
SUM OF SQUARES		1.0152855+00		1.0152794+00
L		0		0
LAMBDA		0.0000000		0.0000000
GAMMA		1.0000000+00		1.0000000+00
ANGLE IN DEGREES		50.5741		52.5035
MAX. PIVOT REDUCTION		3.1164287-01		3.1303595-01
PAR. 1 K1	S	7.1897584-01	S	7.1661857-01
2 K-1		1.1462594+00		1.1419544+00
3 K2		5.0498069-01		5.0472535-01
4 KF		2.7701470-01		2.7691842-01
5 K3	F	4.7000000-02	F	4.7000000-02
6 DV1		1.0438663+01		1.0435429+01
7 DV3	F	1.8900000+01	F	1.8900000+01

CUMULATIVE NO. OF FUNCTION CALLS = 11 ITERATION TIME = .090 SECONDS CUMULATIVE TIME = 1.225 SECONDS

THE LAST ITERATION

			BASE POINT		TEST POINT
ITERATION NO. 15					
SUM OF SQUARES			1.0152774+00		1.0152775+00
L			10		10
LAMBDA			1.5392241+02		1.5108530+02
GAMMA			1.0000000+00		1.0000000+00
ANGLE IN DEGREES			33.2279		33.8469
MAX. PIVOT REDUCTION			1.3877468+00		1.3806169+00
PAR.	1 K1		7.1484788-01		7.1484797-01
	2 K-1		1.1386636+00		1.1386631+00
	3 K2		5.0453240-01		5.0453218-01
	4 KF	S	2.7684771-01	S	2.7684736-01
	5 K3	F	4.7000000-02	F	4.7000000-02
	6 DV1		1.0433041+01		1.0433041+01
	7 DV3	F	1.8900000+01	F	1.8900000+01

CUMULATIVE NO. OF FUNCTION CALLS = 28 ITERATION TIME = .104 SECONDS CUMULATIVE TIME = 1.934 SECONDS

ITERATION TERMINATES:
MAX. RELATIVE CHANGE IN A PARAMETER .LT. TOL(1) = 1.5000000-04

FINAL PARAMETER VALUES

FINAL VALUE SUM OF SQUARES = 1.0152774+00

AR.	1	K1	7.1484788-01
	2	K-1	1.1386636+00
	3	K2	5.0453240-01
	4	KF	2.7684771-01
F	5	K3	4.7000000-02
	6	DV1	1.0433041+01
F	7	DV3	1.8900000+01

ITERATION SUMMARY

ITER NO.	SUM OF SQUARES	L	LAMBDA	GAMMA	ANGLE	NO. PIVOT FAILURES	NO. BOUNDS FAILURES	MAX. PIVOT REDUCTION	TIME IN SECONDS
0	1.1365013+00	0	0.0000000	1.0000000+00	.0000	0	0	1.0000000+00	.000
1	1.0637526+00	0	0.0000000	1.0000000+00	88.6463	0	0	5.2269500-02	.188
2	1.0407103+00	0	0.0000000	1.0000000+00	84.6198	0	0	2.0637511-01	.159
3	1.0259672+00	0	0.0000000	1.0000000+00	80.1231	0	0	2.3378379-01	.088
4	1.0191133+00	0	0.0000000	1.0000000+00	72.4771	0	0	2.6156288-01	.088
5	1.0165125+00	0	0.0000000	1.0000000+00	67.7928	0	0	2.8240304-01	.088
6	1.0156451+00	0	0.0000000	1.0000000+00	62.8085	0	0	2.9619780-01	.089
7	1.0153819+00	0	0.0000000	1.0000000+00	58.1573	0	0	3.0449280-01	.089
8	1.0153076+00	0	0.0000000	1.0000000+00	55.1640	0	0	3.0916217-01	.089
9	1.0152855+00	0	0.0000000	1.0000000+00	50.5741	0	0	3.1164287-01	.089
10	1.0152794+00	0	0.0000000	1.0000000+00	52.5035	0	0	3.1303595-01	.090
11	1.0152780+00	0	0.0000000	1.0000000+00	55.0506	0	0	3.1379437-01	.146
12	1.0152775+00	0	0.0000000	1.0000000+00	40.8098	0	0	3.1418685-01	.089
13	1.0152774+00	6	7.9434180+00	1.0000000+00	50.4615	0	0	7.6783499-01	.194
14	1.0152774+00	10	1.5392241+02	1.0000000+00	33.2279	0	0	1.3877468+00	.176
15	1.0152775+00	10	1.5108530+02	1.0000000+00	33.8469	0	0	1.3806169+00	.104

