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16. Abstract

An evaluation was made of existing data on concentrations of marijuana, secobarbital, diazepam, diphenhydramine, and methaqualone in blood, saliva and urine to assess the feasibility of establishing chemical tests for detecting drug-impaired driving. The study employed standard pharmacokinetic methods to relate urine and saliva concentrations to blood levels, which were related to measures of behavioral impairment in laboratory tasks.

Marijuana was the only drug for which sufficient data were available to suggest the use of urine tests to establish the need to obtain or analyze a blood specimen for THC. Data from numerous studies support the proposal that testing for THC metabolites in urine at or above the 100 ng/ml concentration will provide better than a 50% probability of detecting levels of THC in the blood that may be associated with impairment.

Saliva appears to offer more promise as a body specimen for a presumptive screen of the other drugs included in the study. Analysis of data on secobarbital, as a representative of the barbiturate group of sedatives, suggested saliva concentrations in excess of 0.5 ug/ml may serve as a possible threshold for predicting impairing levels of the drug in the blood. Similarly, a combined concentration of 5 ng/ml of diazepam and its primary metabolite in saliva appeared as a reasonable level. The antihistamine dipehenhydramine gives high saliva concentrations following its use, thus level of 180 ng/ml in saliva was selected as a threshold for conducting a blood analysis. Evaluation of data on methaqualone suggests a threshold level of 150 ng/ml in saliva.

It is cautioned that this was a preliminary study based on existing data. Additional studies and collection of more prevelance data are necessary to further establish the reliability of the suggested threshold levels in order to predict when blood tests for a specific drug are necessary or desirable. Such tests are presently only available for alcohol and marijuana with use limited to the stationhouse or emergency room. At the present state of knowledge, blood is the only body fluid that may serve in a limited manner to relate drug levels to impaired driving.

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FEASIBILITY ASSESSMENT OF CHEMICAL TESTING FOR DRUG IMPAIRED DRIVING

- FINAL TECHNICAL REPORT -

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FEASIBILITY ASSESSMENT OF CHEMICAL TESTING FOR DRUG IMPAIRED DRIVING

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I. INTRODUCTION

The overall objective of this project was to assess the feasibility of chemical testing for drug impairment. The first part of the study was directed towards the question of whether certain concentrations of selected drugs in body fluids can be associated with driving impairment. This required a detailed review of the literature and acquisition of as yet unpublished data that could provide a basis for the evaluation. From the data obtained, it was decided to proceed with the necessary analyses for marijuana, diazepam, secobarbital, diphenhydramine, and methaqualone.

The nature and quality of impairment and/or epidemiological data varied considerably across all of the drugs. Of significant value was the availability of impairment data on all of the drugs from a study conducted by Moscowitz and Sharma under a contract from the National Highway Traffic Safety Administration (NHTSA) and the National Institute on Drug Abuse (NIDA). This study provided uniform performance task measures, which gave some commonality to the levels of impairment. Unfortunately, the study only employed low to moderate doses of the drugs, so that in some cases the performance decrements were too low and variable to permit accurate correlations with blood concentrations. Nevertheless, it was judged that there was sufficient data from other studies to corroborate the time course of impairment for various doses of the drugs.

The impairment measures were all based on laboratory studies and therefore have limited relative validity as measures of driving ability or of a nature that they could predict errors that could lead to a vehicular crash. Behavioral tasks, such as tracking, visual search, reaction times, etc. under various conditions, have tradionally been considered potential indicators of possible impairment in one or more of the functions required for safe operation of a vehicle. Clearly all of the drugs included in this study caused some degree of impairment at the low to moderate doses used. It seems safe to assume that the use of larger and more common doses will cause even more serious impairment. Thus, the study reported here may be considered an assessment of presumptive impairment measures as they relate to body fluids levels, that in turn will provide presumptive indications of impairment.

A separate NHTSA contract provided a review of the epidemiology literature, which gave varying indications that the drugs covered here may all be contributory in motor vehicle crashes or in leading to a DUID arrest. Interpretation of the results was frequently complicated by the concommitant presence of alcohol or other drugs. Of the five drugs covered in this study, the clearest epidemiological picture in regards to the relationship between blood levels and impairment was for methaqualone. A careful study of 536 DUID cases that involved the drug alone revealed a distinct blood level threshold of 1 to 2 ug/ml. Similar data on the other drugs may be available in the records of medical examiners, but this data was not captured in the present study.

II. GENERAL CONSIDERATIONS

As noted above, sufficient data was only available for the five drugs listed. Other drugs of interest, e.g., cocaine and phencyclidine, were not included because no data was available on their potential impairment under controlled studies. Based on the availability of pharmacokinetic data, the analyses reported herein were conducted on urinary concentrations of THC-9-acid, the major THC metabolite, and not the total metabolite concentration, which is more commonly and readily measured.

Data available on the other four drugs revealed that metabolite concentrations in urine tended to continue to rise beyond the periods of demonstrable impairment. Often, detailed studies on single metabolite concentrations were not available, thus preventing any further analysis of the possible use of urine concentrations for these drugs. However, there were sufficient data available on the secretion of these drugs into saliva to permit a detailed analysis of that body fluid. Saliva has long been felt to be a desirable fluid for drug analysis since it may be obtained in an unobtrusive manner.

III. PHARMACOKINETIC METHODOLOGY

In the search for relationships between drug levels in body fluids and drug-induced impairment, it is necessary to characterize the pharmacokinetics, pharmacodynamics, and the interrelationships between the two. This is a difficult task that is still in various stages of development due to active research on many basic issues of direct relevance to the overall problem.

The fate of a drug in the body is the object of pharmacokinetics, which is the study of the nature of drug absorption, distribution, binding, and metabolism within the body and elimination from the body. Technological developments in analytical chemistry and methodological developments in mathematical modeling and analysis have lead to a well developed and accepted procedure for pharmacokinetic analysis of many drugs.

The response of the body to a drug can usually be described by pharmacodynamics to characterize the magnitude and duration of

known pharmacological response. In the case of behavioral or performance impairment of driving-related tasks, pharmacodynamics is still in the early stages of development, with results available for a limited number of drugs. Both pharmacokinetics and pharmacodynamics require time dependence to characterize the fate of a drug and its effect. As a result, interrelationships between them necessarily involve time-dependent correlations that are often complex and frequently not unique.

As will be seen below, many of the drugs discussed do not have a fully characterized profile for either the kinetics or the dynamics. As a result it is often necessary to interpolate, extrapolate, and assume logical extensions to the limited data base. It will be clear that many conclusions drawn on relationships between drug levels in body fluids and drug-induced impairment are tentative, conditional, and approximate. The results of this work have clearly defined the need for a surprisingly limited number of experimental studies that would greatly enhance the data base and definitely lead to considerably strengthened findings and conclusions.

Gibaldi and Perrier (1975) have defined pharmacokinetics as

> "the study of the time course of drug and metabolite(s) levels in different fluids, tissues and excreta of the body, and of the mathematical relationships required to develop models to interpret such data."

The first textbook on the subject was written by F. H. Dost over 30 years ago (Dost, 1953).

The now familiar "concentration versus time curves", which are used to describe the change of drug levels in a body fluid, can usually be described in a compact way by a relatively simple mathematical function. This can be used in place of a large table of numbers derived from measurements of drug concentrations in each of a large number of separately collected biological specimens. The measurement of drug concentrations in a specimen is a demanding task in order to obtain results of the necessary precision and accuracy. Likewise, the construction of a mathematical function to describe this data must be done with similar accuracy and precision in order to have a meaningful representation of the experimental data.

The most common functional form to describe the drug concentration, C, over time, t, is the weighed combination of exponentials, such as

$$C(t) = Ae^{-at} + Be^{-bt} + \ldots$$

By the use of a least-squares procedure the constants A, B, a, b are varied as parameters to find those values for which the function gives the best representation or "fit" to the experimental data points. Since each of the parameters are numerically estimated, they each have a degree of variability which is character-

ized by an estimated standard error. The best representation of the curves requires a balance between minimizing the sum-of-squares of the overall function and obtaining parameters for the function that are meaningful.

The most common example of misleading pharmacokinetic analysis via "automated" computer programs is to add more and more terms to the sum of exponentials thus finding a smaller sum-of-squares difference between the experimental and calculated data points. With the added terms, more parameters are available for the fitting of the function to the experimental points, thus the sum-of-squares will always decrease when more are available. However, the estimated uncertainty in the resulting parameters will eventually increase due to having a fixed number of experimental data points with which to determine the mathematical function. Therefore, it is necessary to find the optimum balance between an increased number of parameters in the function and their respective levels of uncertainty. For example, it is desirable to have an estimated terminal half-life, $t/2(b)$, with an uncertainty less than +/- 50%, if possible. The level of "goodness" of the numerically estimated parameters will depend on the experimental protocol design, the accuracy of the experimental data, and the mathematical analysis of the experimental data. A sad reality is that good experimental data is often "lost" via faulty or naive pharmacokinetic analysis.

Pharmacokinetic analysis of plasma data is usually done by a sum of exponential functions as discussed above. Once the parameters have been obtained one can then develop "compartmental models" to describe disposition of the drug in the body. While these compartments have no physiological meaning, this approach often allows the refinement of studies to pursue mechanistic questions related to disposition of the drug in the body. Also, one can use the parameters to reproduce the experimental curve, interpolate between the actual data points, or simulate curves for doses within the known range of doses for which data exist. On the basis of model building one can obtain "micro rate constants" for drug disposition and then calculate predicted amounts excreted into urine, saliva, etc. As a result of the mathematical procedures for obtaining the micro-rate constants, they often have greater uncertainty than the parameters obtained directly from a plasma-time curve. Further, the models are usually not defined in a unique manner. There are instances, however, when the concepts of compartmental analysis can be exploited, by specifically designed experiments, to provide additional insight.

The prediction of drug concentrations in urine is complicated by the secretory nature of urine flow. The amount of drug in plasma that is excreted into urine can often be accurately estimated on the basis of parameters obtained from analysis of the plasma-time curve. However, the amount of drug excreted per unit time will produce concentrations in urine that vary inversely with the volume of urine formed over the same intervals. Urinary output is influenced by such factors as the state of hydration of the individual, the relative amounts of other substances being excreted, and changes in kidney function. Thus, estimates

of urinary drug concentrations as presented in this study are based on averaged data and attempt to predict ranges of concentrations that might be seen under ordinary living conditions.

Characterization of the amount of drug secreted into saliva has not been thoroughly studied by the application of pharmacokinetics, although considerable interest remains focused on the subject (see Caddy, 1984). Saliva is secreted by several glands in the mouth at variable flow rates, thus making for complexity and uncertainty such as that found in attempting to predict urine volumes and concomitant drug concentrations. However, drug secretion in saliva can be described in terms of basic membrane diffusion processes as it involves transport from plasma to saliva of unbound drug and in general is predictable in physiochemical terms.

In the work reported herein, analysis is limited to experimental data already available in the published literature or in contract reports to the National Highway Traffic Safety Administration (NHTSA) and the National Institute on Drug Abuse (NIDA). Idealy one would design the various drug studies and results would be more specific than those generally available. In many cases the plasma-time data or pharmacokinetic parameters are reported. In these cases we attempted to analyze the experimental data if enough information was available, otherwise we accepted the reported parameters and constructed the mathematical function that allowed reproduction of the plasma-time curve. Care was taken to limit the regenerated curves to the time span defined by the data. In some cases we extrapolated to longer time periods and so noted the approximate nature of the estimated curve. In many cases the needed information was available for several doses of the drug of interest. To consider intermediate doses, we have assumed a linear dependence between dose and plasma levels and then generated interpolated intermediate curves. For some of the saliva information, saliva to plasma ratios were given at only a few time points. In these cases we have assumed the plasma pharmacokinetic function is valid for saliva as well and have rescaled the mathematical function on the basis of the ratio information. This probably yields a highly idealized saliva-time curve, since the available experimental saliva concentration curves are rarely smooth in nature.

IV. MARIJUANA

Figures 1 to 4 are graphic representations of plasma concentrations versus time curves taken from data obtained following the smoking of two potencies of marijuana cigarettes. The figures differ only in the time scale. Concentrations of delta-9-tetrahydrocannabinol (THC), the major psychoactive component in marijuana, versus time curves are simulated using the pharmacokinetic parameters reported by Chiang and Barnett (1984). These parameters came from the analysis of the experimental study of Perez-Reyes et al. (1982), which measured THC blood levels and selected pharmacologic effects of smoking marijuana cigarettes of different potencies.

Figure 5 represents an overlay of the time duration of measured impairment reported in the Moscowitz et al. (1979) studies and for self-reported intoxication obtained by Perez-Reyes from the same subjects in which the plasma concentrations cited above were obtained. The latter data are shown in Figure 6 as correlated with the plasma concentrations by Chiang and Barnett (1984). Note is made of the fact that a linear correlation is obtained only after the plasma concentration reaches psuedo-equilibrium.

Figures 7 and 8 are computer generated relative urinary excretion rates and concentration curves that are based on analysis of blood levels of THC and its 9-acid metabolite. These are only qualitative curves in that limited pharmacokinetic parameters were available from plasma data. For the same reason, these are relative curves. The main feature to be seen in Figure 7 is the relative shapes of the curves. That is, the rate of excretion of THC-9-acid in urine after intake of THC is much faster for smoking than that for oral absorption from a cookie. The top three curves in Figure 7 represent a range of values from different smoked doses while the bottom curve is generated from an orally-consumed THC-spiked cookie.

Figure 8 shows relative urine concentrations of the primary THC-9-acid metabolite plotted for one dose as simulated from one set of plasma concentrations, but for two different rates of urinary output. Thus, following a given dose of THC (more appropriately, following given THC plasma levels), the urine concentration could be expected to vary anywhere within the envelope formed by the upper and lower curves for slow or fast urine flow.

The analysis of urine concentrations of cannabinoids following controlled administration of marijuana was reviewed in order to decide which data would be most useful for calibrating the relative concentrations generated earlier using blood data and the pharmacokinetic parameters. It was hoped that the total urinary metabolites, as are measured in the immunoassays, rather than the major THC metabolite, the 9-acid could be used for the analysis. The former was favored because these assays represent the most likely type of test that would be amenable to use in the stationhouse. Unfortunately all of the data available on total metabolite levels was based on single daily collections or on total 24-hour voidings. Thus, the first calibration effort was made with THC-9-acid concentrations.

The best set of complete data was obtained from a study conducted by Perez-Reyes in collaboration with CompuChem Laboratories (1983). Ten subjects each smoked a marijuana cigarette containing 2.8% THC. Separate urine voidings were collected over the next 24 hours. These were analyzed for THC-9-acid by GC/MS. One subject was eliminated because of marijuana use prior to or during the study. The data are presented in Table I.

Because THC plasma levels were not determined for these subjects, it was necessary to simulate the plasma-time curve for the smoking of a 2.8% cigarette. Figure 9 thus presents plasma-time

TABLE I. Urine Concentration of THC-9-acid for 24 Hours after Smoking a 2.8% Marijuana Cigarette (N = 9)

Time (hr)			Concentration (ng/ml)		
Range	Midpoint	N	Average	SEM	Range
1.3 - 2.2	1.8	5	35	16	8 - 98
2.7 - 4.3	3.5	6	54	16	8 - 112
4.7 - 5.8	5.3	6	68	19	27 - 135
6.5 - 7.7	7.1	6	71	18	18 - 120
8.0 - 11.7	9.9	9	42	11	12 - 116
14.3 - 18.8	16.6	12	38	11	5 - 131
20.3 - 24.0	22.2	15	44	9	5 - 96

curves simulated for the concentration of THC for 12 hours after smoking a 1.3% and 2.5% marijuana cigarette using the pharmacokinetic parameters of Chiang et al. (1984) from the experimental data of Perez-Reyes et al. (1982). In Figure 10, a curve is generated by renormalization of the data in Figure 9 to simulate an estimated THC plasma-time curve for a 2.8% THC dose.

Figure 11 is a presentation of the urine data from Table I. The middle curve is mean values for the seven time intervals over the 24-hour period. The upper and lower curves are the + and - one standard error of the means (SEM) with the number of values for each time interval shown below the curves. Note that the largest variation occurs in the 14.3 - 18.8-hour time interval where 7 of the 12 specimens appeared to be first morning voidings. Similarly, 4 more first voidings occured in the last time interval. The apparent increase in concentration at the latter time points is very likely an artifact of variation in urinary voiding, as analysis of individual data reveals the cummulative amount of THC-9-acid excreted over the 24-hour period is a mathematically "well behaved" curve that rapidly rises at early times and then gradually approaches plateau values at 24 hours. However, since the total amount of THC-9-acid excreted in urine is a small fraction (about 30%) of the dose administered (Wall, 1974; Sadler et al., 1984), one can not draw strong inferences from the cummulative excretion curves.

Figures 12 - 14 are simulations of the THC-9-acid urine concentration data from Figure 11, where the curve is normalized to the maximum concentration (Cmax) of 71 ng/ml and the upper and lower curves are normalized to + and - one SEM. If it is assumed that the mean (middle) curve represents average urinary excre-

tion, then the + and - variation corresponds to a 25% variation in urine flow, which is a reasonable value. To construct the THC-9-acid curve, it was necessary to use the pharmacokinetic rate constant from the terminal portion of the THC plasma curve and the rate constant for THC-9-acid formation. The best estimate for the THC half-life has been reported in the range 18-24 hours (Hunt & Jones, 1980).

The rate constant for formation of the metabolite was estimated from the plasma curve for THC-9-acid by use of the time at which the maximum plasma concentration for THC-9-acid occurs, together with the THC half-life. Since no solid data are available for this determination, only conflicting results were obtainable. Therefore, the THC-9-acid formation rate constant was mathematically varied with the range of THC half-lives in order to adjust the urine data for time of Cmax. In other words, the rate constant for metabolite formation was derived from the experimental data by finding the best visual fit (qualitative) calculated from the mathematically generated urinary excretion curve.

Using the shorter THC half-life (18 hours), Figure 12 shows a fair representation of the experimental data of Figure 11, where the metabolic formation constant is about 1.0. A better fit was apparent in Figure 13 with the longer half-life (24 hours) for THC and a formation constant of 0.3. The most representative simulation is presented in Figure 14, where Cmax occurs at the observed Tmax, about 7 hours, for the THC half-life of 24 hours and the THC-9-acid formation rate constant of 0.40. The exact interpretation of this rate constant is not clear, since THC-9-acid has a moderate half-life (ca. 8 hours) that is produced via the short-lived 11-hydroxy-THC metabolite (<8 hours). In any case, the value of 0.4 stands as a first report for an estimate of the rate constant for the formation of THC-9-acid in plasma as a result of smoking a marijuana cigarette.

The above analysis permitted the generation of theoretical urine concentration curves from any plasma-time curve, within limits imposed by possible saturation of various metabolic or excretion pathways. Examination of the experimental curves in Figure 11, suggests a cut-off for detection of marijuana use within the 8 to 9-hour time frame for impairment to be around 60 ng/ml. However, inspection of at the simulated curves in Figure 14 suggests that something in the order of 80 to 90 ng/ml would be required, although those levels would clearly miss the "average" concentration curve. As was noted above, a number of first morning voidings, occurring in the 18 to 24-hour time frame, kept the terminal part of the average curve from descending through 24 hours. An inspection of the concentrations for individual urine specimens showed that, of the 27 specimens provided prior to 8-9 hours after smoking, only 6 (22%) were above 100 ng/ml and 10 (37%) were above 80 ng/ml. Over the entire 24-hour period, of the 7 that were above 100 ng/ml, 6 (86%) were collected in the first 8 hours, and of the 15 over 80 ng/ml, 10 (66.7%) occurred in less than 9 hours.

The above results suggest two approaches to the setting of a presumptive impairment concentration of the THC-9-acid metabolite in urine. The use of a conservatively high cut-off such as 80 or 100 ng/ml would have given a 67% or 86% probability, respectively, of predicting the 8 hour time frame. However, such cut-offs would have missed from 63 to 78% of the individual specimens provided within 8 hours of smoking a 2.8% marijuana cigarette. But it turns out that the actual data on individual specimens shows that dropping to 60 ng/ml would pick up only one additional specimen in the <8 hour period and one >18 hours. Thus, 60 ng/ml would have given a 65% probability.

If the urine concentration is to be used to predict a plasma level, which in the simulated case for a 2.8% cigarette as shown in Figure 2, has dropped to 2 ng/ml by 8 hours, then a concentration of 80 to 100 ng/ml would be required in order to give a reasonable probability of predicting concentrations over 2 ng/ml. Of course all such predictions and correlations are limited to the acute use situation. Frequent or heavy users would give proportionately higher levels for longer periods of time. However, there is little data to show to what degree they may have developed tolerance to the impairing effects of THC. They may well still be impaired for longer periods of time thereby still showing a reasonable correlation with plasma levels of THC.

During the course of this study, data on frequent users of marijuana were obtained from Dr. Michael Peat. This came from a study that involved two groups of five subjects each. They were classified as "light" users, having admitted smoking no more than one marijuana cigarette a week, and "heavy" users, who claimed to have smoked at least 50 cigarettes per month. The experimental data used for the following analysis were obtained by having each subject smoke a marijuana cigarette containing 18 mg of THC. Blood and urine specimens were collected at several intervals over the first eight hours and daily thereafter for 14 days.

Figure 15 shows the duration in time for which THC and THC-9-acid concentrations could be measured by the assay employed. The THC plasma concentration for light users could be measured for 8 hours and the acid metabolite for 6 days (144 hours) in plasma and urine. For heavy users, THC was observed in plasma for the full 14 days (336 hours), although these concentrations dropped below 1 ng/ml in all subjects after 3 days. THC-9-acid was measurable in both plasma and urine for the 14 days. The range of values for individual subjects was small for plasma concentrations but was extremely large for urine concentrations.

Predose concentrations of THC in plasma were essentially zero in the light users but ranged from 0.4 to 2.4 ng/ml in the heavy users. The predose plasma levels of THC-9-acid in the heavy users ranged from 9 to 109 ng/ml with a mean value of 54 ng/ml. Likewise, the predose concentrations of THC-9-acid in urine in the heavy users were high, ranging 52 to 274 ng/ml for four subjects and 741 ng/ml (!) for the fifth. This last subject had plasma levels of THC-9-acid higher than the mean, but his THC plasma levels were below the mean value. Other than this indi-

cation of possible rapid metabolism, his pharmacokinetic curves appear normal.

Concentration versus time curves for the three measurements for heavy users are presented in Figures 16 to 18. The data for light users over 6 days are shown in Figures 19 to 21. In all cases, the symbols are mean experimental data and the solid curves are the nonlinear best fit functions to represent the data. Due to the long period of time covered by the curves, best fit functions were adjusted for the longer time interval portions of the curves, i.e., 24 hours between specimens. This resulted in some neglect for the very early time portions of the curves. To improve the early-time fits to the data during 0-2 hours would not alter the fits shown, however.

Due to the highly variable nature of the data, a quantitative comparison of pharmacokinetic parameters is unwarrented. Qualitative inspection of Figures 17 and 18, however, show that the apparent terminal half-life of THC-9-acid is much greater in urine (about 100+ hours) than in plasma (50+ hours) for heavy users. This does not appear to be the case for light users, however, as the apparent terminal half-life of THC-9-acid in urine and plasma are approximately the same, about 24 hours, which agrees with almost all other single dose studies.

A review of this data does not suggest very good prospects for establishing a urine threshold level based on the single THC-9-acid metabolite. The range of values found for urine THC-9-acid concentrations for heavy users is too wide and variable. For example, at the 24-hour collection time, the mean was 180 ng/ml with a S.E.M. of 51 ng/ml, and a range of 80 to 367 ng/ml.