SINGULAR VALUES AND VECTORS AT TERMINAL POINT

SING. VALUES			2.0531543+01	7.5750927+00	2.0538434+00	5.4714388-01	3.1483706-01
PAR.	1	K1	.0410932	-.0291798	.9151459	.1993113	-.3467603
	2	K-1	-.0187844	.0386053	-.3582099	.7889792	-.4973472
	3	K2	.2554981	-.9639790	-.0588085	-.0016672	-.0447649
	4	KF	-.9657458	-.2568304	.0296751	-.0095734	-.0200206
F	5	K3	***	***	***	***	***
	6	DV1	-.0291798	.9151459	.1993113	-.3467603	.0000020
F	7	DV3	***	***	***	***	***

NORMALIZING ELEMENTS AND CORRELATION MATRIX

PARAMETER NO.			1	2	3	4	5	6
NORM. ELTS.			1.2427101+00	2.1459824+00	1.9337679-01	8.8998049-02	***	2.7369520+00
PAR.	1	K1	1.0000000					
	2	K-1	.8202319	1.0000000				
	3	K2	.5960934	.5411018	1.0000000			
	4	KF	.6341729	.3799864	.7211083	1.0000000		
F	5	K3	***	***	***	***	***	
	6	DV1	.6915977	.4198046	.6863758	.7285116	***	1.0000000
F	7	DV3	***	***	***	***	***	***

PARAMETER NO.			7
NORM. ELTS.			***
PAR. F	7	DV3	***

CONFIDENCE LIMITS ON LINEAR HYPOTHESIS

			LOWER LIMIT	FINAL VALUE	UPPER LIMIT
PAR.	1	K1	2.0365294-01	7.1484788-01	1.2260428+00
	2	K-1	2.5590318-01	1.1386636+00	2.0214241+00
	3	K2	4.2498590-01	5.0453240-01	5.8407889-01
	4	KF	2.4023792-01	2.7684771-01	3.1345750-01
F	5	K3	•••	4.7000000-02	•••
	6	DV1	9.3071828+00	1.0433041+01	1.1558900+01
F	7	DV3	•••	1.8900000+01	•••

EXPLORATION

			LOWER TEST	SUM OF SQUARES	LINEAR EST. OF SUM OF SQUARES	UPPER TEST	SUM OF SQUARES	LINEAR EST. OF SUM OF SQUARES
PAR.	1	K1	5.8704915-01	1.0891182+00	1.0857894+00	8.4264661-01	1.0793176+00	1.0857894+00
	2	K-1	9.1797353-01	1.0718083+00	1.0633190+00	1.3593538+00	1.0514349+00	1.0633190+00
	3	K2	4.8464578-01	1.0485589+00	1.0472539+00	5.2441902-01	1.0459016+00	1.0472539+00
	4	KF	2.6769526-01	1.0486782+00	1.0485286+00	2.8600015-01	1.0476126+00	1.0485286+00
F	5	K3	4.7000000-02	•••	•••	4.7000000-02	•••	•••
	6	DV1	1.0151577+01	1.0497730+00	1.0497794+00	1.0714506+01	1.0497868+00	1.0497794+00
F	7	DV3	1.8900000+01	•••	•••	1.8900000+01	•••	•••

FINAL FUNCTION VALUES AND RESIDUALS

WEIGHTED ROOT MEAN SQUARE RESIDUAL = 2.0567747-01 NO. DEGREES OF FREEDOM = 24
THIS IS THE SCALE UNIT IN THE GRAPH OF THE WEIGHTED RESIDUALS.