Applying the previously suggested threshold level of 100 ng/ml of THC-9-acid in urine to the light users, 7 of the 8 (87.5%) urines over that level were collected within 8 hours of smoking. The heavy users produced 11 out of 16 (69%) urines at that concentration during the same period. These results agree qualitatively with the data from the earlier study.

However, since plasma concentrations were also collected from these subjects, the original premise of predicting plasma levels was put to the test. That is, to rate how many urine specimens at or over 100 ng/ml of THC-9-acid would successfully predict blood/plasma levels that may be associated with impairment, as described above. Urines over 100 ng/ml (N = 8) in light users predicted no plasma levels over 5 ng/ml, and only 3 over 1 ng/ml (37%). In heavy users, 3 specimens over 100 ng/ml (N = 18) predicted plasmas over 5 ng/ml and 7 additional ones over 1 ng/ml (12/18, 67%). Collectively, this group of 10 subjects would have only had 58% of plasma levels over 1 ng/ml predicted from the urine level. This would also have missed all high plasma levels during the first 2 hours after smoking in the light user group.

Although this study included only a limited number of subjects, the rather disappointing results seen here has led to the conclusion that it would be more prudent and certainly easier to

screen urines for total cannabinoids metabolites with a quick, portable assay, such as the existing EMIT system, to select those suspects for blood specimens. It would appear that a cut-off of 100 or 200 ng/ml would be appropriate.

This observation again raised the question of the possible use of saliva tests for marijuana use. Fortunately, a recent article had appeared on the measurement of THC in saliva following the smoking of one-half to two marijuana cigarettes by occassional and chronic users (Gross et al., 1985). Saliva concentrations in the chronic male users ranged from a mean of 329 (S.D 77.4) ng/ml at 30 minutes after smoking to 6.3 (S.D. 7.0) ng/ml at five hours. No THC was detected at 6 hours. During the same period, serum levels of THC were 19.5 (S.D. 4.45) ng/ml at 30 minutes, dropping below detectability at 5 hours. The correlation of saliva to serum levels was 0.91.

The occassional male smokers gave a similar pattern with THC concentrations of 154.7 (S.D. 47.6) ng/ml at 30 minutes and dropping below detectability at five hours. Serum levels were 11.7 (S.D. 1.6) ng/ml at 30 minutes and undetectable at 4 hours. Their correlation with saliva was 0.86. Similar results were obtained with female subjects.

This study suggests that the detection of THC in saliva in a quantitative manner may be a better predictor for the 4 to 5-hour time period following the smoking of marijuana than would a urine test. Quantitation or the setting of a threshold of detection appears necessary since other studies have shown the presence of THC in saliva as long as 24 hours after smoking (Jones and Peat, unpublished). Also, the Gross et al. study showed passively absorbed/adsorbed levels in saliva of 18 ng/ml at 15 minutes following exposure.

Marijuana provided the most complete and satisfying results using the analysis described herein. This drug has been the object of hundreds of studies, many of which provided sufficient data for this analysis. Extensive pharmacokinetic studies conducted by NIDA and behavioral studies supported by NHTSA and NIDA served as the major source of useful data. Thus, it was possible to establish reasonably reliable plasma concentrations versus impairment correlations. Although the pharmacokinetic evaluation helped to establish a linkage between plasma levels of THC and urine concentrations of the primary THC metabolite, the delay in reaching threshold levels in urine by infrequent users of marijuana, has suggested a quick simple test for total immunoassay cross-reacting metabolites is as good or better a predictor of impairing levels of THC in plasma/blood.

V. SECOBARBITAL

It was felt that secobarbital would be a model drug for initiating comparisons of plasma and saliva levels. The plasma levels shown in Figure 22 were constructed to simulate the reported mean levels for the 3.3 mg/kg (about 200 mg) oral dose

reported by Clifford et al. (1975), who reported a range of parameters for both rapid and slow absorption and elimination. The highest plasma levels, which occur for fast absorption and slow elimination, were the data used to generate the curves shown in the figures. Other reported plasma levels (e.g., Faulkner et al., 1978) are consistent with the results shown in the Figures. The data are scaled to simulate plasma levels for doses of 1.89 and 1.26 mg/kg, those used in the Moscowitz NHTSA/NIDA studies on impairment effects of secobarbital on performance.

The theoretical estimate for the saliva to plasma ratio (S/P) for secobarbital is 0.39 to 0.42 by the Henderson-Hasselbach equation (Sharp et al., 1983). The experimental data of Jeffcoat (1981) shows a S/P of 0.31 for a dose of 1.22 mg/kg and 0.33 for a dose of 0.61 mg/kg. Sharp et al. (1983) reported for an oral dose of 50 mg (about 0.7 mg/kg) mean values for S/P of 0.30 at 1 hour, 0.29 at 2 hours, and 0.31 at 3 hours. Therefore, Figures 23 - 26 were generated to show saliva concentrations for "low" saliva secretion with a S/P of 0.30 and "high" saliva secretion with a S/P of 0.42. Figures 23 - 25 are separate simulations for the three plasma levels shown in Figure 22. Figure 26 is a composite of the low and high secretion levels for the three doses, which was constructed to show the range of predicted levels at each dose. Figure 27 represents the saliva-time pharmacokinetic curves expected on the basis of the best experimental mean data available.

Some effort was made to try to generate a plasma vs. impairment curve for the data obtained by Moscowitz. Unfortunately, the relatively low dose of secobarbital used made the performance data too "noisey" for a meaningful correlation. It was therefore decided to look for a time frame of impairment based on the duration of such effects for various doses as listed in Table II. The literature is rather old, except for the data of Moscowitz.

TABLE II. Reported Duration of Effects for Secobarbital

Tmax (hr)	Dose	Test	Reference
6	100 mg	Auto Simulator	Loomis et al. (1958)
14-15	200 mg	Psychological Performance	Kornetsky et al. (1959)
22	200 mg	Flight Simulator	McKenzie et al. (1965)
6-8	1.89 mg/kg	Laboratory Performance	Moskowitz et al. (1979)
4	1.26 mg/kg	"	"

TABLE III. Time Intervals and Plasma Levels Predicted from Saliva Concentrations

Saliva Levels (ug/ml)	Predicted: Low Secreters Plasma Levels	Predicted: Low Secreters Time Interval	Predicted: High Secreters Plasma Levels	Predicted: High Secreters Time Interval
0.8	2.67	--	1.9	<1 - 10
0.6	2.0	<1 - 6	1.4	<1 - 25
0.5	1.67	<1 - 15	1.2	<1 - 31
0.3	1.0	<1 - 36* <1 - 11**	0.7	<1 - 36

*At 3.3 mg/kg dose.
**At 1.89 mg/kg dose.

Moscowitz does report some "hangover" effect of impaired performance at 22 hours, in agreement with the flight simulator data. Otherwise the most significant data from the Moscowitz study shows impairment, at significance levels of p 0.01 to 0.05, for doses of 1.89 and 1.26 mg/kg with most of the tests employed for the times shown.

The cut-off levels were thus set based on the secobarbital saliva levels generated in the figures. The question is one of what saliva concentration has the best probability of predicting a time interval that can be correlated with the time course of impairment measures. From the duration of drug effects listed in Table II, saliva levels can be selected that are indicative of drug-induced impairment. For example, a cut-off level of 0.8 ug/ml or greater covers the time interval from <1 to 10 hours for the "high" secreters only. During this time interval impairment has been reported for doses comparable to the 3.3 mg/kg dose. At a cut-off of 0.6 ug/ml the time span is <1 to 22 hours for "high" secreters and only <1 to 6 hours for "low" secreters. This would be a conservative cut-off because it would only identify time intervals and plasma levels that fall within the longest time interval. However, the 22 hr span of impairment is based on old data in one case and on lower levels of significance in the case of the Moscowitz data. Furtheremore, in the latter study all subjects went home between the 12 and 22 hour evaluations and the "hangover" findings are accordingly highly speculative.

However, it was noted that the "high" saliva levels represent the theoretical maximum level while the "low" levels are based on experimental mean data. Setting a cut-off at 0.5 ug/ml

would give a moderately conservative time interval of <1 to 15 hours for "low" but expected levels, while picking up some "high" secreters out to 31 hours. These relationships are shown in Table III.

Secobarbital concentrations in urine continue to rise up to 10 to 12 hours after oral administration of conservative doses, e.g., 200 mg. Thus, it peaks long after any reported period of significant impairment. Therefore, urine levels would only show presence of the drug and would have no use predicting impairment.

VI. DIAZEPAM

Figure 28 shows the plasma-time curve for a 10 mg oral dose of diazepam according to the data of Kaplan et al. (1973). It is reported that the drug is rapidly and completely absorbed. Assumming linearity for all the processes in the biodisposition of diazepam, the other curves presented in this report are based on the data of Figure 28 by dose renormalization to simulate plasma curves for doses of 2.5 and 5. In Figure 29, estimated theoretical curves are generated for 20 and 40 mg doses on the same assumption, although this is above the range of available data.

The series of reports of de Gier et al. (1980, 1981) have clearly established a saliva concentration to plasma concentration ratio (S/P) over an extended range of concentrations in both fluids. For a plasma concentration range of approximately 100-1200 ng/ml and a saliva range of 1-25 ng/ml, a strong linear correlation ($r = 0.901$) was reported to give a S/P = 0.013 (S.D. 0.002). Similar results were found for the metabolite desmethyldiazepam where they reported a stronger correlation ($r = 0.967$) for a S/P = 0.018 (S.D. 0.004). Saliva curves of diazepam concentrations over time are shown in Figure 30 for doses of 5 to 40 mg using the S/P ratio stated above.

The desmethyl metabolite is known to have a very long half-life, thus only approximate parameters to describe its pharmacokinetics are available. From the data of Kaplan et al. (1973) an approximate mean formation half-life is 1.65 hours and from Breimer et al. (1980) an elimination half-life is 50-99 hours. The maximum plasma level of the metabolite found for the 10 mg dose was 26-37 ng/ml. Using the values given here (terminal half-life 50 hours), we have constructed an approximate plasma curve for the parent drug and the metabolite in Figure 31 for the 10 mg dose. Using the S/P values cited above we present in Figure 32 saliva curves for both diazepam and metabolite for 24 hours after oral administration of 10 mg of diazepam. In Figure 33 saliva concentration-time curves are presented for parent drug and metabolite after oral doses of 5, 10 and 20 mg.

Urinary excretion of diazepam shows that little if any of the parent drug appears in the urine. The drug is extensively metabolized, and metabolite concentrations tend to rise over the first 24 hours or so. There was not sufficient urinary data to attempt establishing any urinary cut-off.

TABLE IV. Duration of Effects of Diazepam

Tmax (hr)	Dose	Test	Reference
24	20-160 mg	Cognitive	Griffiths et al. (1984)
12	40-160 mg	Psychomotor	"
8	40-160 mg	Subjective	"
6	0.126 mg/kg	Reaction time	Moscowitz (1978)
6	0.126 mg/kg	Tracking	"
4	0.126 mg/kg	Search errors	"
3	0.062 mg/kg	Tracking	"

Also, it was not possible to establish a blood versus impairment correlation. It had been hoped that the data of Moscowitz and Sharma (1978) could serve that purpose, but the performance measures were too "noisey" to make any meaningful correlation. Therefore, an approach used for other drugs is used here. Table IV lists the duration of effect for various doses of diazepam on selected performance assays as reported by Griffiths et al. (1984) and by Moscowitz and Sharma (1978). For a 6-hour duration of effect, the plasma cut-off level would be about 150 ng/ml as seen in Figure 28 for the 10 mg dose, and the saliva cut-off would be 2 ng/ml. If a saliva assay were sensitive to both parent drug and metabolite, a saliva level of 2.5 ng/ml would be appropriate. For a 12-hour duration of effect, the saliva cut-off for a simulated 40-mg dose would be 7 ng/ml for diazepam, 3 ng/ml for the metabolite, and 10 ng/ml for both.

VII. DIPHENHYDRAMINE

Figure 34 presents diphenhydramine (DPH) plasma levels simulated to the mean data of Peat et al. (1980) on subjects from the NIDA/DOT study carried out by Moscowitz and Sharma (1978). In agreement with other literature, e.g., Albert et al. (1975) and Carruthers et al. (1979), the DPH plasma peak levels after oral administration occur at 2-3 hours, the levels then decrease rapidly during 4-12 hours, and then have a very slow decline. For the three doses 0.32, 0.63 and 0.94 mg/kg, the mean maximum concentrations (Cmax) are 26, 38 and 62 ng/ml, respectively. DPH is excreted primarily in urine as metabolites with about 5% of the dose excreted as unchanged drug (Glasko et al., 1974).

Figure 35 represents approximate mean saliva curves from the same study for the three doses as estimated (Licko, 1981) via

curves fitted to the experimental data by a nonlinear regression analysis procedure. A 2-3 fold range was found in individual values, thus Figure 36 shows for the high dose the mean curve as well as the estimated upper and lower range of DPH saliva levels. Figure 37 shows the plasma and saliva curves for the 0.94 mg/kg dose. The same data along with the upper and lower range for the saliva data are shown in Figure 38. A similar set of curves is shown in Figure 39 for the DPH dose of 0.63 mg/kg.

The saliva to plasma ratio (S/P) of concentrations for DPH appears to be a point of conflict in the literature. The data reported here from the NHTSA/NIDA study clearly show the S/P ratio considerably greater than unity. The S/P ratios from the data of Jeffcoat (1981) presented in Table V show values greater than unity from 1.5 to 11 hours after an oral dose of 100 mg (ca. 1.33 mg/kg) and similar results for two subjects at a dose of 50 mg (ca. 0.67 mg/kg). Theoretical estimates of S/P via the Henderson-Hasselbach relationship have been reported as S/P = 0.82 (Caddy, 1984) and S/P = 0.16 - 0.05 (Sharp et al., 1983). Caddy used an estimate for DPH plasma protein binding of 79%, while Sharp et al. used the value of 98% reported by Albert et al. (1975). The latter data was an *in vitro* study with blood from two subjects evaluated at 0.5 hour after dosing. The data in Table V show a mean value for S/P of 0.6 at 0.5 hour, while the ratio is greater than 1.0 for all later time points. It is likely that the drug binding to plasma protein varies with drug concentration and it may well vary over time in clinical or other *in vivo* studies. The apparent agreement between the Albert and Jeffcoat data is quite likely fortuitous. It was not immediately clear why the experimental results for Sharp et al., ca. 0.3 - 0.4, were so different from those of Jeffcoat over the same time time interval and doses. If it is assumed that the data in their table is backwards, their value should be 3.2, which agrees with Jeffcoat. Furthermore, it is clear that the theoretical estimates are not in agreement with either Jeffcoat's data nor with Licko's estimate based on curve fitting to the experimental data

TABLE V. Saliva/Plasma Values after a 100 mg Oral Dose of Diphenhydramine

Time (hr)	Range	Mean	(S.D)	N
0.5	0.3 - 1.3	0.6	(0.4)	5
1.5	3.0 - 8.6	5.1	(2.1)	7
3.0	2.0 - 4.8	3.7	(0.9)	6
6.0	0.9 - 2.8	1.5	(0.6)	7
11.0	0.9 - 2.8	1.5	(0.6)	7

R. Jeffcoat, 1981.

of Peat and Moscowitz. The method used in the theoretical calculations has no time, concentration, nor active transport dependence, thus it is not surprizing to find it in error. The assumptions that go into the theoretical estimation of saliva concentrations of exogenous compounds are well reviewed by Caddy (1984).

The experimental data of both the NHTSA study (Jeffcoat, 1981) and the NHTSA/NIDA study (Moscowitz and Sharma, 1978; Peat et al. 1984; Licko, 1981) clearly establish the saliva concentration of DPH as considerably greater than the plasma concentration. Therefore, the curves presented here are at least qualitatively accurate and currently the best approximation available for this drug.

In the NHTSA/NIDA study, it was not possible to establish a good plasma versus effect correlation. Therefore, as with the other drugs, the reported durations of effect for various oral doses of DPH were compared (Table VI). For a dose of 0.94 mg/kg, the duration is reported to be 3-4 hours, and for a 0.63 mg/kg dose to about 3 hours. From the curves in Figure 34, a plasma cut-off level of 65+ ng/ml to detect impairment in tracking and 35+ ng/ml to detect impairment in visual search, according to the reports of Moscowitz and Sharma. This same time span would require a saliva cut-off of 180+ ng/ml for the mean value and upper range saliva curves of Figure 36 to detect tracking impairment. For visual search impairment, a saliva cut-off determined from

TABLE VI. Duration of Effects of Diphenhydramine

Tmax (hr)	Dose	Test	Reference
2.5	50 mg	Signal detection	Linnoila (1973)
2.0	0.74 mg/kg	Tracking	Burns & Moscowitz (1980)
2.0	0.32 "	Tracking	Moskowitz (1978)
2-3	0.63 "	Visual search	"
3.0	0.94 "	Tracking	"
3-4	0.94 "	Visual search	"
7-8	0.63 - 0.94 "	Reaction time and tracking	Licho (1981)*
2-3	50 mg	Sedation test	Carruthers et al. (1978)
4.0	50 mg	Reaction time	"

*Using smoothed fits to all time points for mean data per dose compared to means for placebo. Taken from Moscowitz (1978).

Figure 35 would need to be 70+ ng/ml to detect the mean values and upper estimate curves. However, it must be kept in mind that the saliva values are approximate.

VIII. METHAQUALONE

Figure 40 is a simulation of the plasma-time curve for the concentration of methaqualone (MQL) for 24 hours after an oral dose of 300 mg. The simulation uses the pharmacokinetic parameters reported by Nayak et al. (1974) based on their study with 8 subjects. Figure 41 presents the curve for the MQL dose of 300 mg which is then normalized to simulate plasma-time curves for oral doses of 200, 100, and 50 mg. The simulated curves give concentrations in reasonable agreement with other plasma level data available in the literature (Sharp et al., 1983; Alvan et al., 1974; Morris et al., 1972; White et al., 1976; Gupta et al., 1983, Smith et al., 1973).

Figure 42 presents the plasma curve for the 300 mg dose and an estimated saliva curve for MQL. The saliva curve is based on the data of Sharp et al. (1983), who reported a saliva to plasma ratio (S/P) of 0.11 of 3 hours after an oral dose of 250 mg. The only other S/P data available is from the Moscowitz study (1978) as reported by Peat and Finkle (1980) and Licho (1981). For one subject the S/P ratio was approximately 0.1 over most of a 24-hour post-dose period for a dose of 0.72 mg/kg (ca. 50 mg). However, the same subject had a S/P of 0.4 - 0.6 for a dose of 1.43 mg/kg (about 100 mg). The theoretical estimates for S/P based on the Henderson-Hasselbach equation are 0.08 as reported by Sharp et al. (1983), who used a value for the plasma protein binding of 92%. Alvan et al. (1974) had reported only 8% binding, which would yield a larger estimate for S/P from the theoretical equation. All further saliva curves are based on a S/P value of 0.1.

Figure 43 represents the estimated saliva concentration of MQL for the 300 mg oral dose, based on the S/P estimate of 0.1. Figure 44 gives saliva-time curves for the MQL concentration for 24 hours after an oral dose of 300 to 50 mg. Again, the data is approximated by renormalizing the 300 mg plasma data and then using the S/P value of 0.1.

The reported duration of effects for MQL impairment is 3 hours or less in all reports at doses from 50 to 200 mg (Moscowitz and Sharma, 1978; Alvan et al., 1974). The tests used for impairment were the visual search task, where both reaction time and errors in response were impaired for about 3 hr for doses of 1.43 mg/kg in the Moskowitz and Sharma study, and a critical flicker-fusion task for a dose of 4 mg/kg in the Alvan et al. study.

Metabolites of MQL have been identified in plasma but very little data is available. Sharp et al. (1983) reported a hydroxy metabolite to have a plasma concentration of 0.3 ug/ml at 4-8 hours for the 250 mg/ml dose. Heck et al. (1978) carried out a long term urinary excretion study in one subject and found 0.6%

of the drug excreted unchanged in the urine over ca. 700 hours. There is one report of total immunoassay cross-reacting metabolites in urine that exceeded 50 ug/ml for only a little over 1 hour.

Based on the time course for impairment of 3 hours, an appropriate cut-off for plasma using the simulated plasma curves would be 1.5 to 2 ug/ml for doses of 200 - 300 mg. A saliva cut-off of 150 ng/ml would coincide. This would apparently slightly underestimate the level that seems to correlate with actual blood levels in people arrested on DUID charges (McCurdy et al., 1981). Here it was noted that in 536 cases which were positive for MQL only that a blood cut-off of 1.0 ug/ml seemed apparent for probable intoxication and 2.0 ug/ml for obviously intoxicated. A blood level of 1.0 ug/ml is equivalent to a plasma level of about 1.1 ug/ml. Perhaps the 1.5 ug/ml plasma level is a comfortable compromise.

IX. FEASIBILITY OF DEVELOPING FIELD TESTS

It was recognized at the outset of this study that chemical tests for the on-site identification of the drugs of interest were only available for urine specimens. This technology, EMIT (Enzyme Multiplied Immunoassay Technique), which is manufactured by the Syva Company, is available in a portable kit form, EMIT-st, and in a larger version that could be used in the station-house or emergency room. The portable version is only qualitative and thus indicates the presence of the drug or metabolite. The EMIT-d.a.u. version can provide semi-quantitative results and could possibly be used to assess if certain threshold levels were exceeded. However, as the results described above suggest, urine appears only to be useful in this approach for THC metabolites.

Several other potential on-site test methods were investigated through interviews with researchers and companies. The only candidates that offered any feasibility were based on color spot tests that are very cheap and relatively fast to use. They were all based on paper squares that are impregnated with various metal salts. Unfortunately, the test is rather nonspecific and little is known about their sensitivity. They did not appear to provide reliable quantitation. One version only worked on urine specimens in its present form. These tests do not appear feasible for the type of testing being suggested in this report.

As mentioned above, a saliva collection kit for THC has been marketed by Immunalysis Inc. and is available through MetPath Inc. laboratories. However, the specimen must be sent to the laboratory for radioimmunoassay analysis. It would not be useful for deciding whether or not a blood specimen should be taken, but could serve as a preliminary screen if a blood specimen had already been obtained at the same time as the saliva.

The Syva Company has addressed the question of the feasibility of developing saliva tests for the other drugs of interest. They are presently engaged in completing some demonstration

studies on a new technology that utilizes the proven specificity and sensitivity of antibodies. The method would be very simple to use on-site, such as in the stationhouse or emergency room, would require no electricity, and would provide a visual detection system. Unfortunately, it is estimated that it would take about two years of effort and as much as $1 million to bring such a system to the market for the saliva tests suggested. In order for the Company to justify such an undertaking, considerable interest and potential applications of the tests would have to be demonstrated.

The Syva Company also indicated interest in developing saliva tests for THC as well as the other drugs of interest. They have already conducted studies on THC and have shown that a dipstick-type test can be made. However, as pointed out above, in order for the Syva Company to justify such an undertaking, considerable interst and potential applications of the tests would have to be demonstrated.

X. CONCLUSIONS

The methods described in this Report were applied only to single dose studies since data on the impairing effects of larger or multiple doses of the drugs are not available. It is possible to generate blood and saliva concentrations-time profiles for such doses, but it was not felt to be useful without adequate behavioral information for making correlations. Thus, drug levels chosen here as presumptive indicators of impairment are likely to overestimate the degree of impairment in drug tolerant individuals for some drugs.

The initial conclusions on presumptive levels of the drugs studied are shown in Table VII. As noted above, these concentrations are based on the single administration of low to moderate doses in controlled settings. It is obvious that individuals that use or abuse these drugs will probably take larger and more frequent doses. Therefore, the drug levels that may be seen in these individuals will probably exceed the levels selected here. Because of this and the variability seen between individuals, the levels presented must be considered threshold concentrations for the possible detection of impairment, especially for urine.

This implies a conservative approach, suggesting that it is relatively safe to discount concentrations below those shown, but that all concentrations above those in Table VII could possibly be associated with observed impairment. Consideration is given to the fact that the body specimen will probably only be obtained for drug analyses following an arrest for a traffic violation or after a crash. The most desirable scenario would call for the testing of a saliva and/or urine sample in the stationhouse or emergency room, as is presently done for alcohol, with positive results indicating the necessity of collecting and/or testing a blood specimen. As mentioned earlier, this is currently only done in a few jurisdictions following a blood or breath alcohol assay that shows less than 0.10% BAC.

TABLE VII.

THRESHOLD DRUG CONCENTRATIONS FOR PRESUMPTIVE IMPAIRMENT

DRUG	IMPAIRMENT CORRELATION	CONCENTRATIONS		
		PLASMA/ BLOOD	SALIVA	URINE
Marijuana	Linear Correlation	P 2 ng/ml B 1 ng/ml	No	80 - 100 ng/ml THC-9-acid
Diazepam	Time Course	Plasma 150 ng/ml	2 - 7 ng/ml	None Determined
Diphenhydramine	Time Course	Plasma 65 ng/ml	180 ng/ml	None Determined
Secobarbital	Time Course	Plasma 1.67 ug/ml	0.5 ug/ml	None Determined
Methaqualone	Time Course	P and B 1.5 ug/ml	150 ng/ml	None Determined

This Report concludes that there is a reasonable basis for setting concentrations for the drugs and fluids shown in Table VII. They are reasonable based on the data and scientific approach used. In addition, the thresholds selected for saliva and urine specimens to serve as minimal guides for judging when to obtain and/or analyze blood specimens are also reasonable and conservative. Use of these thresholds would help enforcement personnel to avoid the more invasive and expensive blood collection and/or analysis. If the epidemiological data continues to implicate that these and other drugs are involved in traffic crashes or violations, it will be increasingly important to have some means available to enforce laws against driving under the influence of drugs. The availability of simple detection tests for sites other than in a laboratory, such as in the stationhouse or emergency room, to assist in the selection of suspects that should provide blood specimens could serve as a significant deterrent. Unfortunately at the present time, drug users know enough to choose breath when the choice is afforded them. With the availability of presumptive tests, it may also be possible to modify the laws to permit presumptive tests to be used as a prerequisite for requiring the subsequent collection of a blood specimen. It is also apparent that the tests themselves will not become available until their use is permitted or indicated from the collection of more prevalence data.

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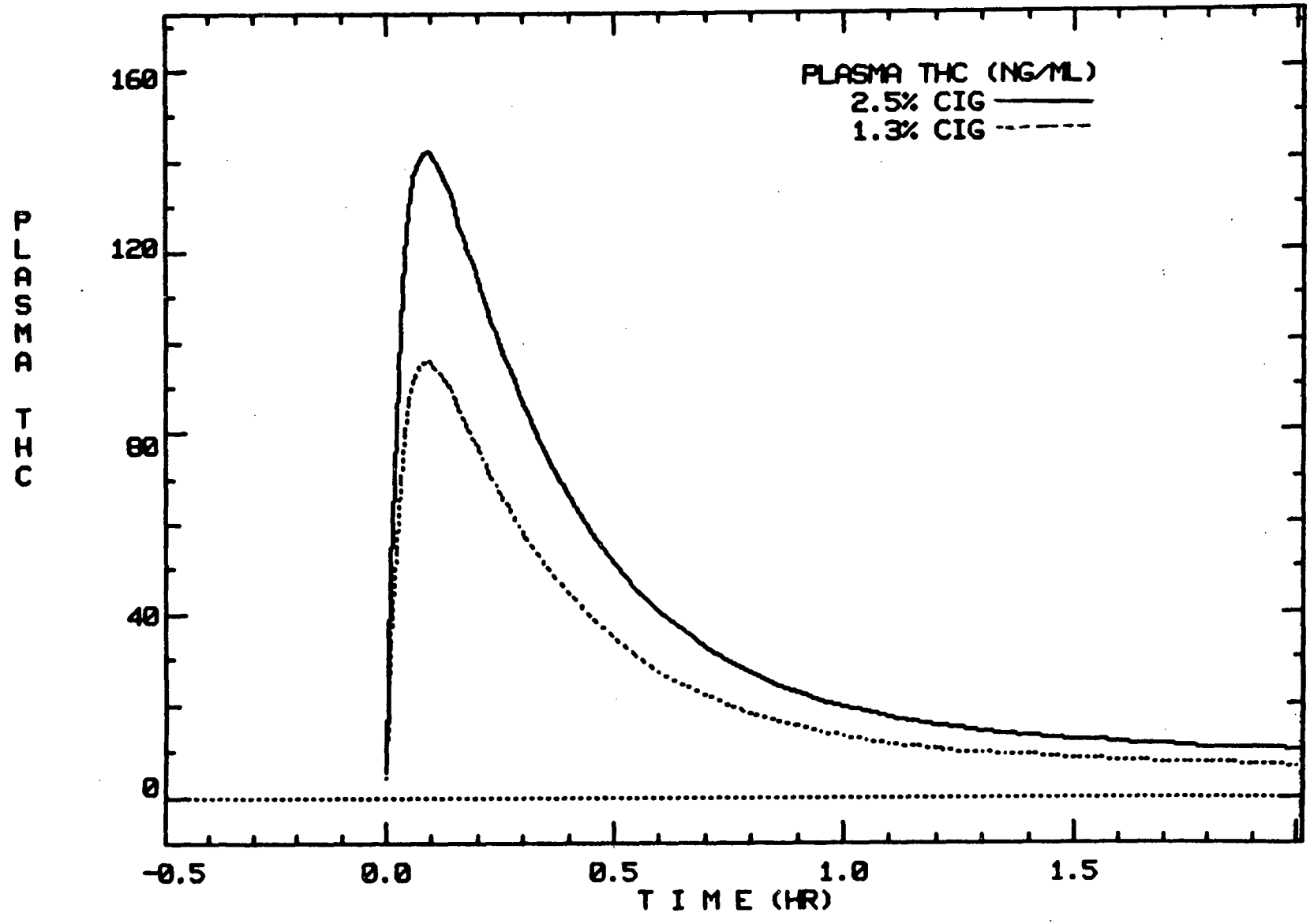

PLASMA THC (NG/ML)
2.5% CIG
1.3% CIG
PLASMA THC
160
120
80
40
0
-0.5
0.0
0.5
1.0
1.5
T I M E (HR)

FIGURE 1

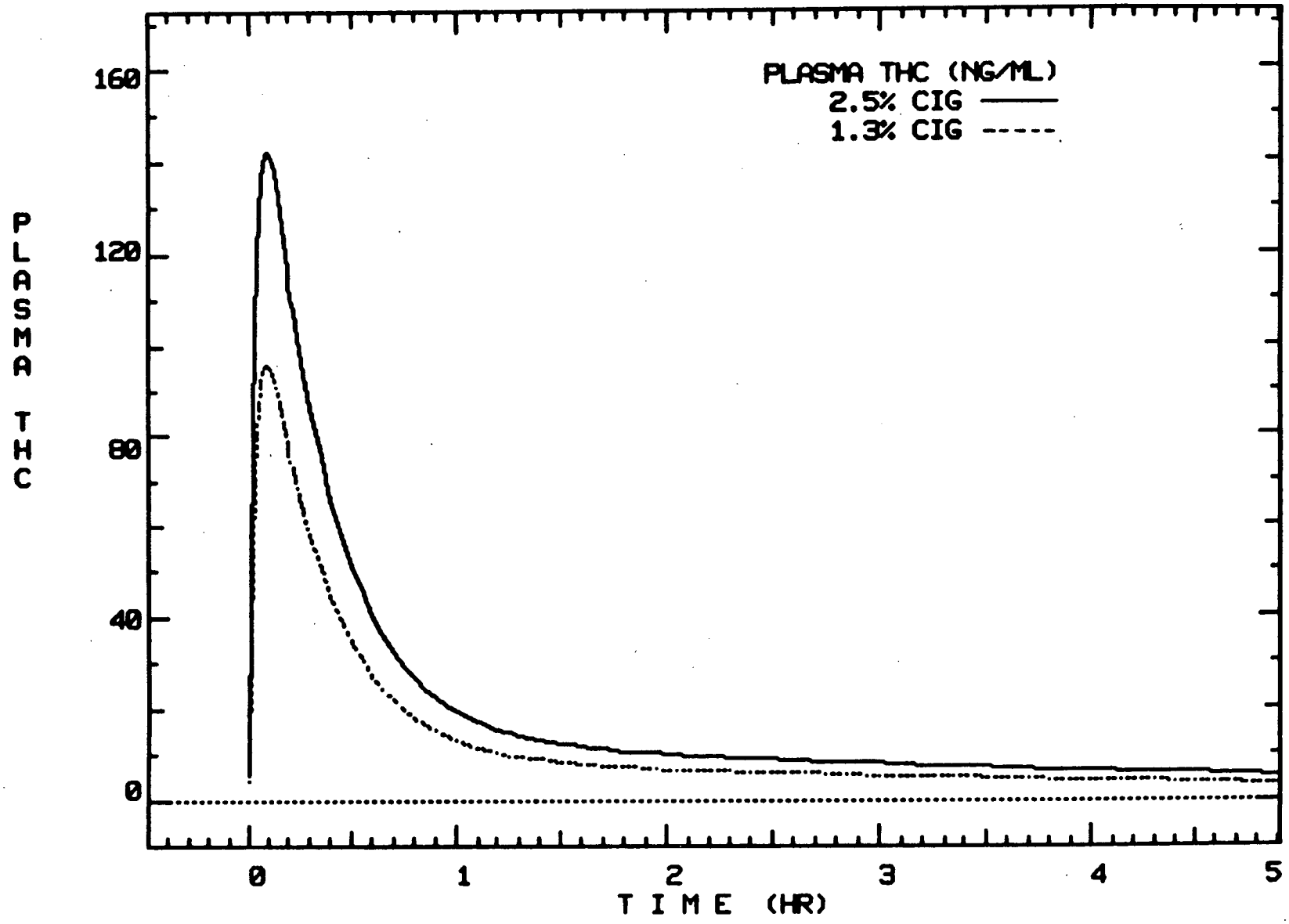

PLASMA THC (NG/ML)
2.5% CIG
1.3% CIG
PLASMA THC
160
120
80
40
0
0
1
2
3
4
5
T I M E (HR)

FIGURE 2

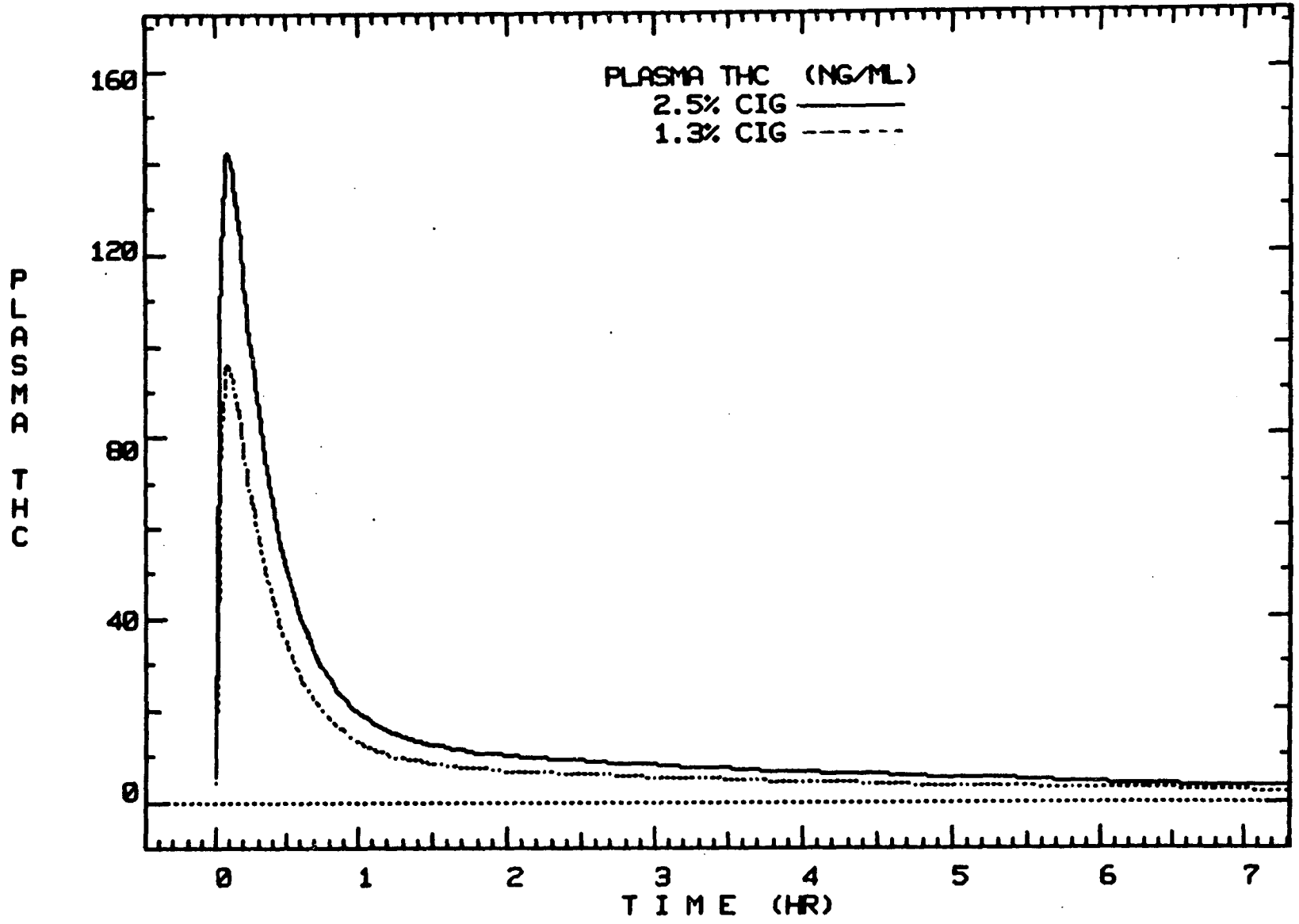

PLASMA THC (NG/ML)
2.5% CIG
1.3% CIG
160
120
80
40
0
PLASMA THC
0
1
2
3
4
5
6
7
TIME (HR)

FIGURE 3

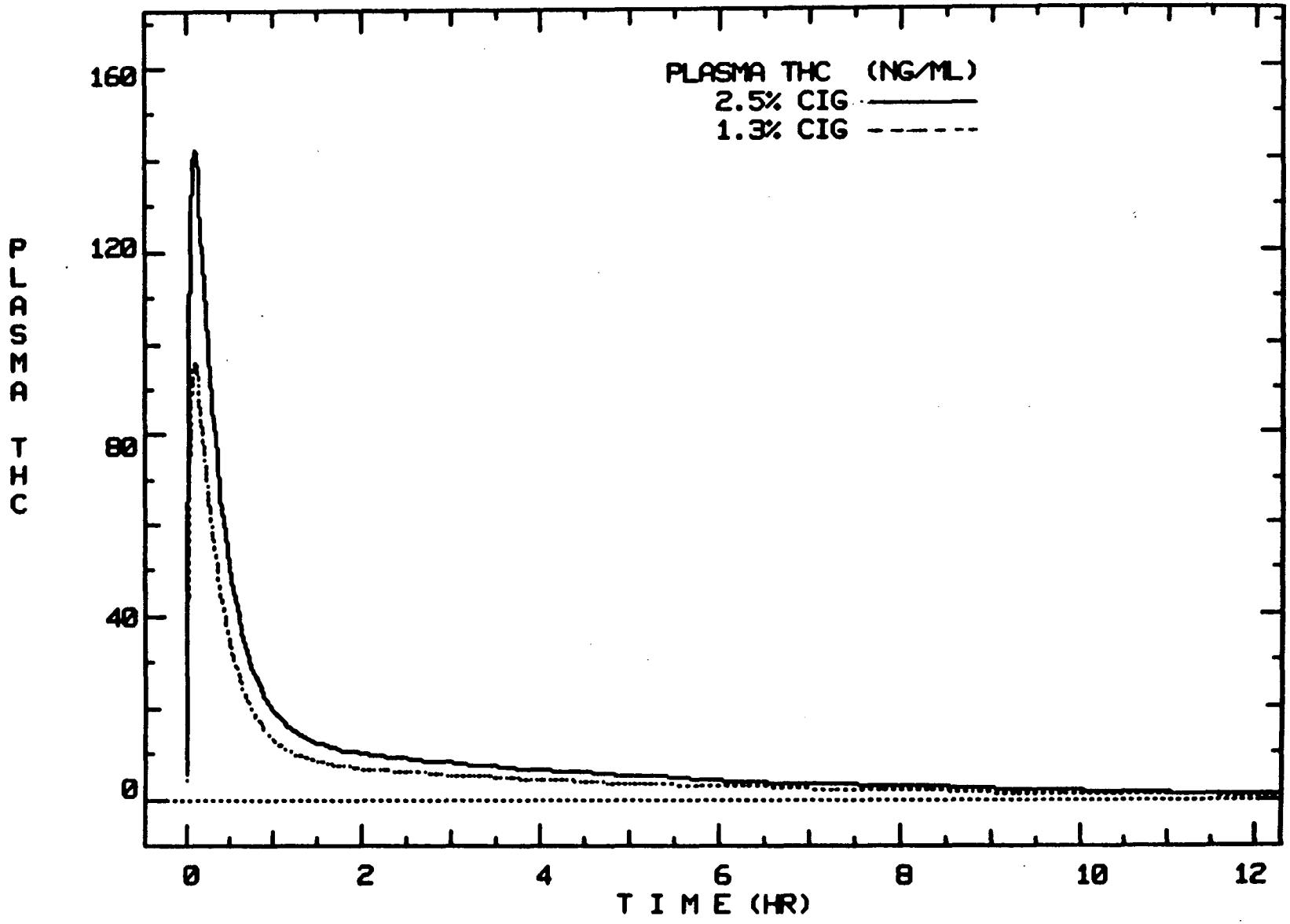

PLASMA THC (NG/ML)
2.5% CIG
1.3% CIG
PLASMA THC
160
120
80
40
0
0
2
4
6
8
10
12
TIME (HR)

FIGURE 4

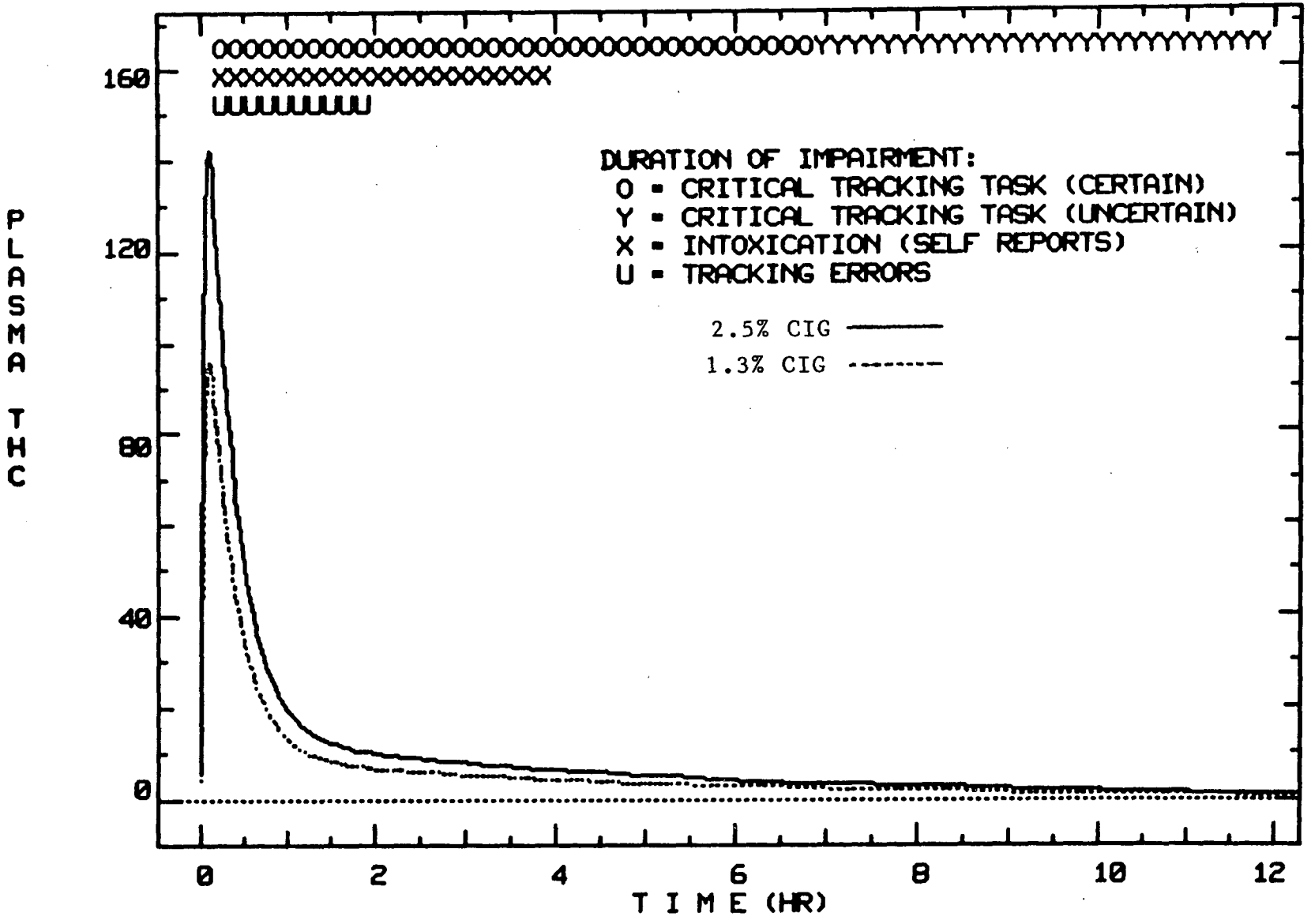

DURATION OF IMPAIRMENT:
O = CRITICAL TRACKING TASK (CERTAIN)
Y = CRITICAL TRACKING TASK (UNCERTAIN)
X = INTOXICATION (SELF REPORTS)
U = TRACKING ERRORS
2.5% CIG
1.3% CIG
PLASMA THC
160
120
80
40
0
0
2
4
6
8
10
12
TIME (HR)