EXPT. NO.	VAR. NO.	PREDICTION	OBSERVATION	RESIDUAL	WEIGHTED RES.	GRAPH OF WEIGHTED RESIDUAL (-2 -1 0 +1 +2)
1	1	9.9787569+00	1.0700000+01	7.2124302-01	2.1994956-01	
2	1	9.2804216+00	8.5999999+00	-6.8042171-01	-2.3174328-01	
3	1	7.3662154+00	6.7000000+00	-6.6621542-01	-2.5716260-01	
4	1	5.4804437+00	5.3000000+00	-1.8044370-01	-7.8446331-02	
5	1	4.2823373+00	4.7000000+00	4.1766268-01	1.9275936-01	
6	1	3.4886816+00	3.9000000+00	4.1131839-01	2.0811247-01	
7	1	2.5317002+00	2.9000000+00	3.6829981-01	2.1632716-01	
8	1	1.9680364+00	1.8000000+00	-1.6803640-01	-1.2529702-01	
9	1	1.2821248+00	1.3000000+00	1.7875180-02	1.5675218-02	
10	1	8.5712982-01	9.0000000-01	4.2870179-02	4.5186876-02	
11	1	5.7541756-01	5.9999999-01	2.4582438-02	3.1738964-02	
12	1	3.8655368-01	4.0000000-01	1.3446320-02	2.1260498-02	
13	1	3.6691214-01	5.9999999-01	2.3308786-01	3.0094522-01	
14	1	1.0177188+00	1.4000000+00	3.8228121-01	3.2302197-01	
15	1	1.7424948+00	2.0000000+00	2.5750524-01	1.8208370-01	
16	1	2.2834884+00	2.9000000+00	6.1651158-01	3.6211856-01	
17	1	2.7046753+00	2.6000000+00	-1.0467532-01	-6.4949329-02	
18	1	3.3246357+00	3.4000000+00	7.5364292-02	4.0863851-02	
19	1	3.7616347+00	3.3000000+00	-4.6163473-01	-2.5410884-01	
20	1	4.3145909+00	4.4000000+00	8.5409045-02	4.0692727-02	
21	1	4.5967946+00	4.5000000+00	-9.6794605-02	-4.5606594-02	
22	1	4.7076648+00	4.2000000+00	-5.0766486-01	-2.4766554-01	
23	1	4.7077284+00	4.5000000+00	-2.0772839-01	-9.7875126-02	
24	1	4.5215347+00	4.3000000+00	-2.2153473-01	-1.0693498-01	
25	1	4.2224821+00	4.4000000+00	1.7751783-01	8.4577513-02	
26	1	3.8917753+00	4.4000000+00	5.0822473-01	2.4214121-01	
27	1	2.2406746+00	2.4000000+00	1.5932536-01	1.0288521-01	
28	1	1.2750088+00	1.3000000+00	2.4991229-02	2.1915470-02	
29	1	7.2539110-01	5.0000000-01	-2.2539110-01	-3.1875115-01	

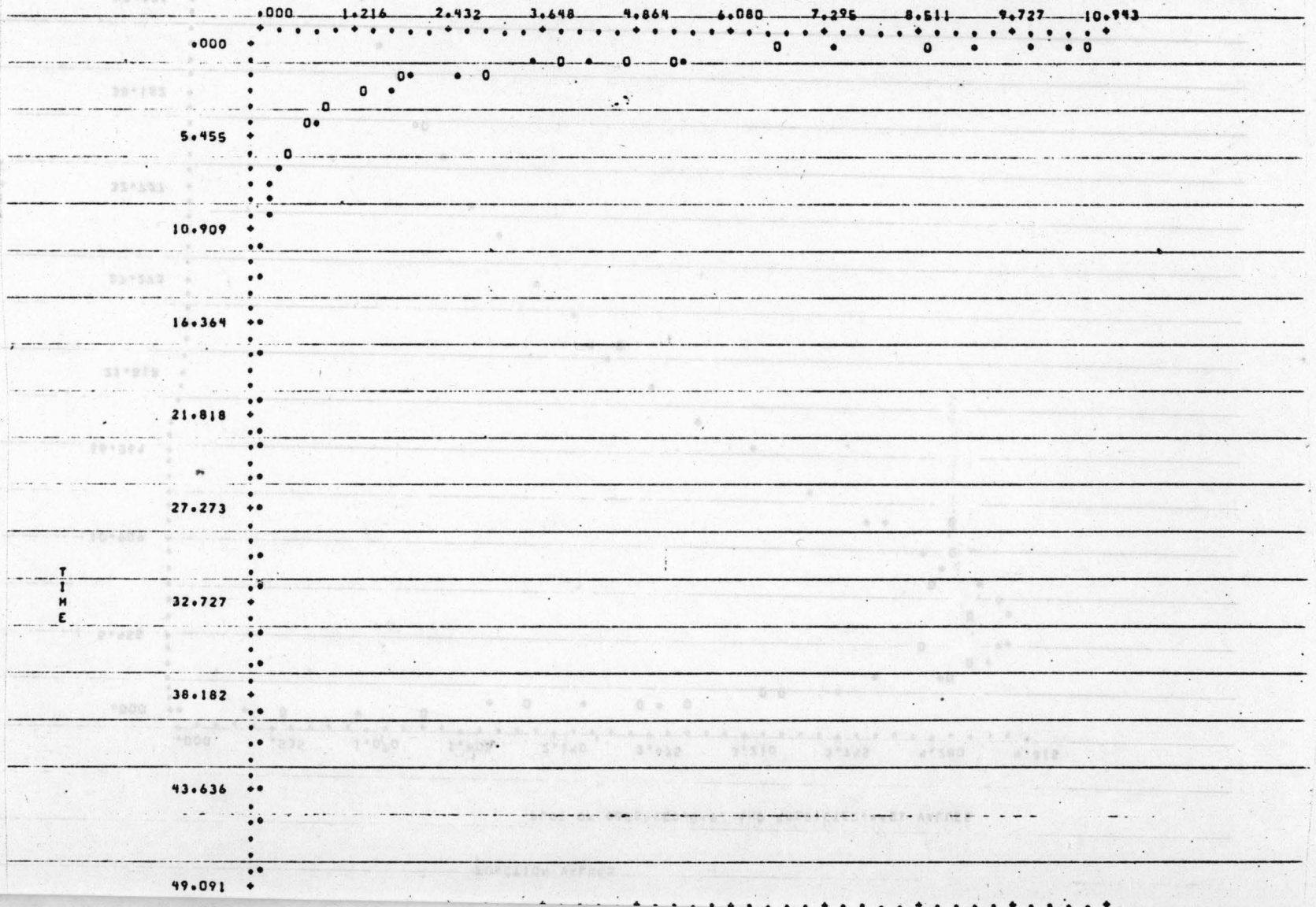
TIME SINCE END OF THE LAST ITERATION = .839 SECONDS TOTAL TIME = 2.775 SECONDS

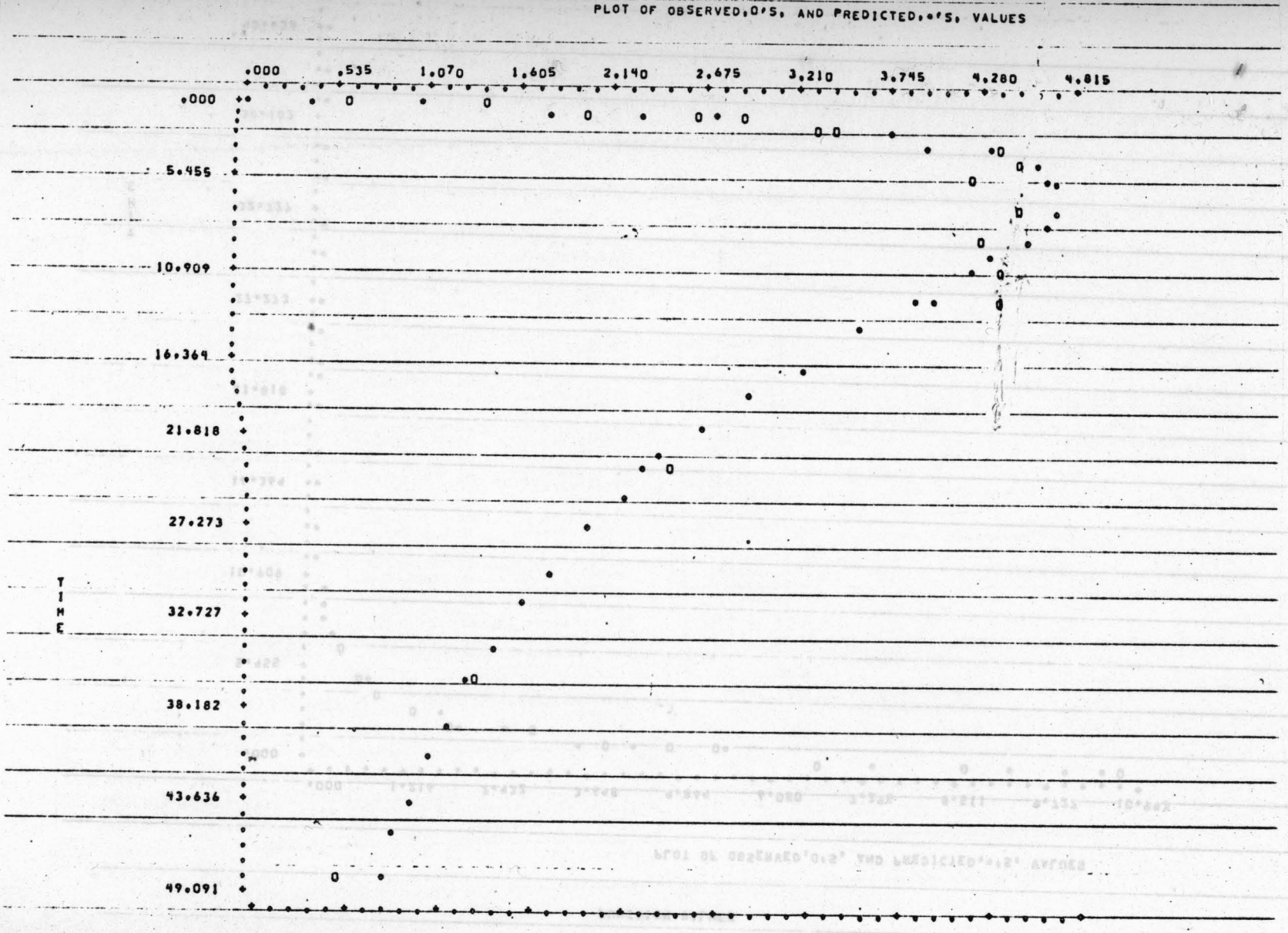
R-SQUARED FOR FUNCTION1 = .9937
COR FOR FUNCTION1 = .9931

R-SQUARED FOR FUNCTION2 = .9914
COR FOR FUNCTION2 = .9928
OVER ALL R-SQUARED= .9928
ALPHA = 2.23719 BETA = .39770

FUNCTION VALUES

PLOT OF OBSERVED,O'S, AND PREDICTED,•'S, VALUES




PLOT OF OBSERVED,O'S, AND PREDICTED,•'S, VALUES
.000
.535
1.070
1.605
2.140
2.675
3.210
3.745
4.280
4.815
.000
5.455
10.909
16.364
21.818
27.273
32.727
38.182
43.636
49.091
TIME

```
$FIN

    RUNID:  815365   PROJECT: 41000          USER: 3895003204

  ITEM                                AMOUNT      COST(DOLLARS)

CPU TIME                          00:00:17.815      $0.67
FILE I/O REQUESTS                          502      $0.23
FILE I/O WORDS                          486787      $0.22
MEMORY USAGE                             0.491      $0.31
CARDS IN                                   244      $0.30
PAGES PRINTED                               48      $1.88
ER + CC                                     16      $0.16
JOB CHARGE                                   1      $0.20

TOTAL COST                                          $3.97

    THE ABOVE DOLLAR AMOUNTS ARE APPROXIMATE AND ARE BASED ON RATES FOR STANDARD RUNS
USER BALANCE                                      $481.38

    INITIATION TIME:   13:27:11-JUL 30,1975

    TERMINATION TIME:  13:30:32-JUL 30,1975

  PREVIOUS RUN TIME:   16:47:32-JUL 29,1975

123456789012    45 PAGES COST    $1.78    USER BALANCE    $481.48 789012345678901234567890123456789012345678901234567890**SEQ NO. 01
123456789012345678901234567890123456789012345678901234567890123456789012345678901234567890123456789012345678901234567890**SEQ NO. 01
123456789012345678901234567890123456789012345678901234567890123456789012345678901234567890123456789012345678901234567890**SEQ NO. 01