FIGURE 5

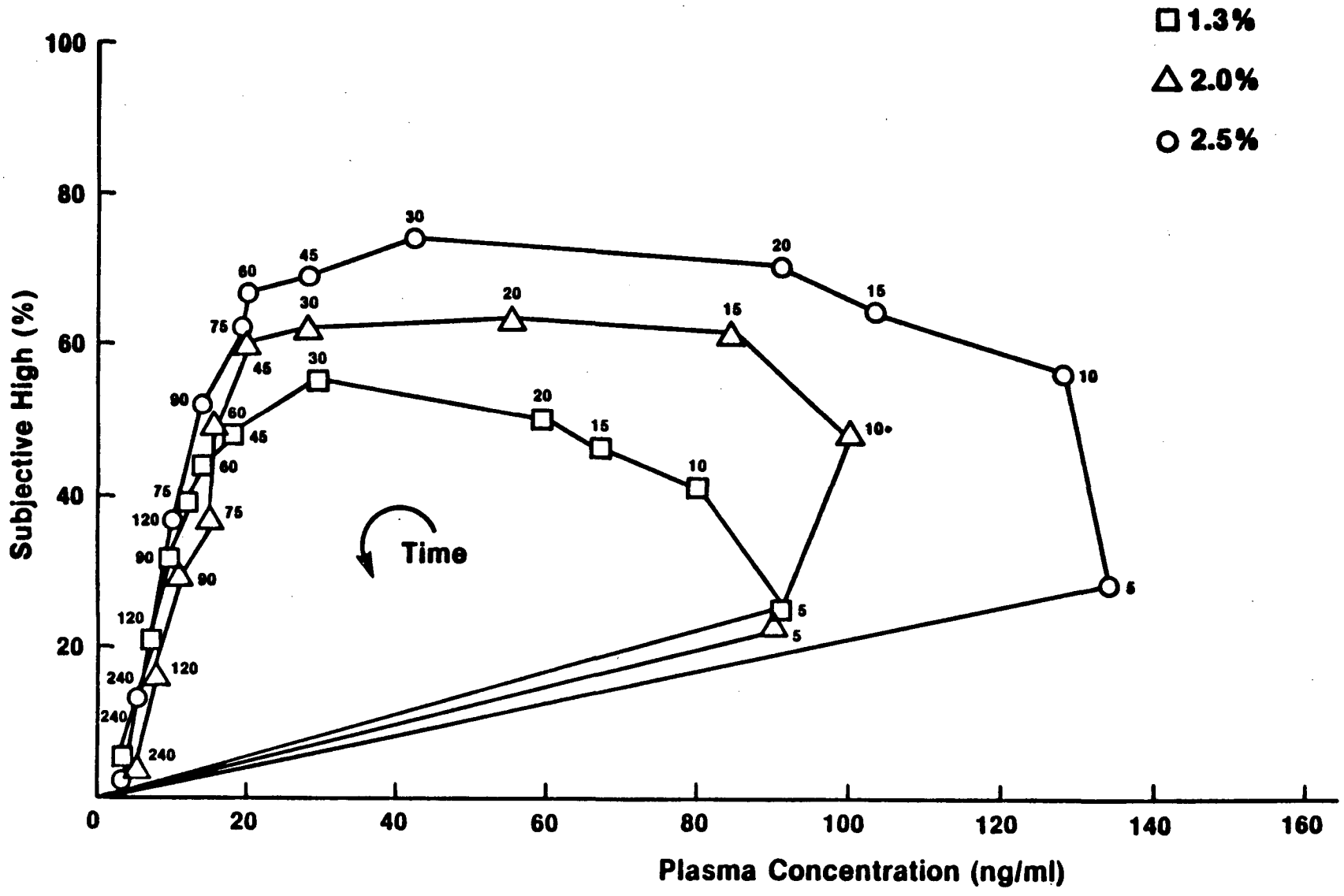
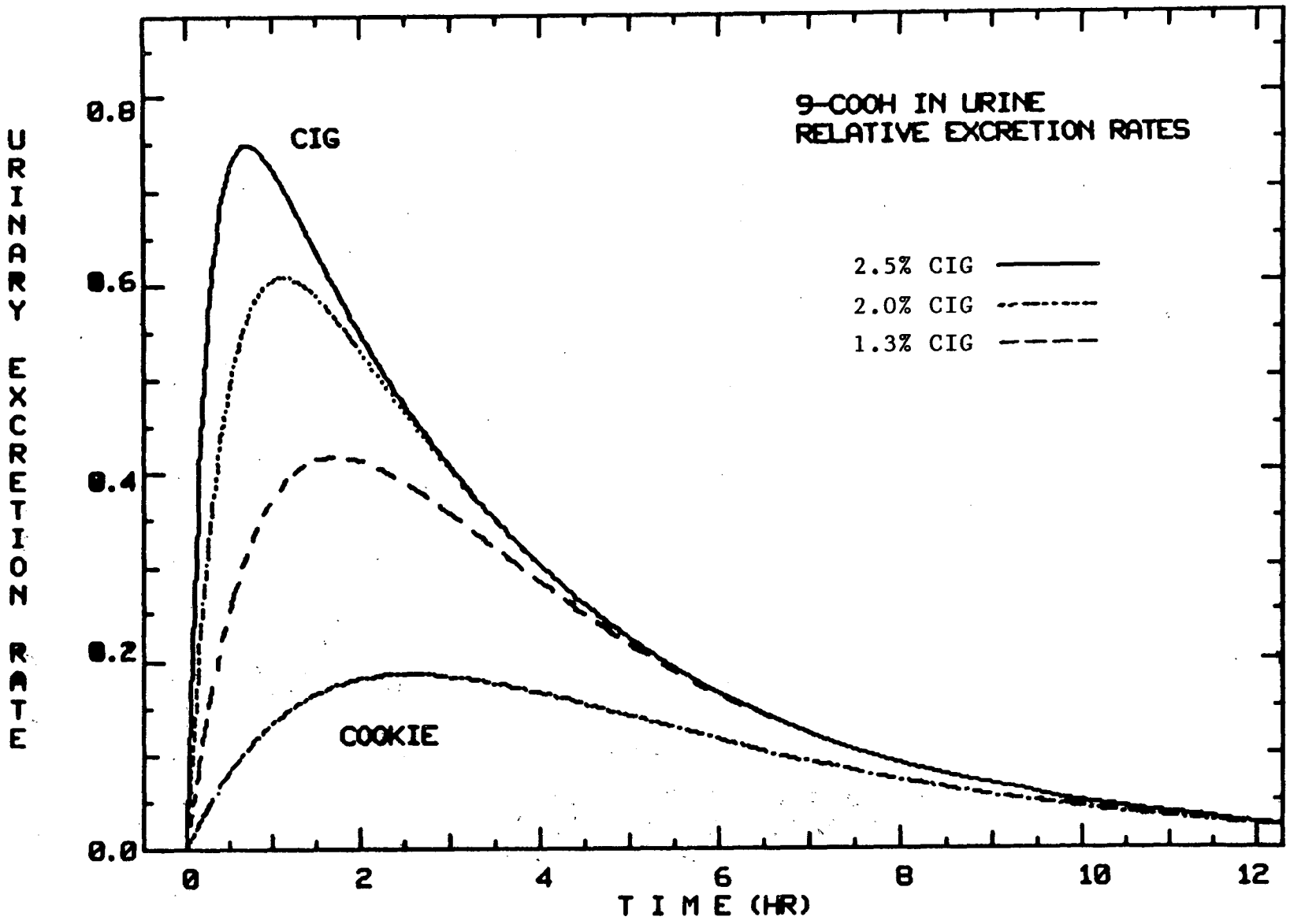

1.3%
2.0%
2.5%
Subjective High (%)
Plasma Concentration (ng/ml)
Time
100
80
60
40
20
0
20
40
60
80
100
120
140
160

FIGURE 6



RELATIVE CURVES

FIGURE 7

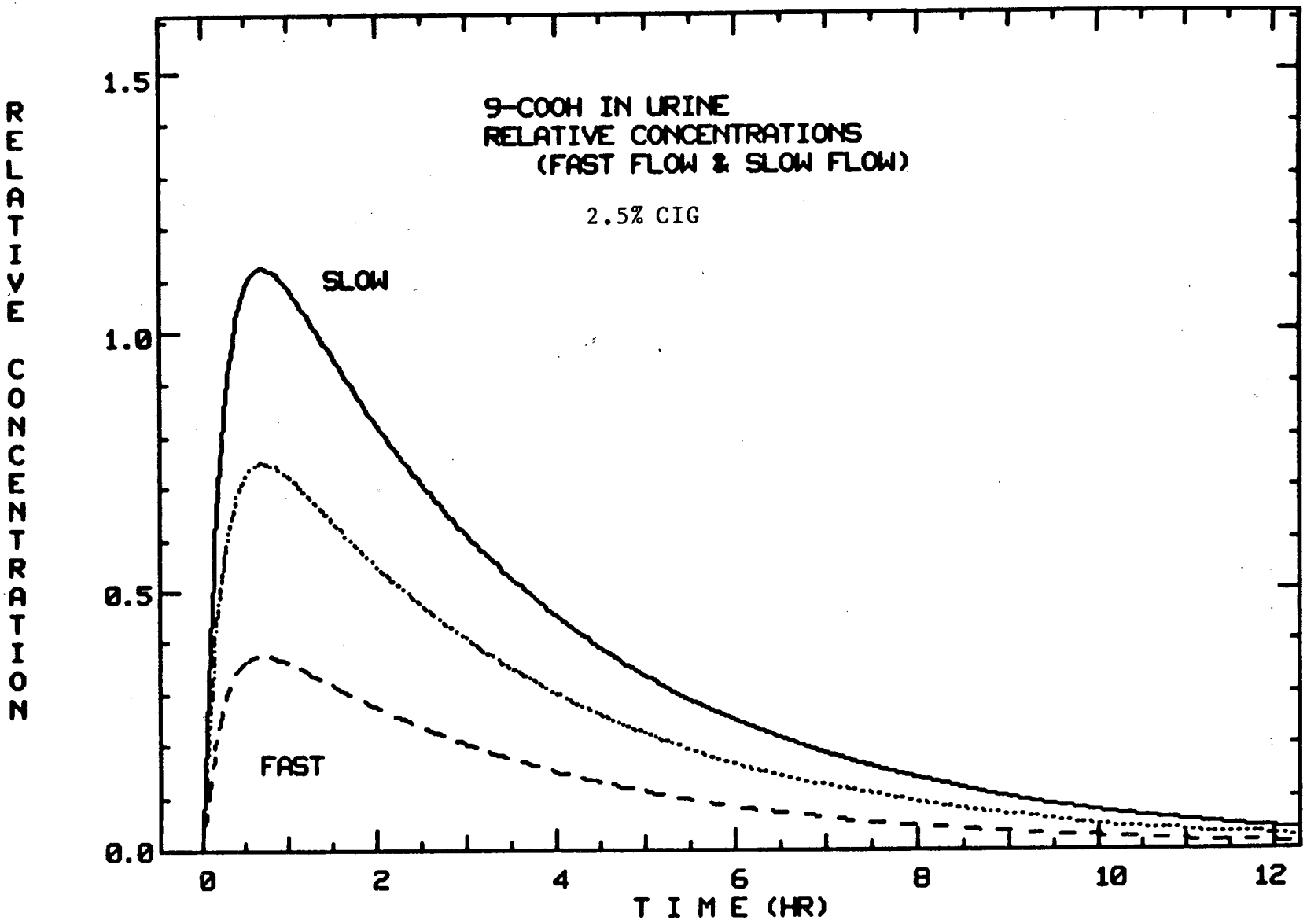

9-COOH IN URINE
RELATIVE CONCENTRATIONS
(FAST FLOW & SLOW FLOW)
2.5% CIG
SLOW
FAST
RELATIVE CONCENTRATION
1.5
1.0
0.5
0.0
0
2
4
6
8
10
12
T I M E (HR)

FIGURE 8

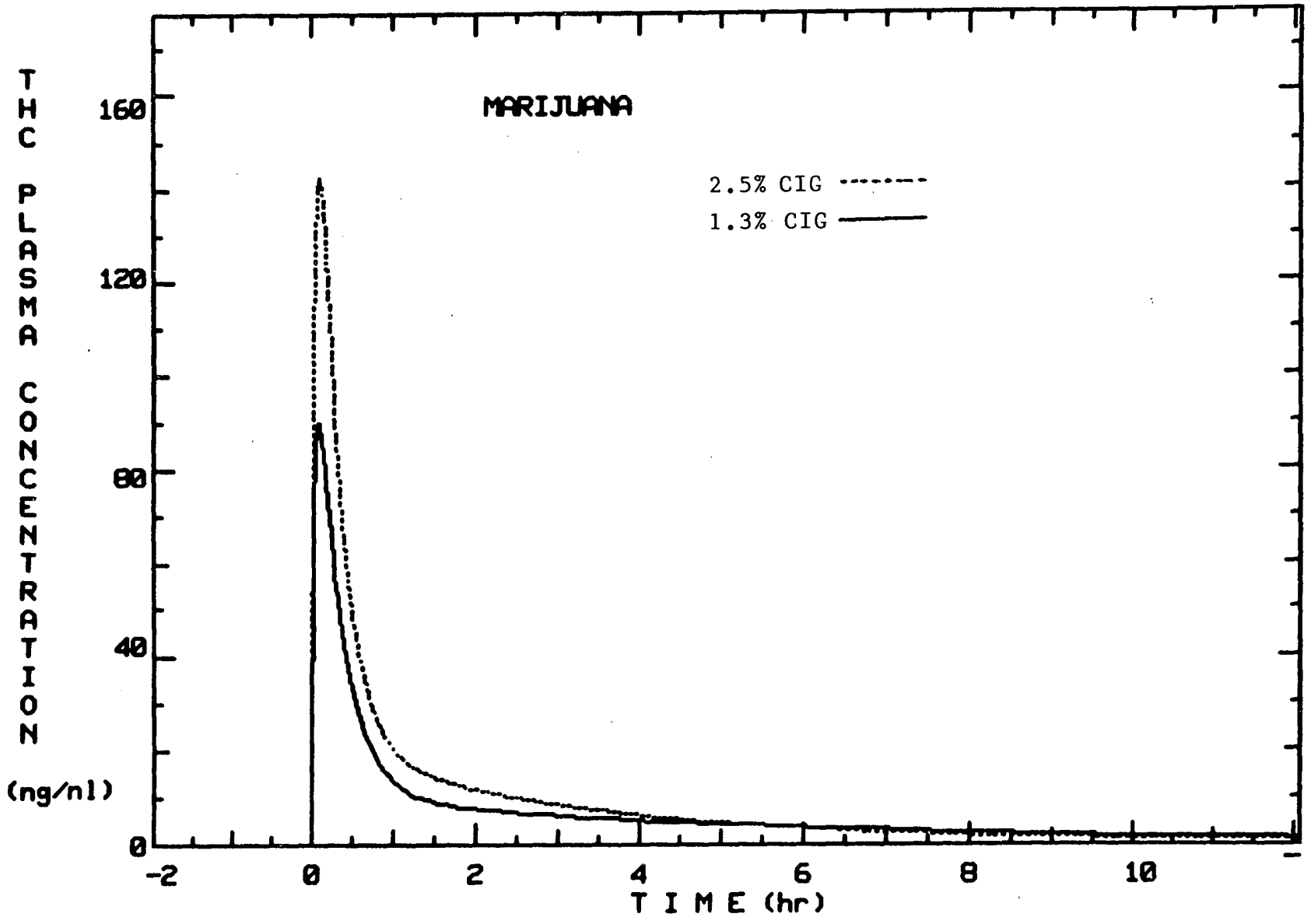


FIGURE 9. PLASMA CONCENTRATION OF THC FOR 12 HR AFTER SMOKING A 1.3% OR 2.5% NIDA MARIJUANA CIGARETTE.

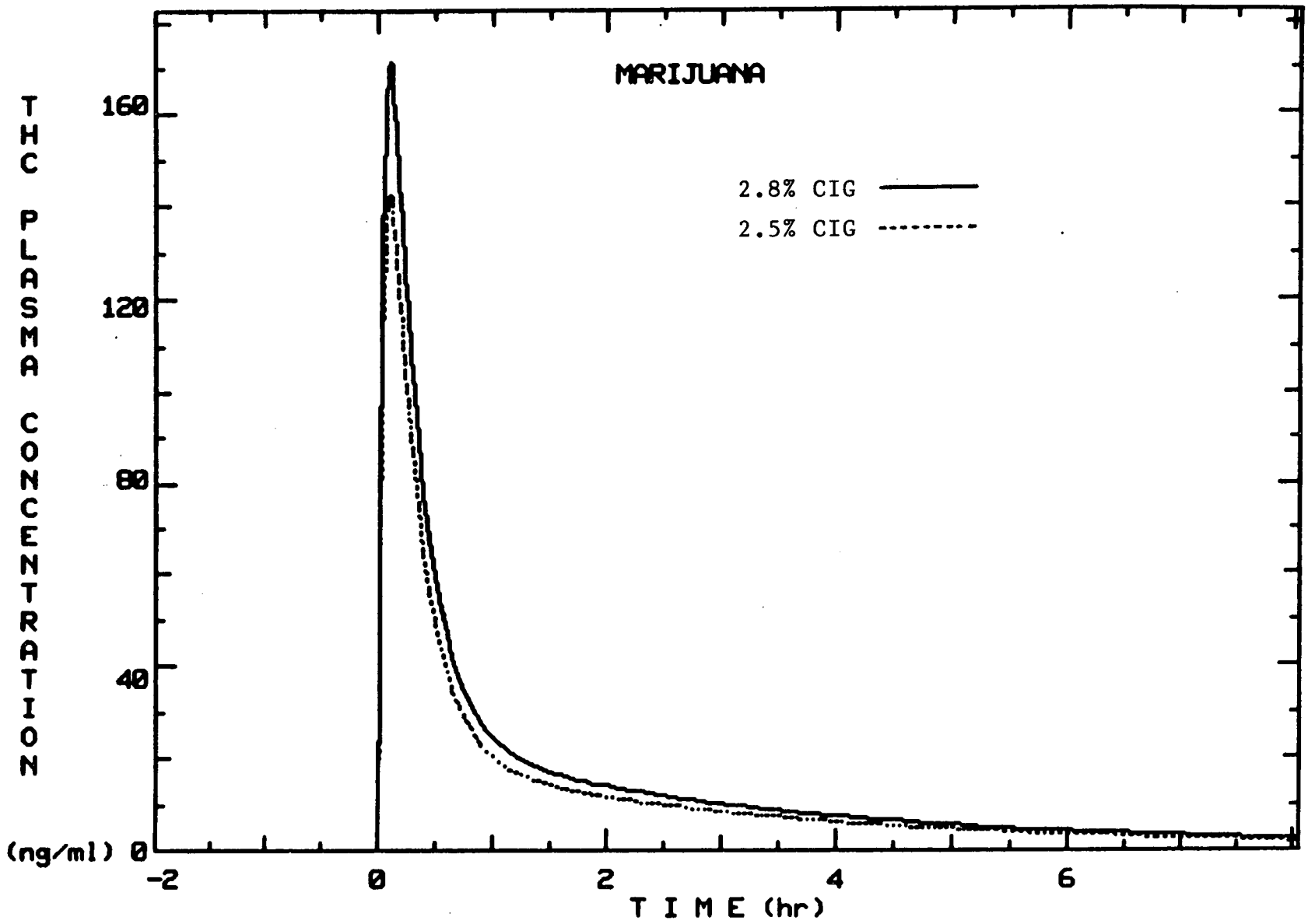


FIGURE 10. PLASMA CONCENTRATION OF THC FOR 12 HR AFTER SMOKING A 2.5% AND 2.8% NIDA MARIJUANA CIGARETTE.

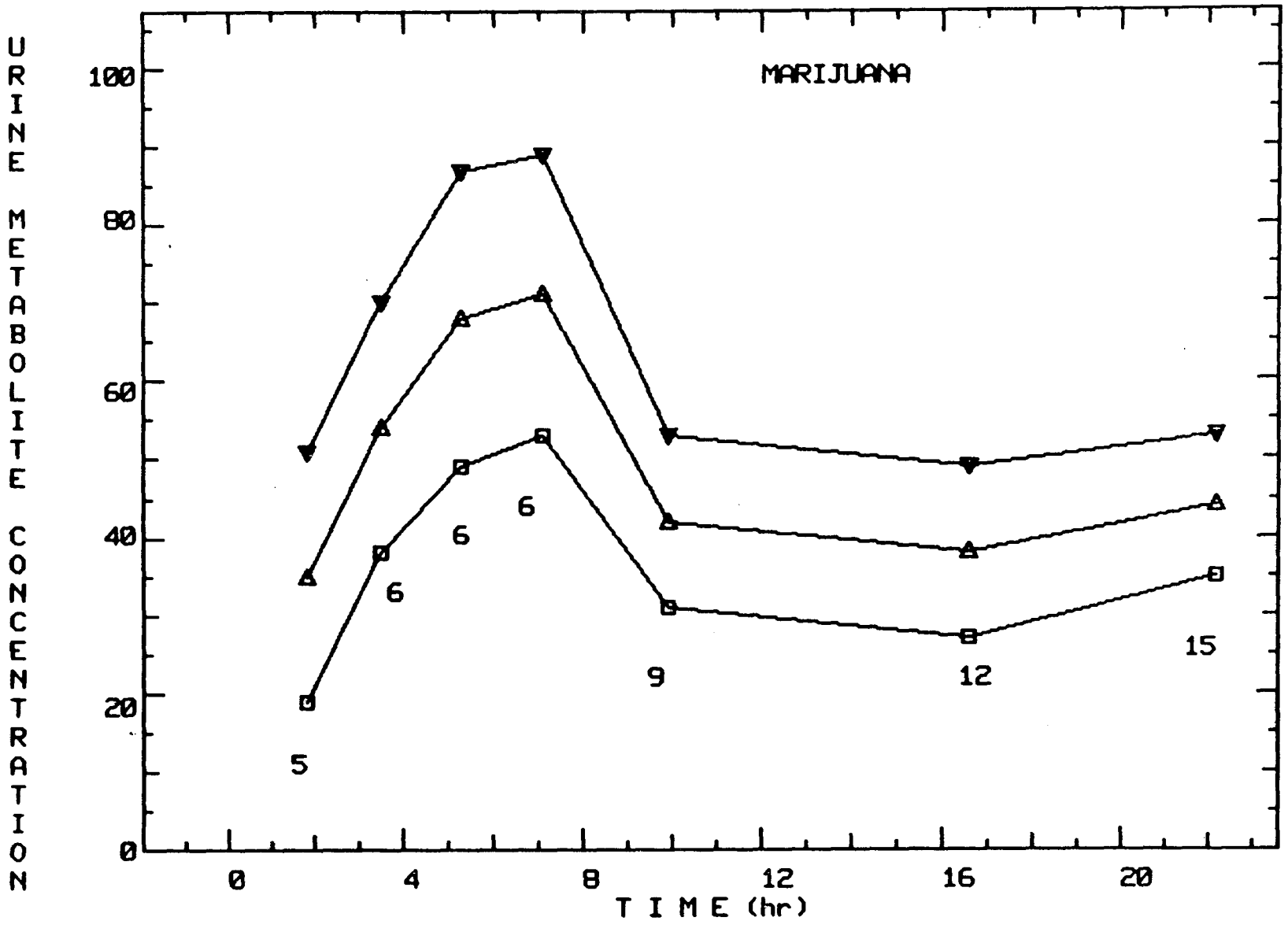


FIGURE 11. URINE CONCENTRATION OF 9-COOH METABOLITE FOR 24 HR AFTER SMOKING A 2.8% NIDA MARIJUANA CIGARETTE. MIDDLE CURVE IS MEAN VALUES. UPPER AND LOWER CURVES ARE + AND - STANDARD ERROR OF THE MEANS. N VALUES ARE GIVEN BELOW CURVES.