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123456789012345678901234567890123456789012345678901234567890123456789012345678901234567890123456789012345678901234567890**SEQ NO. 02
123456789012345678901234567890123456789012345678901234567890123456789012345678901234567890123456789012345678901234567890**SEQ NO. 02
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APPENDIX B

Derivation of Equations Describing Drug Blood Level vs Time Profiles Appropriate to Scheme III

The differential equations describing the amounts of drug in the central and tissue compartments and amount of metabolite in its central compartment as a function of time, appropriate to Scheme III, are:

$$\frac{dA_1}{dt} = k_{-1}A_2 - (k_1 + k_f + k_2)A_1 \qquad \text{Eq. B1}$$

$$\frac{dA_2}{dt} = k_1A_1 - k_{-1}A_2 \qquad \text{Eq. B2}$$

$$\frac{dM_b}{dt} = k_fA_1 - k_3M_b \qquad \text{Eq. B3}$$

The application of the Laplace transform to linear differential equations is useful since it converts them into linear algebraic equations. The Laplace transform of a time function f(t) is F(s) as defined by equation B4,

$$F(s) = \int_0^\infty e^{-st}f(t)dt \qquad \text{Eq. B4}$$

where s is a real number such that the integral converges for some finite value of s and all greater values. The Laplace transforms of functions common to pharmacokinetics do not have to be calculated with equation B4 each time but can be found in Laplace transform tables (21).

The Laplace transforms of equations B1-B3 are

$$(s + k_1 + k_f + k_2)\bar{A}_1 + (-k_{-1})\bar{A}_2 = D \qquad \text{Eq. B5}$$

$$(-k_1)\bar{A}_1 + (s + k_{-1})\bar{A}_2 = 0 \qquad \text{Eq. B6}$$

$$(-k_f)\bar{A}_1 + (s + k_3)\bar{M}_b = 0 \qquad \text{Eq. B7}$$

where the bar represents the Laplace transform of that quantity and D is the dose of methsuximide.

This set of linear algebraic equations (B5-B7) can be solved for $\bar{A}_1$, $\bar{A}_2$ and $\bar{M}_b$ by matrix algebra utilizing Cramer's rule. Hence, the matrix of coefficients is