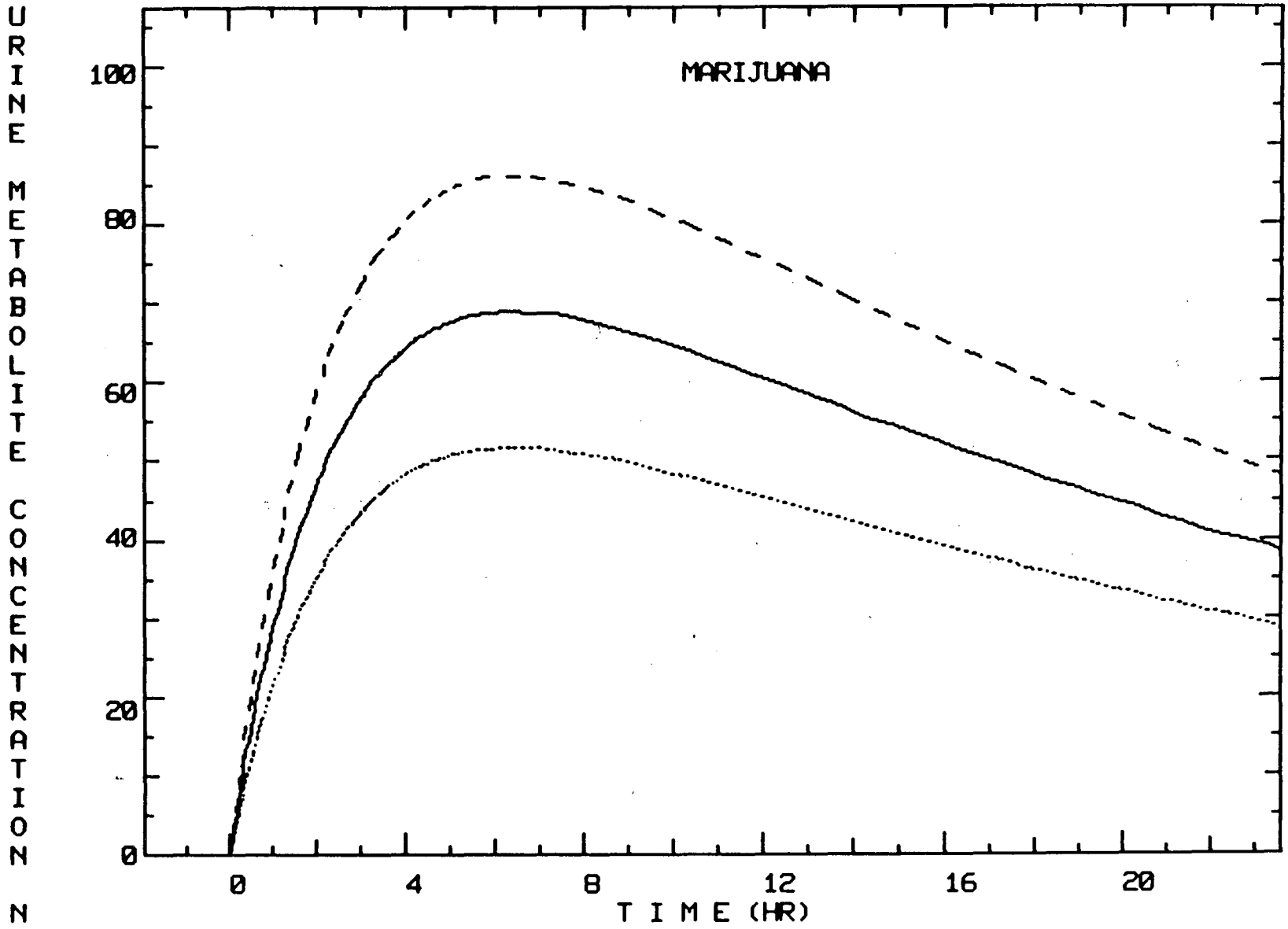


FIGURE 12. URINE CONCENTRATION OF 9-COOH METABOLITE FOR 24 HR AFTER SMOKING A 2.8% NIDA MARIJUANA CIGARETTE.

THC TERMINAL CONSTANT 0.04
9-COOH FORMATION 1.0

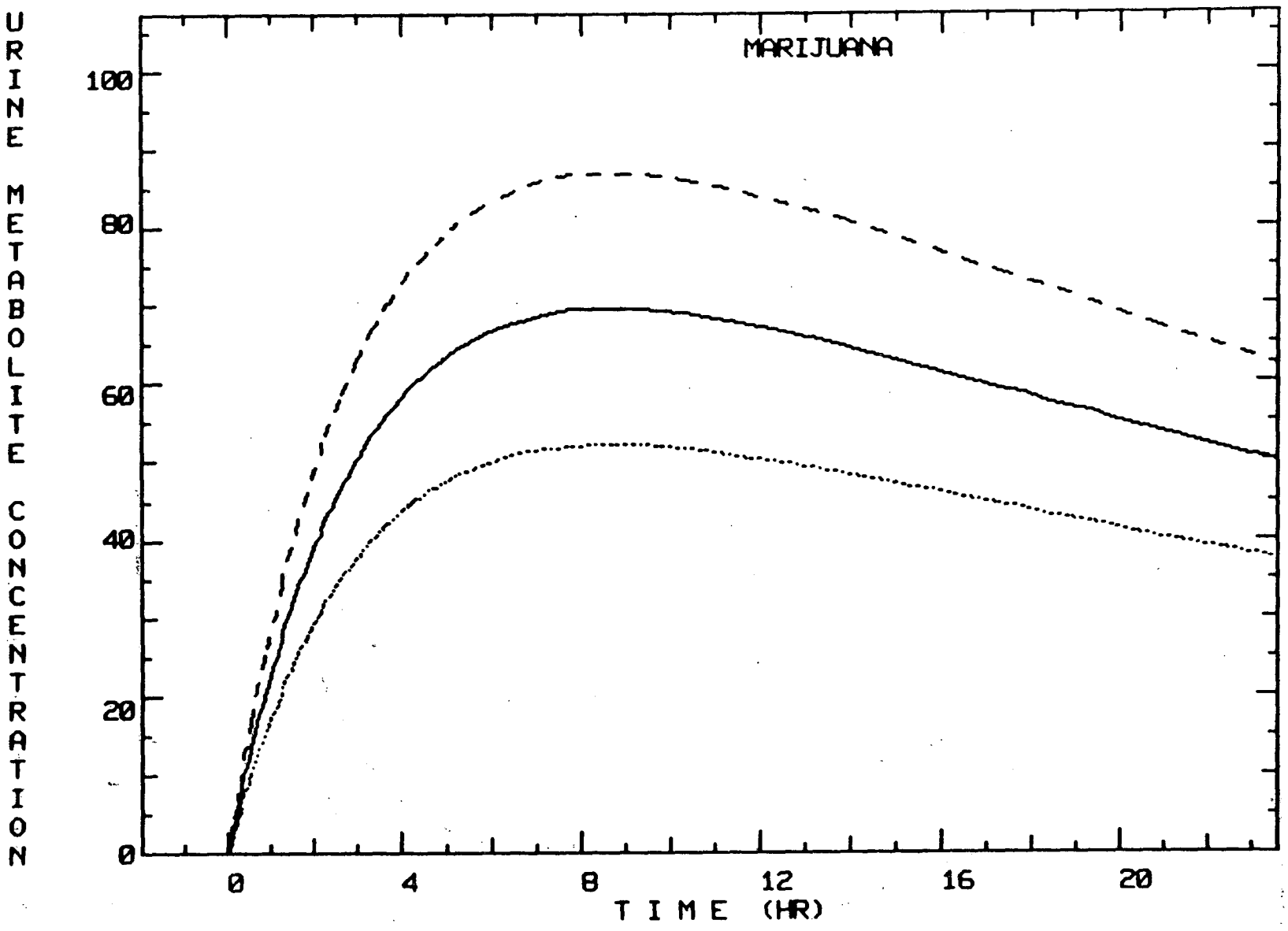


FIGURE 13 .URINE CONCENTRATION OF 9-COOH METABOLITE FOR 24 HR AFTER SMOKING A 2.8% NIDA MARIJUANA CIGARETTE.

THC TERMINAL CONSTANT 0.029
9-COOH FORMATION 0.3

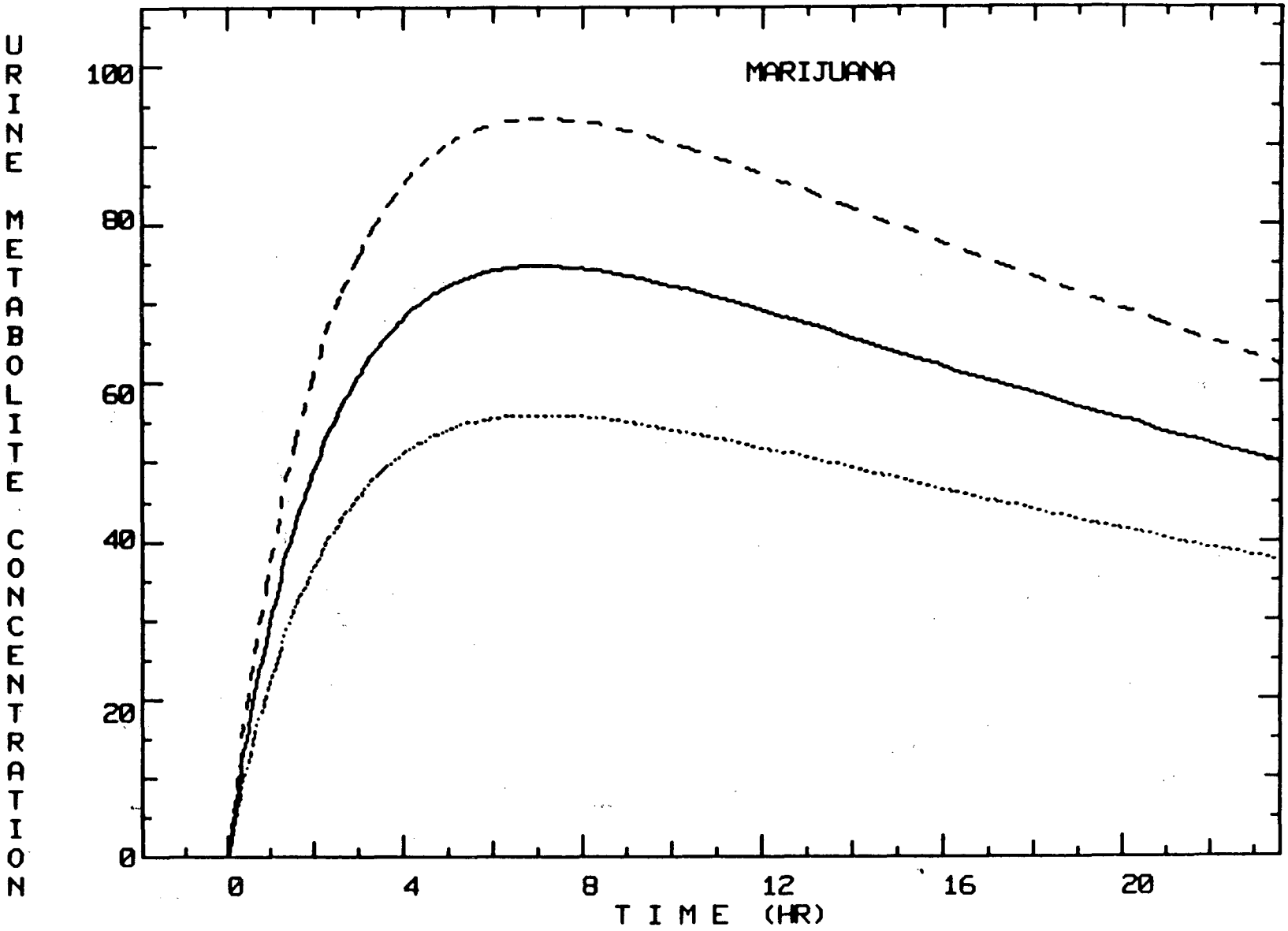


FIGURE 14. URINE CONCENTRATION OF 9-COOH METABOLITE FOR 24 HR SMOKING A 2.8% NIDA MARIJUANA CIGARETTE.

BETA-0.029
9-COON K FORM=0.4

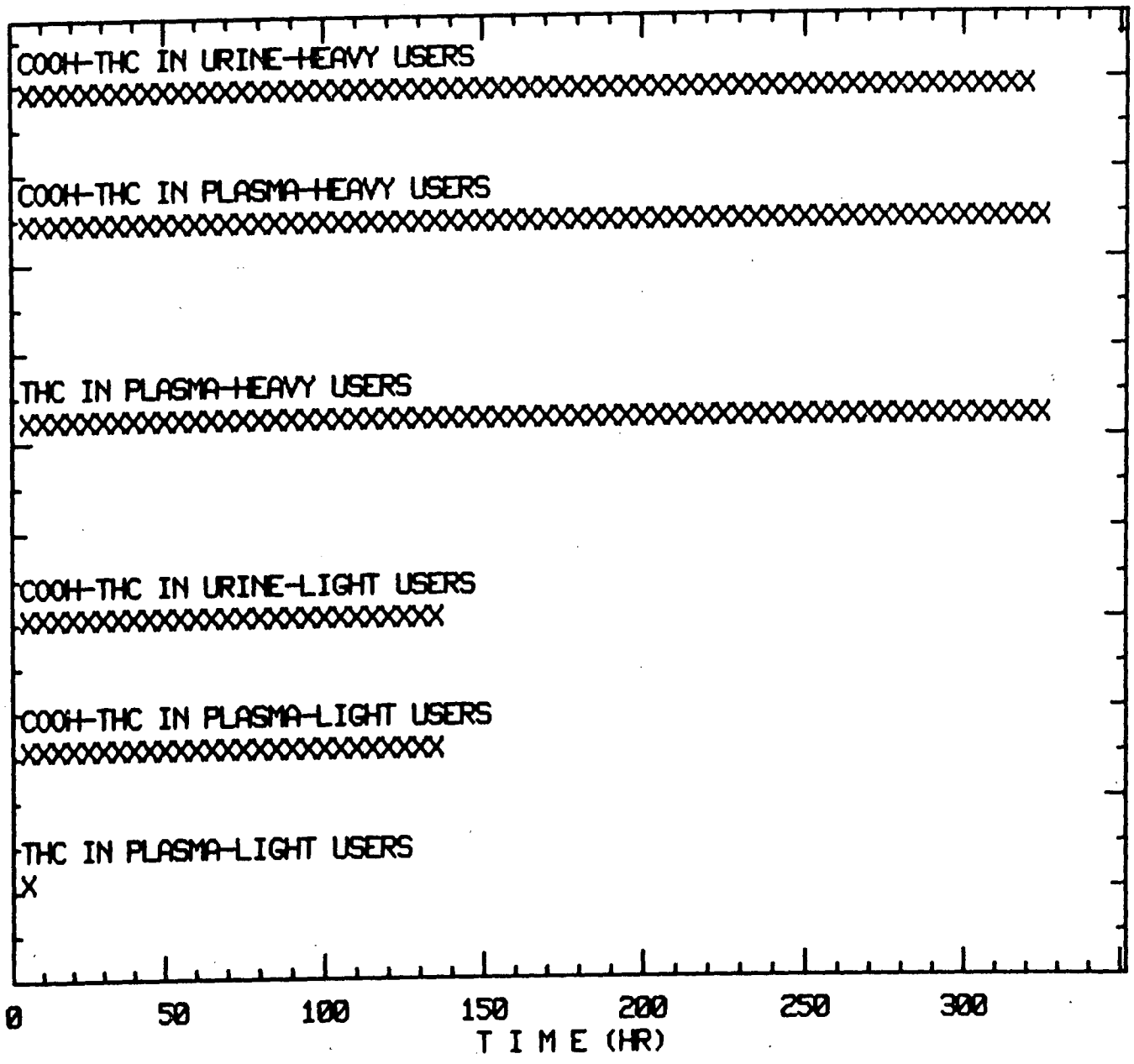


FIGURE 15 . DURATION OF TIME FOR WHICH ANALYSIS OF BODY FLUIDS GAVE MEASURABLE LEVELS OF THC AND COOH-THC. FROM PEAT DATA.

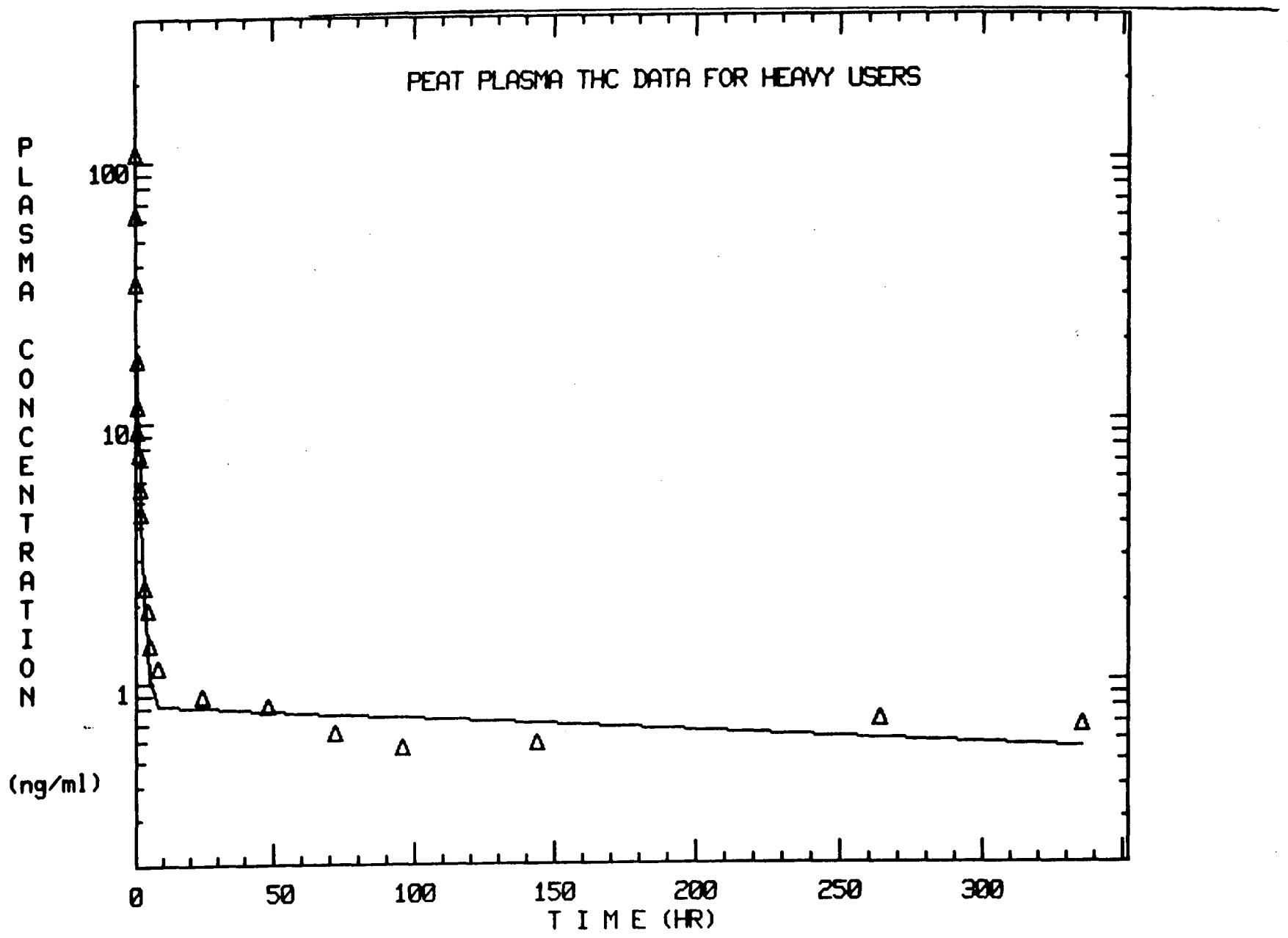


FIGURE 16 .PLASMA CONCENTRATION OF THC. SYMBOLS ARE MEAN VALUES OF PEAT EXPERIMENTAL DATA. CURVE IS BEST FIT TO EXPERIMENTAL DATA.

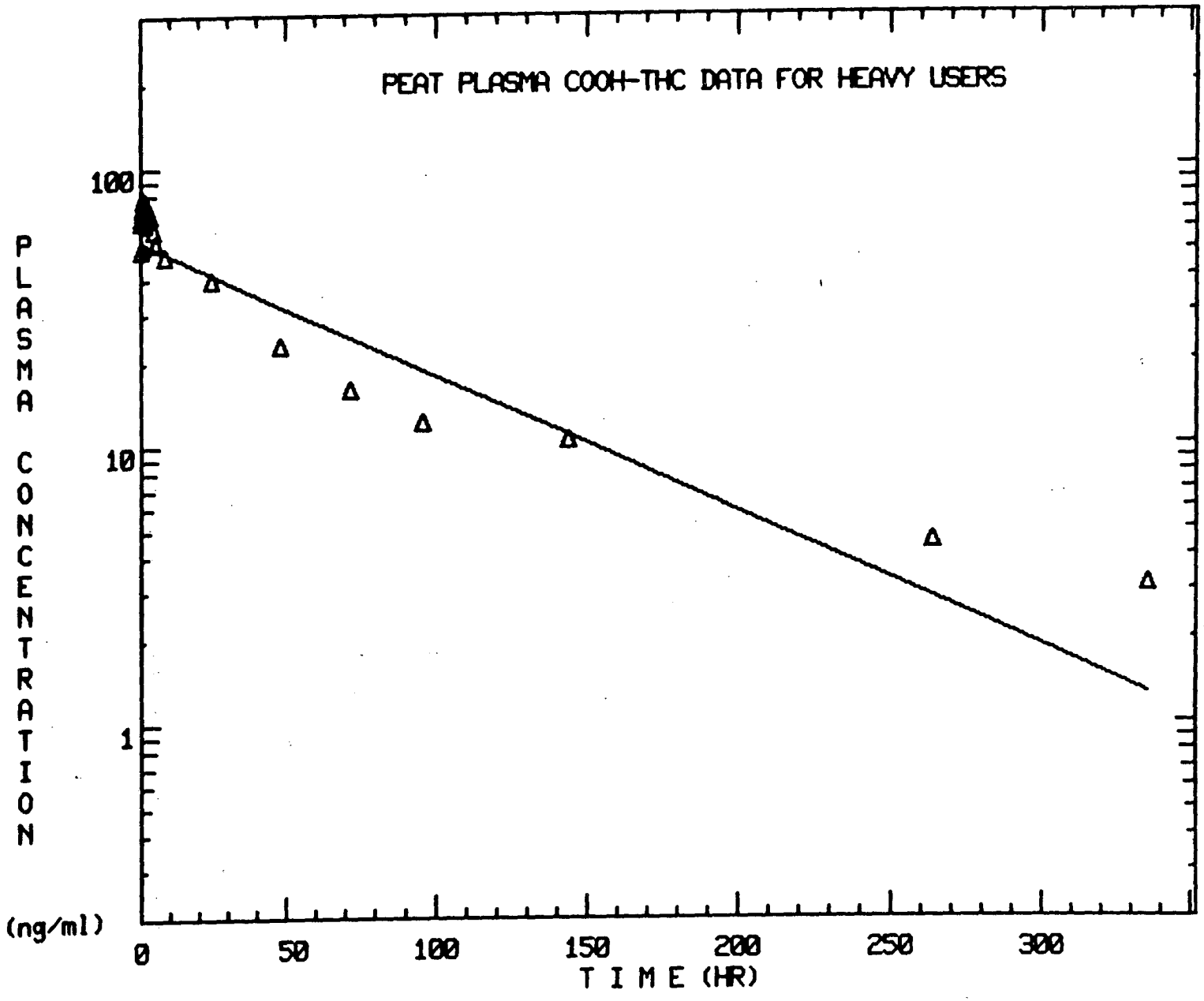


FIGURE 17. PLASMA CONCENTRATION OF COOH-THC FOR HEAVE USERS. SYMBOLS ARE MEAAN EXPERIMENTAL DATA FROM PEAT.

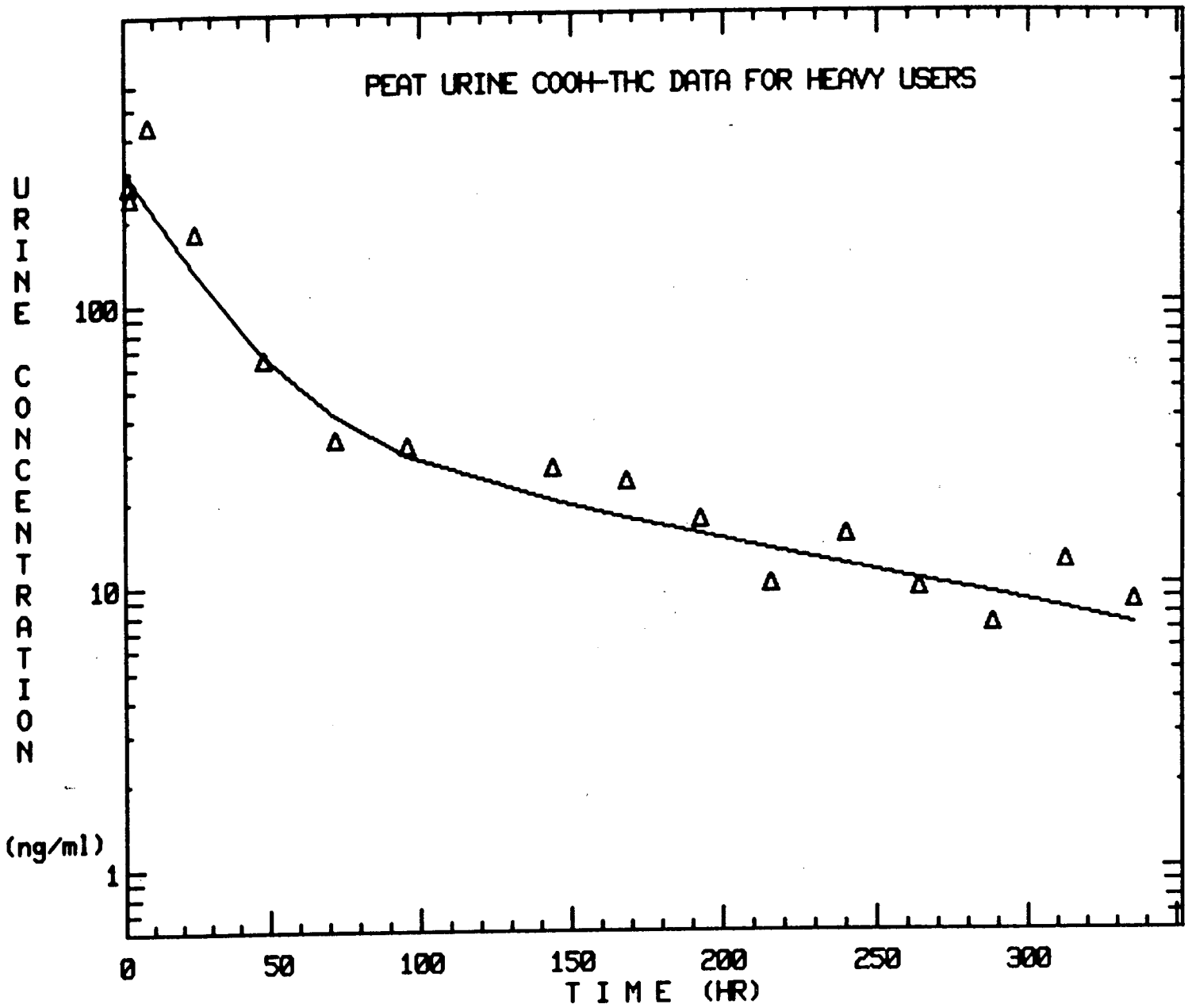


FIGURE 18 . URINE CONCENTRATION OF COOH-THC FOR HEAVY USERS. SYMBOLS ARE MEAN EXPERIMENTAL DATA FROM PEAT.

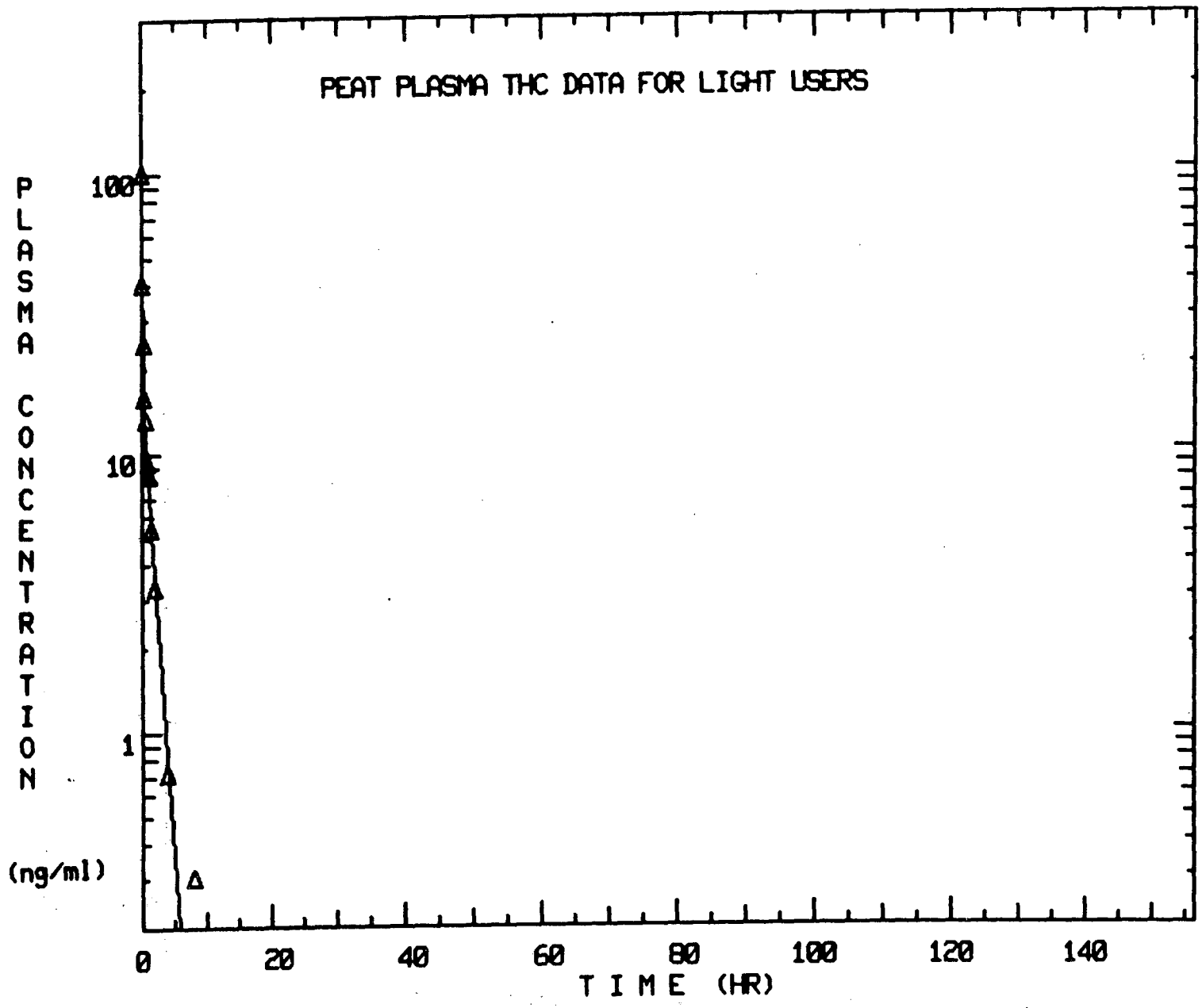


FIGURE 19. PLASMA CONCENTRATION OF THC FOR LIGHT USERS. SYMBOLS ARE MEAN EXPERIMENTAL VALUES FROM PEAT.

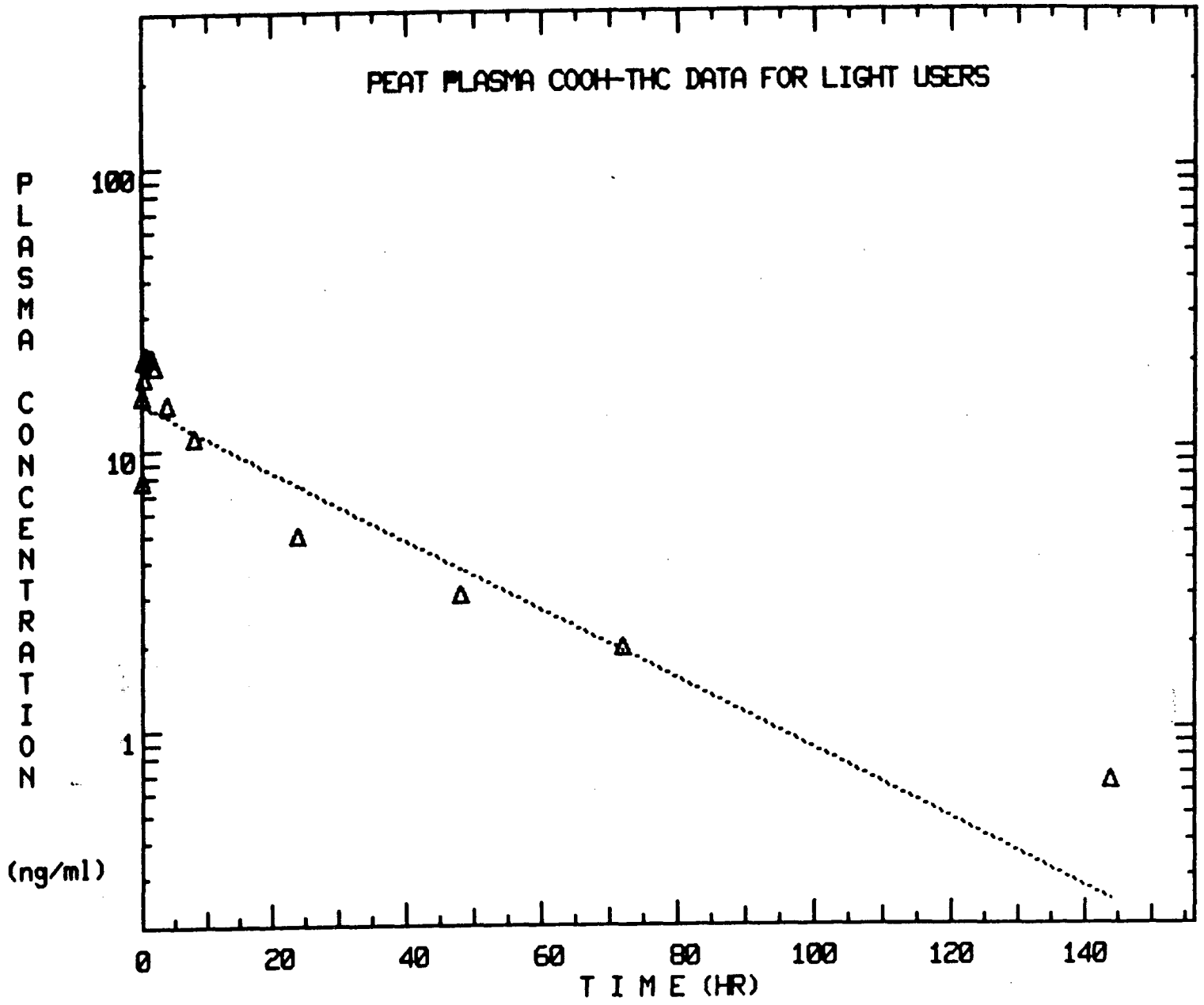


FIGURE 20. PLASMA CONCENTRATION OF COOH-THC FOR LIGHT USERS. SYMBOLS ARE MEAN EXPERIMENTAL VALUES FROM PEAT.

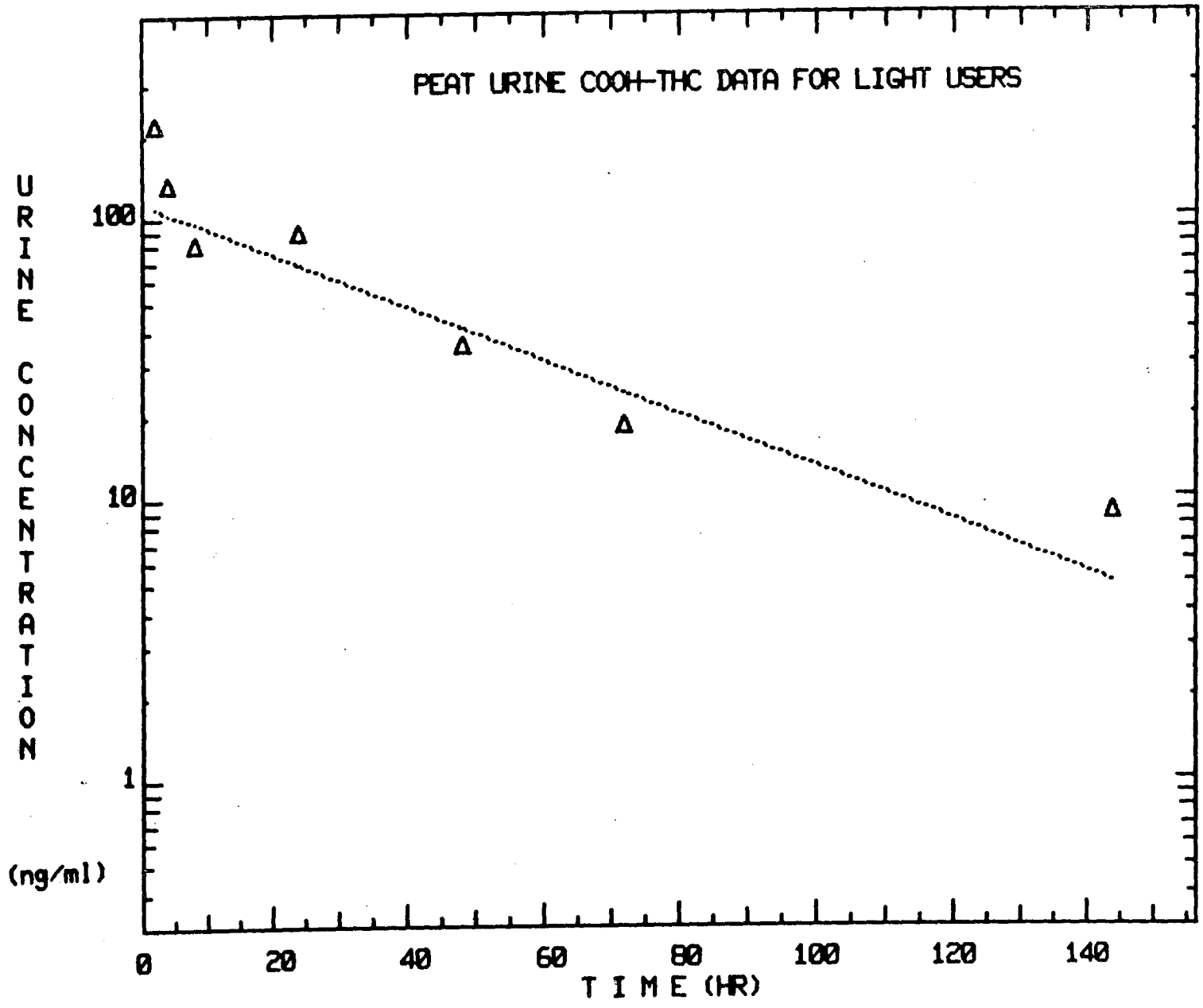


FIGURE 21. URINE CONCENTRATION OF COOH-THC FOR LIGHT USERS. SYMBOLS ARE MEAN EXPERIMENTAL DATA FROM PEAT.

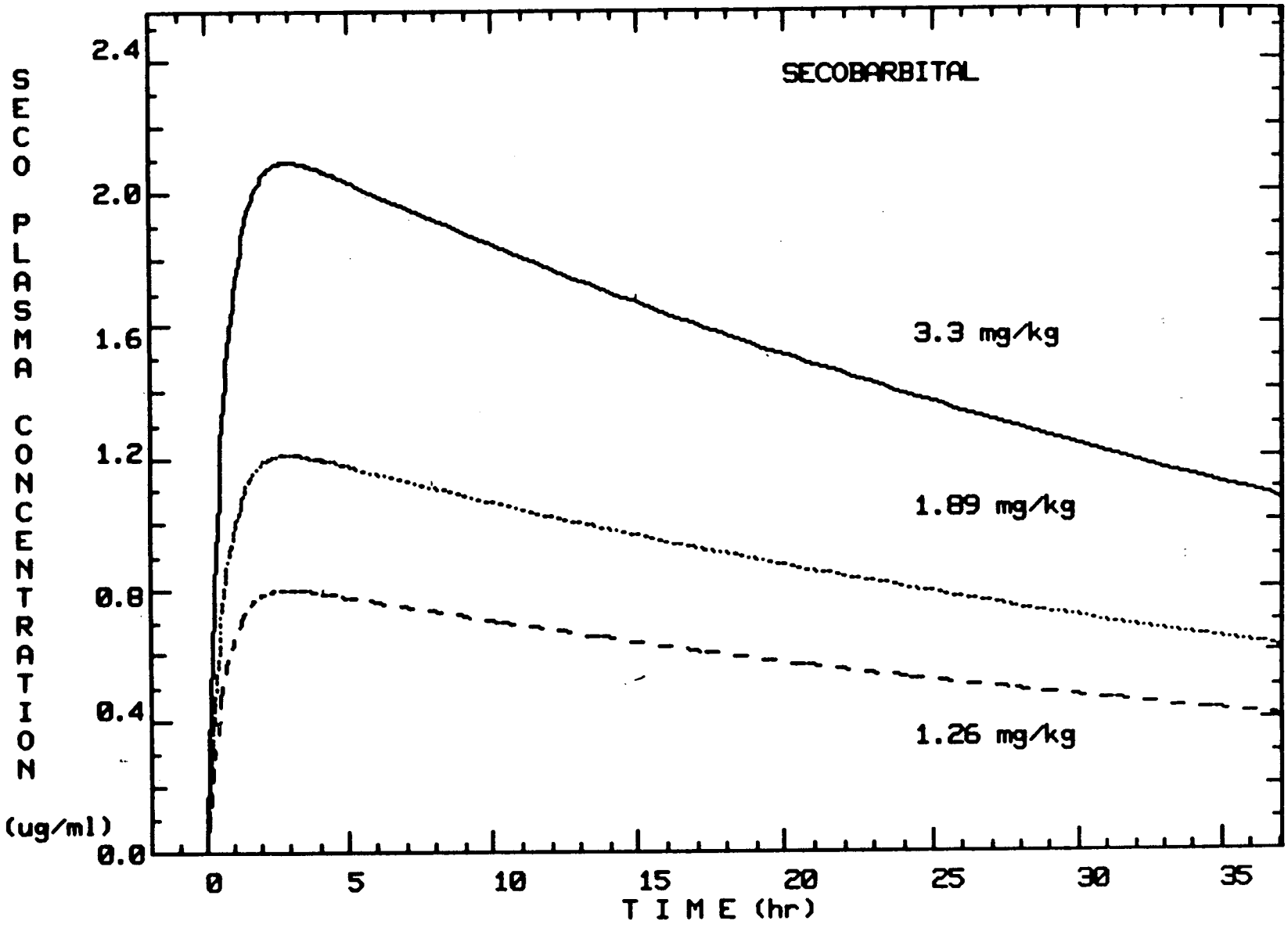


FIGURE 22 SECOBARBITAL PLASMA CONCENTRATION FOR 36 HR AFTER AN ORAL DOSE OF 3.3 mg/kg, 1.89 mg/ml 1.26 mg/kg.

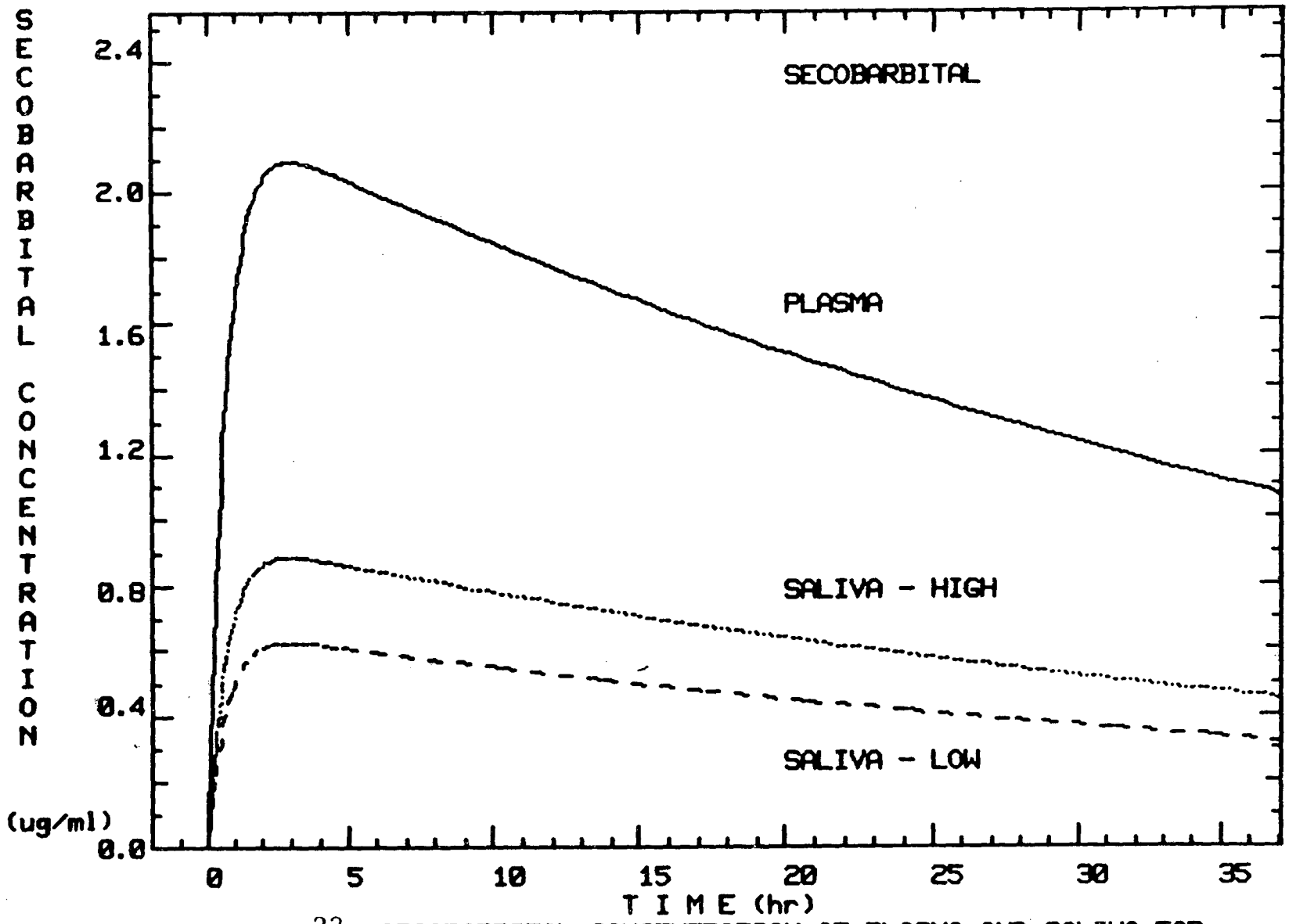


FIGURE 23 SECOBARBITAL CONCENTRATION OF PLASMA AND SALIVA FOR 36 HR AFTER AN ORAL DOSE OF 3.3 mg/kg.