$$\Delta = \begin{vmatrix} (s + k_1 + k_f + k_2) & -k_{-1} & 0 \\ -k_1 & (s + k_{-1}) & 0 \\ -k_f & 0 & (s + k_3) \end{vmatrix} \qquad \text{Eq. B8}$$

which upon expansion becomes

$$\Delta = (s + k_3)\left\{s^2 + (k_1 + k_f + k_2 + k_{-1})s + k_{-1}k_f + k_2k_{-1}\right\} \qquad \text{Eq. B9}$$

If α and β are defined as

$$\begin{matrix}\alpha \\ \beta\end{matrix} = \frac{1}{2}\left\{(k_1 + k_f + k_2 + k_{-1}) \pm \sqrt{(k_1 + k_f + k_2 + k_{-1})^2 - 4(k_{-1}k_f + k_2k_{-1})}\right\} \qquad \text{Eq. B10}$$

then equation B9 reduces to B11.

$$\Delta = (s + k_3)(s + \alpha)(s + \beta) \qquad \text{Eq. B11}$$

The $\bar{A}_1$ matrix is given by equation B12

$$\Delta\bar{A}_1 = \begin{vmatrix} D & -k_{-1} & 0 \\ 0 & (s + k_{-1}) & 0 \\ 0 & 0 & (s + k_3) \end{vmatrix} \qquad \text{Eq. B12}$$

which upon expansion becomes

$$\Delta\bar{A}_1 = D(s + k_{-1})(s + k_3) \qquad \text{Eq. B13}$$

The value of the Laplace transformed A_1 is then

$$\bar{A}_1 = \frac{\Delta\bar{A}_1}{\Delta} \qquad \text{Eq. B14}$$

$$\text{or} \quad \bar{A}_1 = \frac{Ds + Dk_{-1}}{(s + \alpha)(s + \beta)} \qquad \text{Eq. B15}$$

The anti-Laplace of equation B15, found in Tables (21), is

$$A_1 = \frac{(Dk_{-1} - D\alpha)e^{-\alpha t} - (Dk_{-1} - D\beta)e^{-\beta t}}{\beta - \alpha} \qquad \text{Eq. B16}$$

which rearranges to equation B17, the desired equation, which describes the amount of methsuximide in the central compartment as a function of time, i.e. text equation 19.

$$A_1 = \frac{D}{(\alpha - \beta)}\left\{(k_{-1} - \beta)e^{-\beta t} - (k_{-1} - \alpha)e^{-\alpha t}\right\} \qquad \text{Eq. B17}$$

Utilizing a similar development (equations B18-B20) yields equation B21 which describes the amount of methsuximide in the tissue compartment as a function of time, i.e. text equation 20