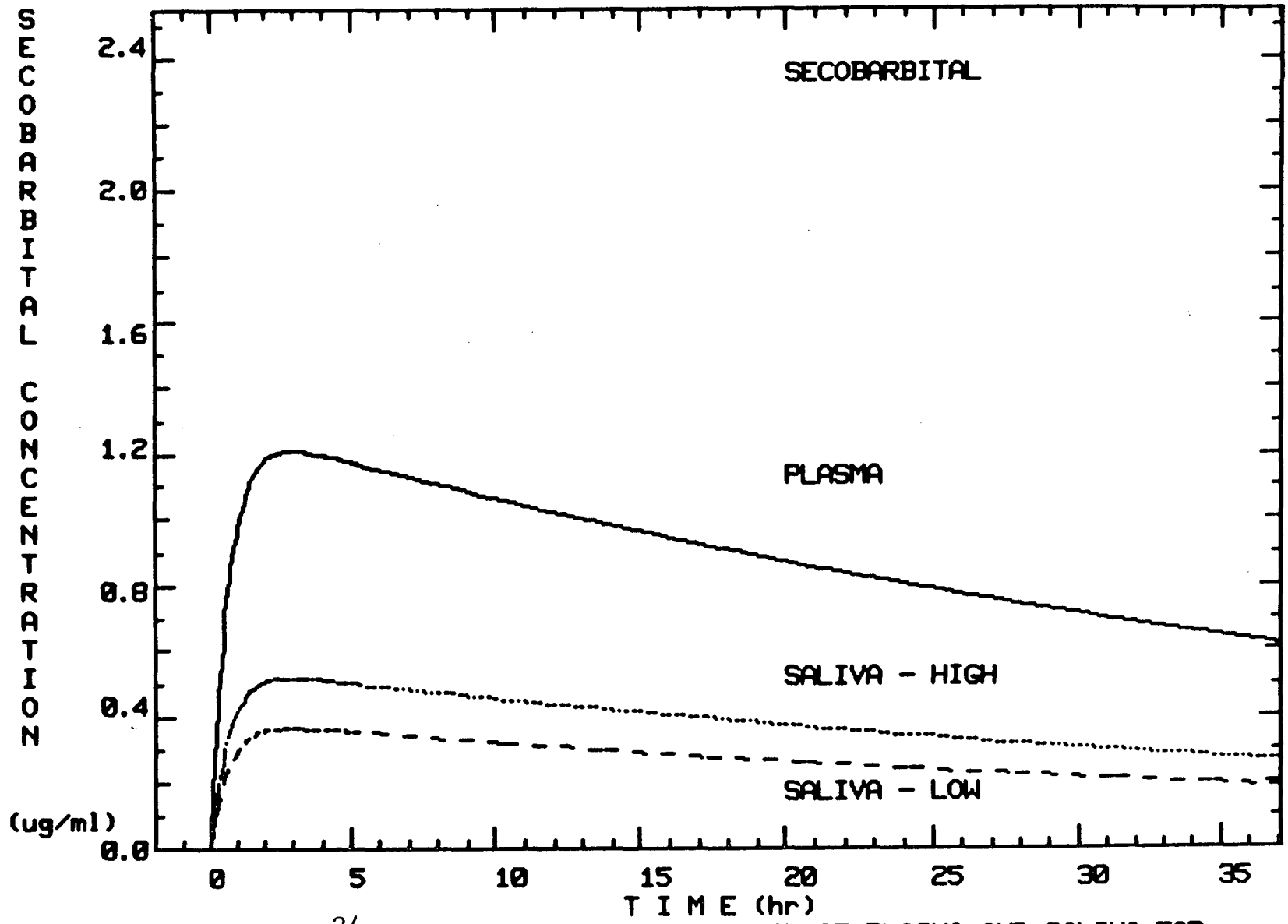


FIGURE 24 SECOBARBITAL CONCENTRATION OF PLASMA AND SALIVA FOR 36 HR AFTER AN ORAL DOSE OF 1.89 mg/kg.

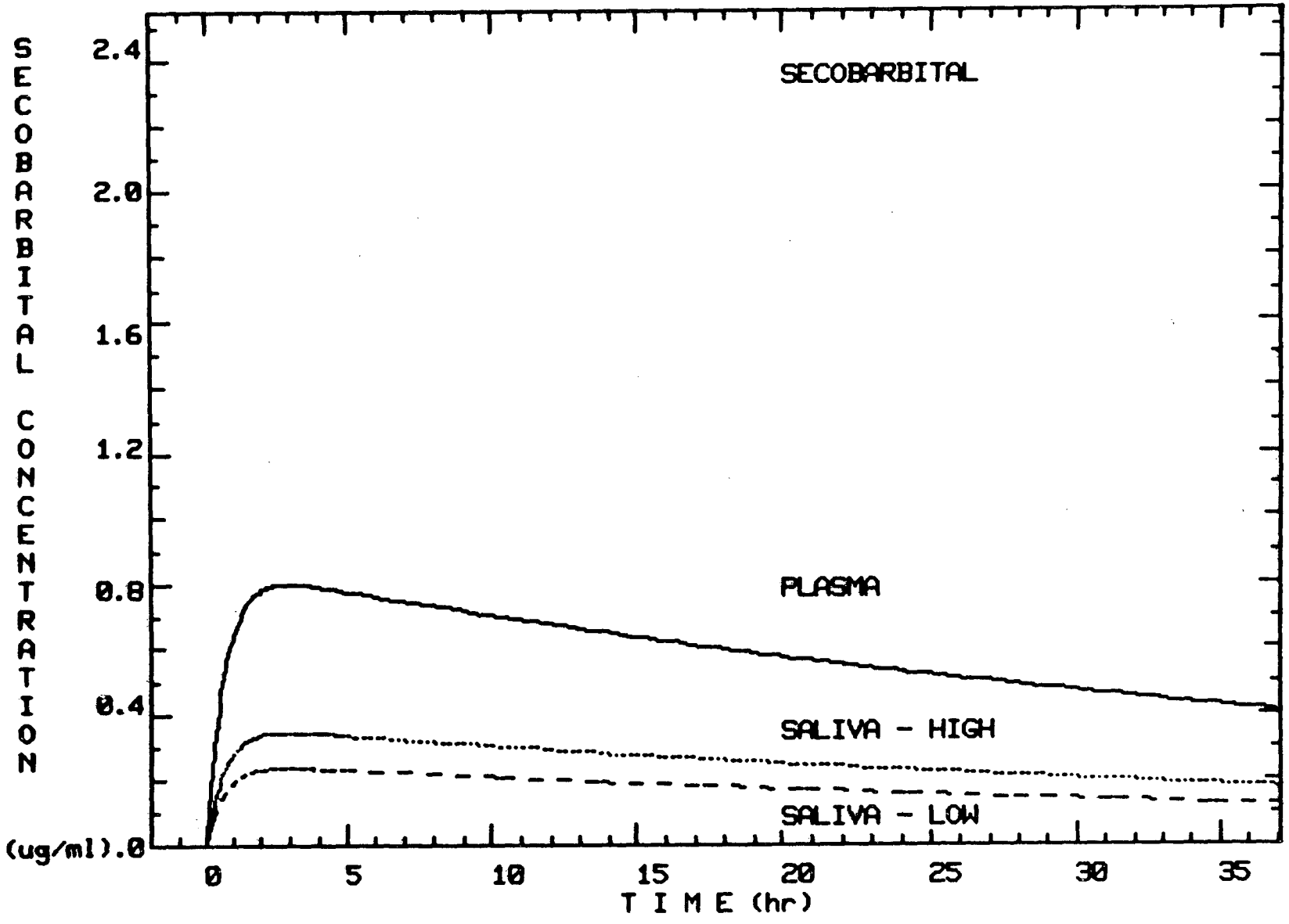


FIGURE 25 SECOBARBITAL CONCENTRATION OF PLASMA AND SALIVA FOR 36 HR AFTER AN ORAL DOSE OF 1.26 mg/kg.

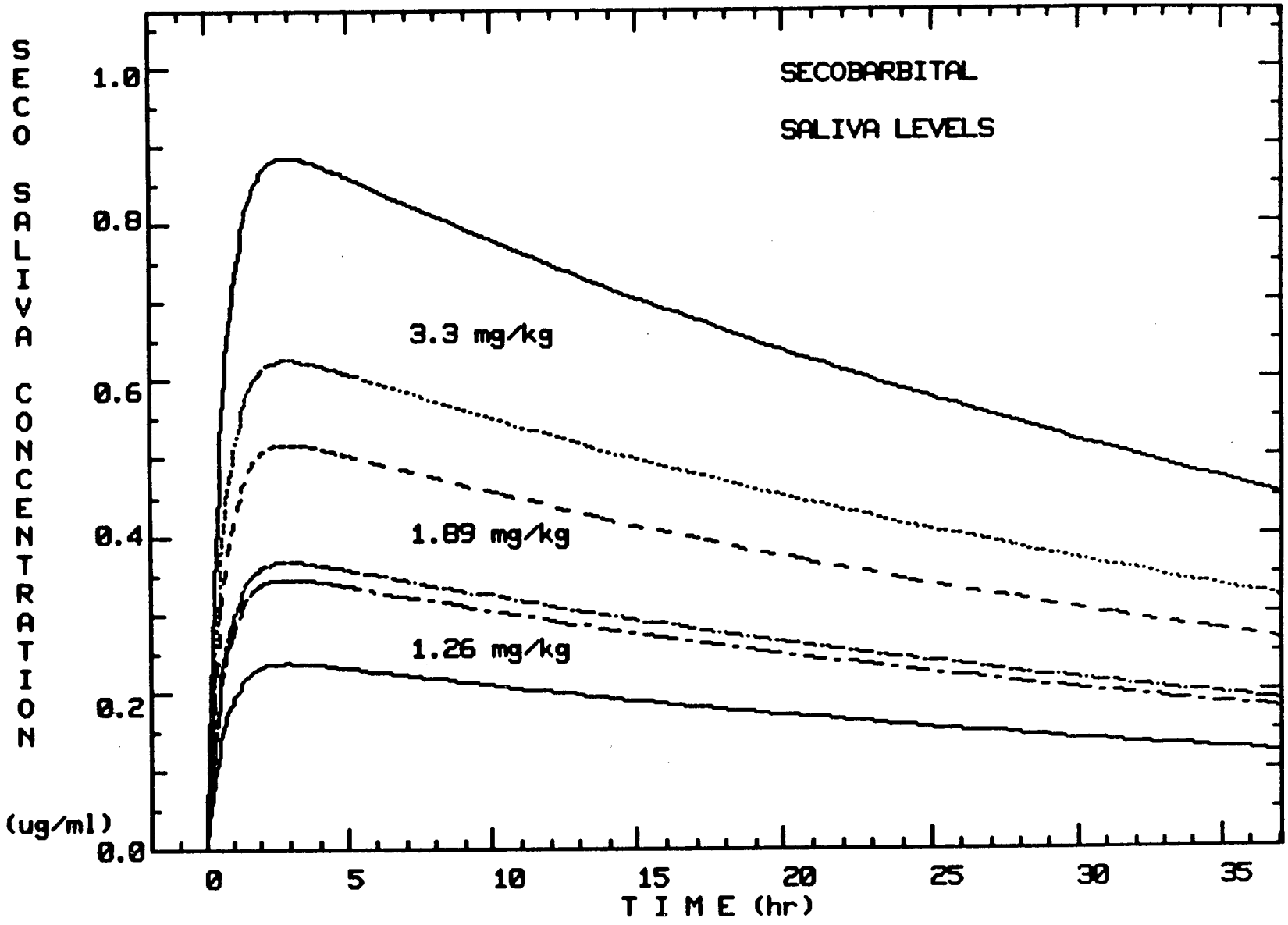


FIGURE 26 .SECOBARBITAL SALIVA CONCENTRATION FOR 36 HR AFTER AN ORAL DOSE OF 3.3 mg/kg, 1.89 mg/kg, 1.26 mg/kg. THERE ARE 2 SALIVA CURVES FOR EACH DOSE WITH S/P RATIOS OF 0.42 (HIGH) AND 0.30 (LOW).

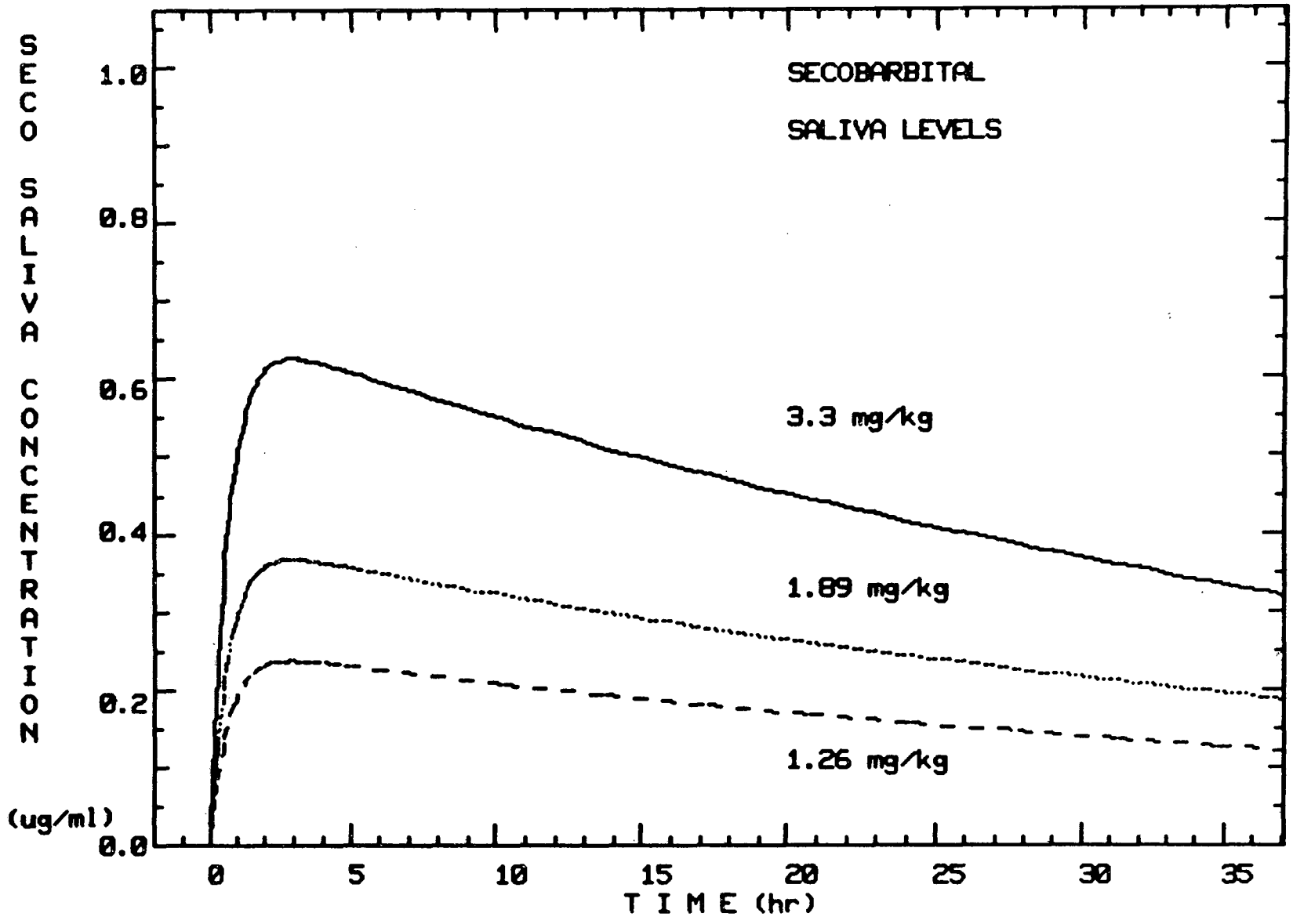


FIGURE 27. SECOBARBITAL SALIVA CONCENTRATION FOR 36 HRS AFTER AN ORAL DOSE OF 3.3 mg/kg,, 1.89 mg/ml, 1.26 mg/ml. THE S/P RATIO IS 0.30 WHICH IS THE BEST MEAN EXPERIMENTAL DATA AVALIABLE.

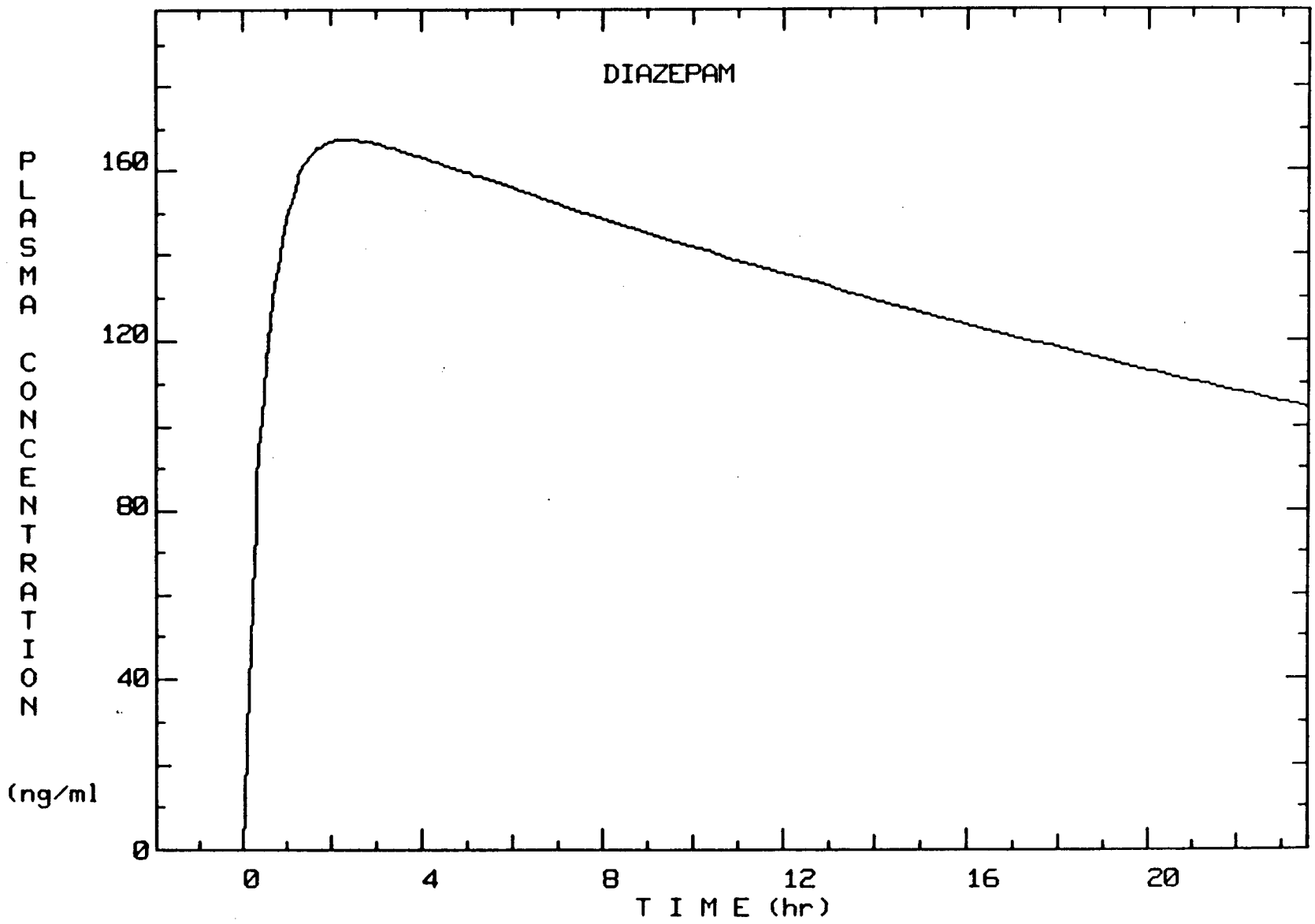


FIGURE--28--PLASMA CONCENTRATION OF DIAZEPAM FOR 24 HR AFTER AN ORAL DOSE OF 10 mg.

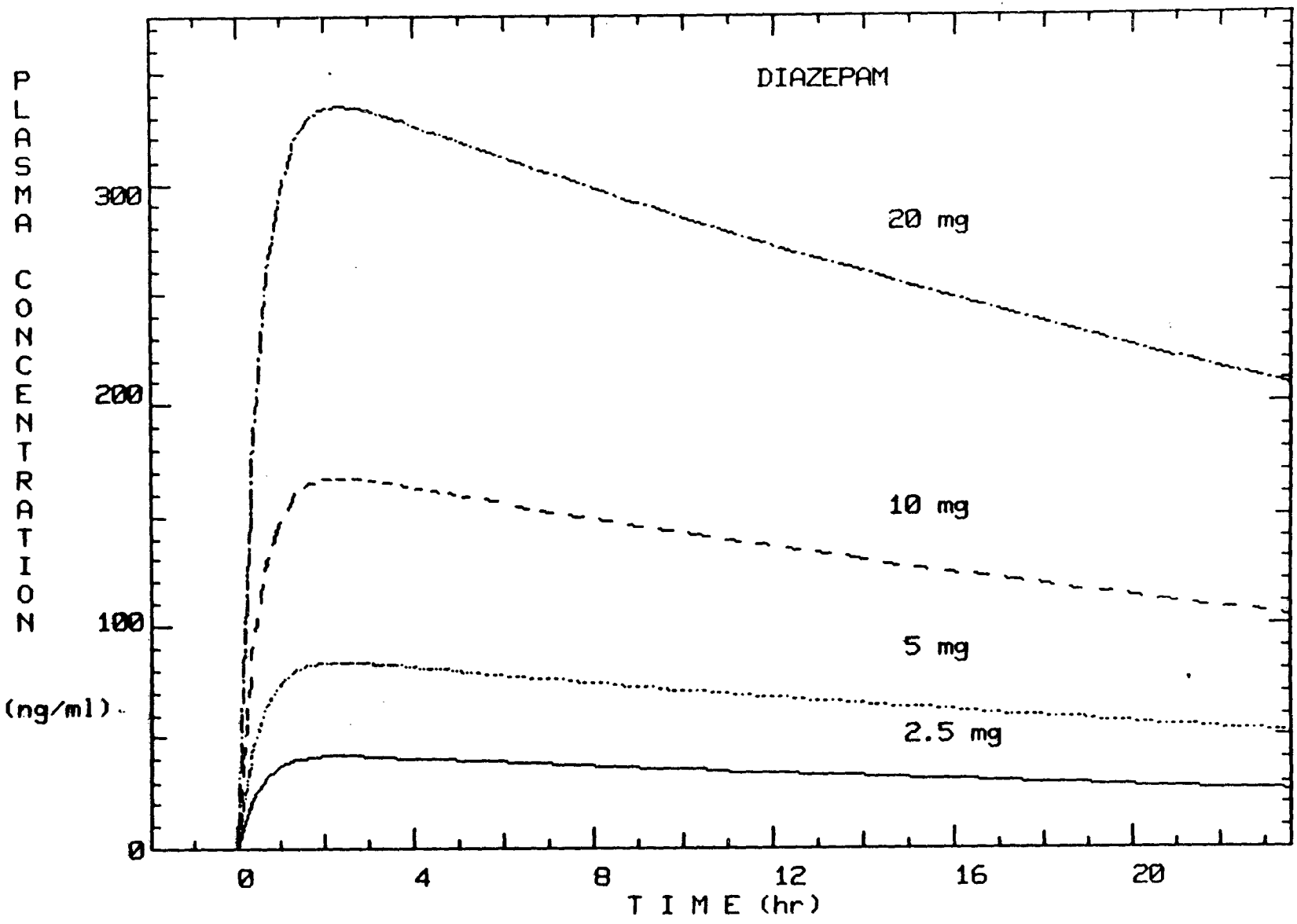


FIGURE 29. PLASMA CONCENTRATION OF DIAZEPAM FOR 24 HR AFTER AN ORAL DOSE OF 20 mg, 10 mg, 5 mg, 2.5 mg.