$$\Delta\bar{A}_2 = \begin{vmatrix} (s + k_1 + k_f + k_2) & D & 0 \\ -k_1 & 0 & 0 \\ -k_f & 0 & (s + k_3) \end{vmatrix} \qquad \text{Eq. B18}$$

$$\Delta\bar{A}_2 = Dk_1(s + k_3) \qquad \text{Eq. B19}$$

$$\bar{A}_2 = \frac{\Delta\bar{A}_2}{\Delta} = \frac{Dk_1}{(s + \alpha)(s + \beta)} \qquad \text{Eq. B20}$$

$$A_2 = \frac{Dk_1}{(\alpha - \beta)}(e^{-\beta t} - e^{-\alpha t}) \qquad \text{Eq. B21}$$

Similarly, the development (equations B22-B24) for 2-methyl-2-phenylsuccinimide results in equation B25, i.e. text equation 21

$$\Delta\bar{M}_b = \begin{vmatrix} (s + k_1 + k_f + k_2) & -k_{-1} & D \\ -k_1 & (s + k_{-1}) & 0 \\ -k_f & 0 & 0 \end{vmatrix} \qquad \text{Eq. B22}$$

$$\Delta\bar{M}_b = Dk_f(s + k_{-1}) \qquad \text{Eq. B23}$$

$$\bar{M}_b = \frac{\Delta \bar{M}_b}{\Delta} = \frac{Dk_f(s + k_{-1})}{(s + k_3)(s + \alpha)(s + \beta)} \qquad \text{Eq. B24}$$

$$M_b = Dk_f\left\{\left[\frac{\alpha - k_{-1}}{(k_3 - \alpha)(\alpha - \beta)}\right]e^{-\alpha t} + \right. \qquad \text{Eq. B25}$$

$$\left.\left[\frac{\beta - k_{-1}}{(\beta - k_3)(\alpha - \beta)}\right]e^{-\beta t} + \left[\frac{k_3 - k_{-1}}{(\beta - k_3)(k_3 - \alpha)}\right]e^{-k_3 t}\right\}$$

It is to be noted that the units of D, the dose of methsuximide, should be in μmoles since biotransformation of methsuximide to 2-methyl-2-phenylsuccinimide is on a mole for mole basis not μg for μg. However, in these experiments concentrations were measured as μg ml^{-1}, dose was in mg and distribution volumes were in liters. Therefore, the dose in mg was prefixed by the ratio of molecular weights of metabolite to methsuximide (189/203) so that C_{M_b} units of μg ml^{-1} could be used. When the computer uses equation B26 to calculate C_{M_b} with D in mg and V in l the unit will be μg ml^{-1}.

$$C_{M_b} = \frac{189Dk_f}{203V_3}\left\{\left[\frac{\alpha - k_{-1}}{(k_3 - \alpha)(\alpha - \beta)}\right]e^{-\alpha t} + \right. \qquad \text{Eq. B26}$$

$$\left.\left[\frac{\beta - k_{-1}}{(\beta - k_3)(\alpha - \beta)}\right]e^{-\beta t} + \left[\frac{k_3 - k_{-1}}{(\beta - k_3)(k_3 - \alpha)}\right]e^{-k_3 t}\right\}$$

APPENDIX C

Area Under the Metabolite Curve After Intravenous Methsuximide Dosing

Equation C1 gives the concentration of the metabolite in the body after an intravenous methsuximide dose as a function of time.

$$C_{M_b} = \frac{189}{203}\frac{Dk_f}{V_3}\left\{\left[\frac{\alpha - k_{-1}}{(k_3 - \alpha)(\alpha - \beta)}\right]e^{-\alpha t} + \left[\frac{\beta - k_{-1}}{(\beta - k_3)(\alpha - \beta)}\right]e^{-\beta t} + \left[\frac{k_3 - k_{-1}}{(\alpha - k_3)(k_3 - \alpha)}\right]e^{-k_3 t}\right\} \qquad \text{Eq. C1}$$

The area under this curve is given by equation C2 which becomes equation C3 after integration.

$$\text{Area } C_{M_b} = \frac{189k_fD}{203V_3}\left\{\int_0^\infty \frac{(\alpha - k_{-1})}{(k_3 - \alpha)(\alpha - \beta)} e^{-\alpha t}dt + \int_0^\infty \frac{(\beta - k_{-1})}{(\beta - k_3)(\alpha - \beta)} e^{-\beta t}dt + \int_0^\infty \frac{(k_3 - k_{-1})}{(\beta - k_3)(k_3 - \alpha)} e^{-k_3 t}dt\right\} \qquad \text{Eq. C2}$$

$$\text{Area } C_{M_b} = \frac{189k_fD}{203V_3}\left\{\frac{1}{\alpha}\frac{(\alpha - k_{-1})}{(k_3 - \alpha)(\alpha - \beta)} + \frac{1}{\beta}\frac{(\beta - k_{-1})}{(\alpha - \beta)(\beta - k_3)} + \frac{1}{k_3}\frac{(k_3 - k_{-1})}{(\beta - k_3)(k_3 - \alpha)}\right\} \qquad \text{Eq. C3}$$

When the quantities within the bracket in equation C3 are put over the common denominator and simplified equation C4 results (text equation 26),

$$\text{Area } C_{M_b} = \frac{189}{203} \frac{D}{V_3} \frac{k_f k_{-1}}{k_3 \alpha \beta} \qquad \text{Eq. C4}$$

where D is the dose of methsuximide in mg, V_3 is the distribution volume of the metabolite in l and all rate constants have units of $hour^{-1}$. The units of area C_{M_b} is then $\mu g\ hr\ ml^{-1}$.

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