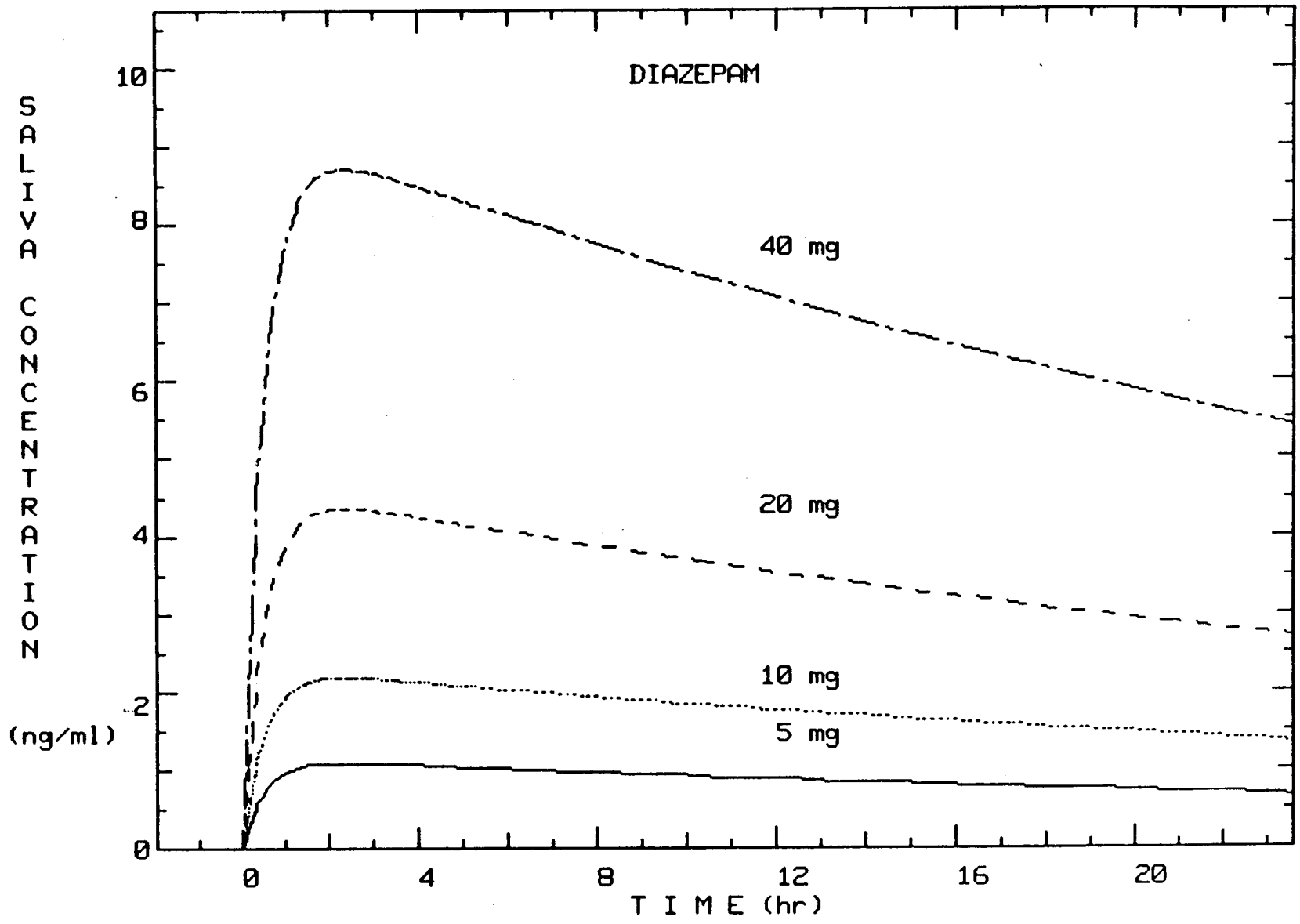


FIGURE 30. SALIVA CONCENTRATION OF DIAZEPAM FOR 24 HR AFTER ORAL DOSE OF 5 mg, 10 mg, 20 mg, 40 mg.

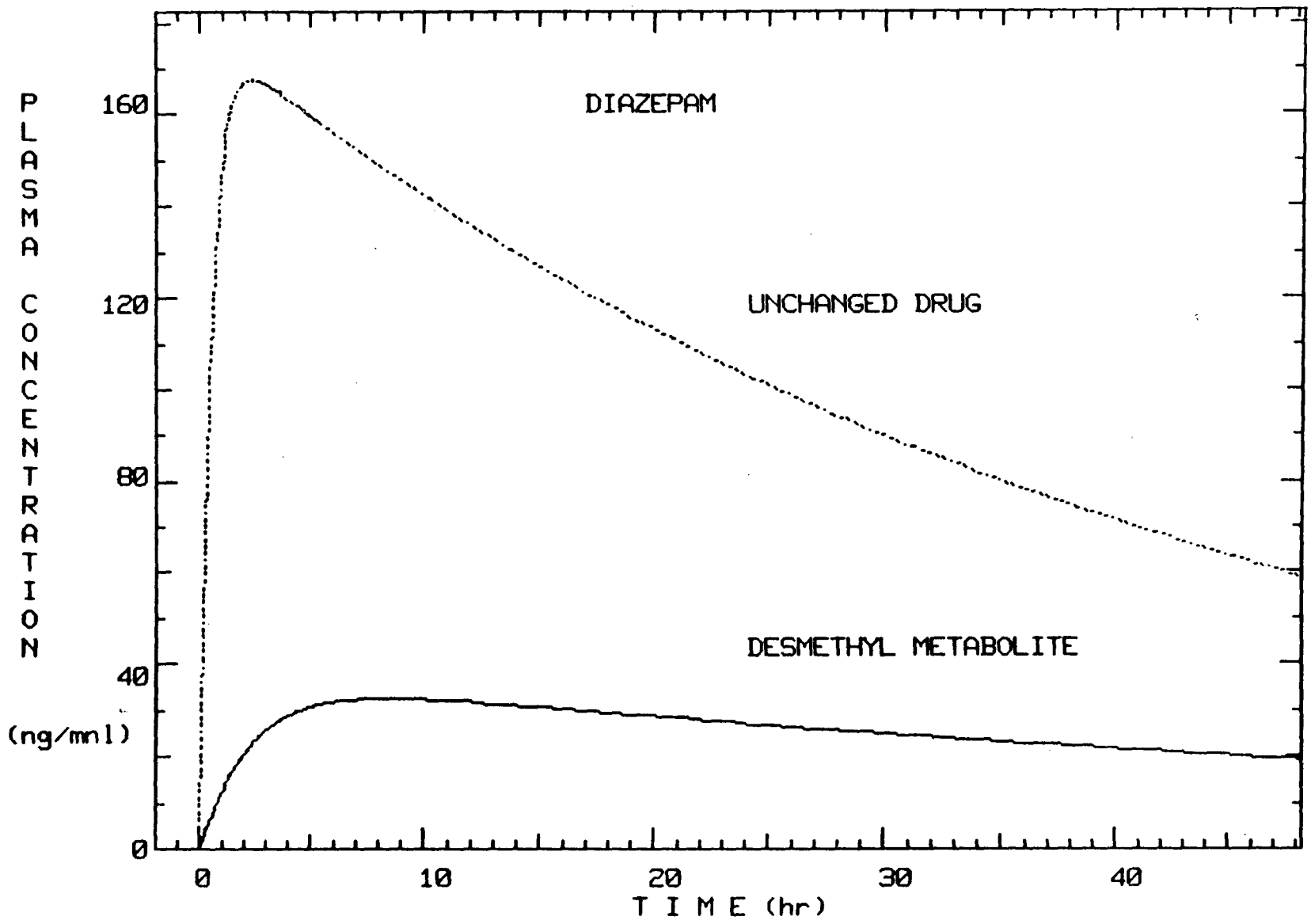


FIGURE 31. PLASMA CONCENTRATION OF DIAZEPAM AND DESMETHYLDIAZEPAM FOR 48 HR AFTER AN ORAL DOSE OF 10 mg PF DIAZEPAM.

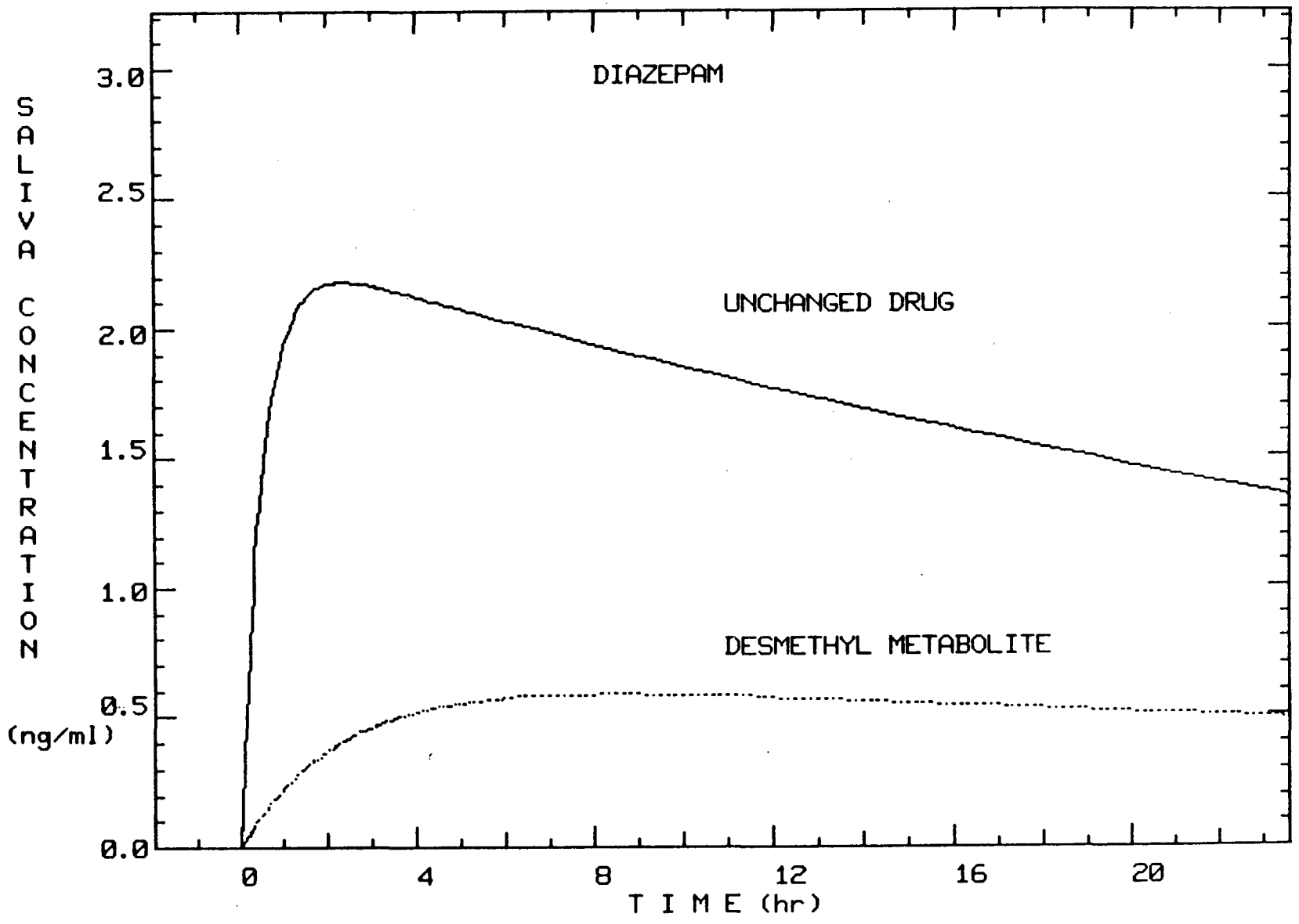


FIGURE 32. SALIVA CONCENTRATION OF DIAZEPAM AND DESMETHYDIAZEPAM FOR 24 HR AFTER AN ORAL DOSE OF 10 mg OF DIAZEPAM

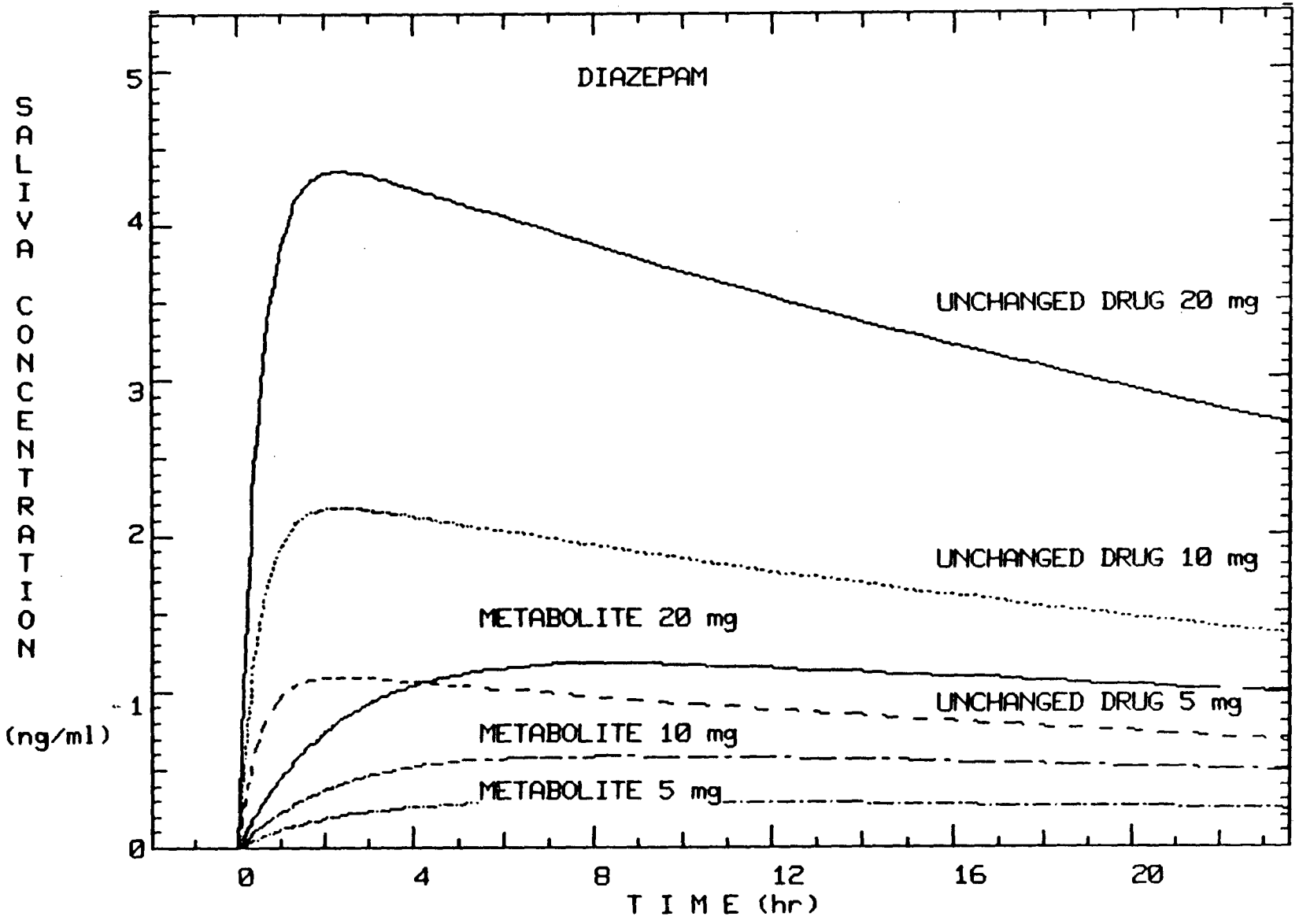


FIGURE 33 SALIVA CONCENTRATION OF DIAZEPAM AND DESMETHYLDIAZEPAM FOR 24 HR AFTER AN ORAL DOSE OF 5 mg, 10 mg, 20 mg OF DIAZEPAM.

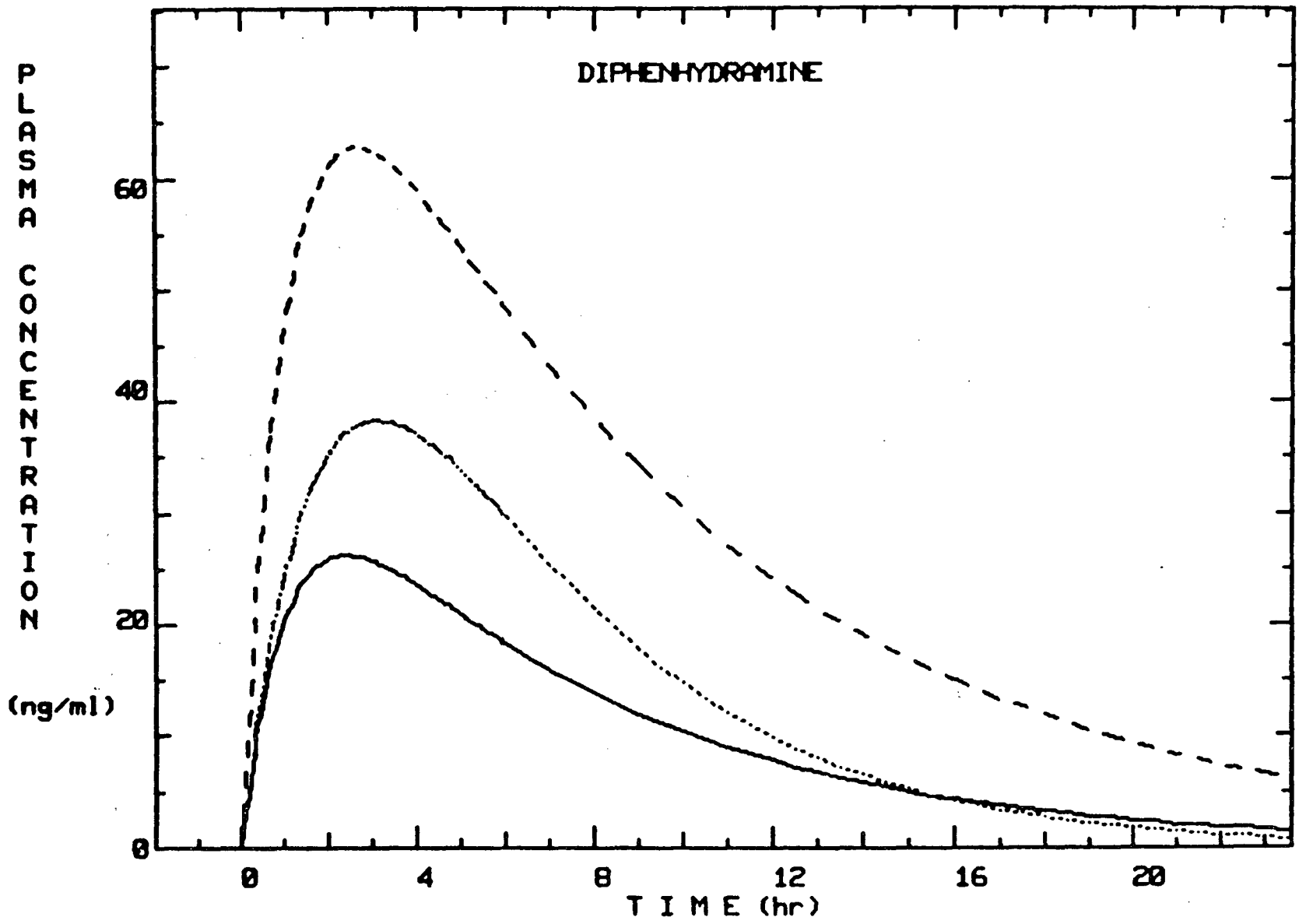


FIGURE 34 PLASMA CONCENTRATION OF DIPHENHYDRAMINE FOR 24 HR AFTER AN ORAL DOSE OF 0.32 mg/kg, 0.63 mg/kg, 0.94 mg/kg.

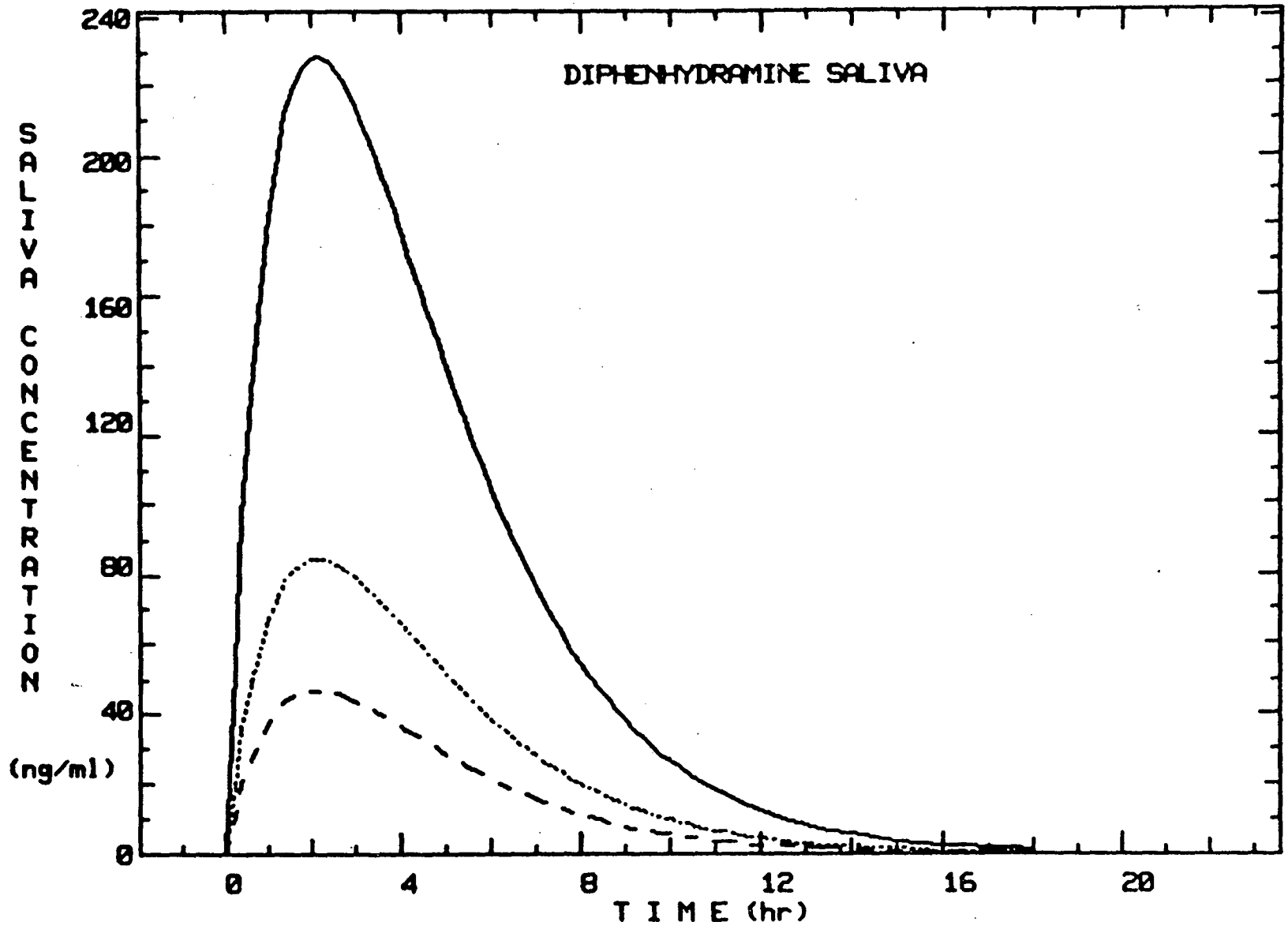


FIGURE 35. APPROXIMATE SALIVA CONCENTRATION OF DIPHENHYDRAMINE FOR 24 HR AFTER AN ORAL DOSE OF 0.32mg/kg, 0.63mg/kg, 0.94mg/kg.

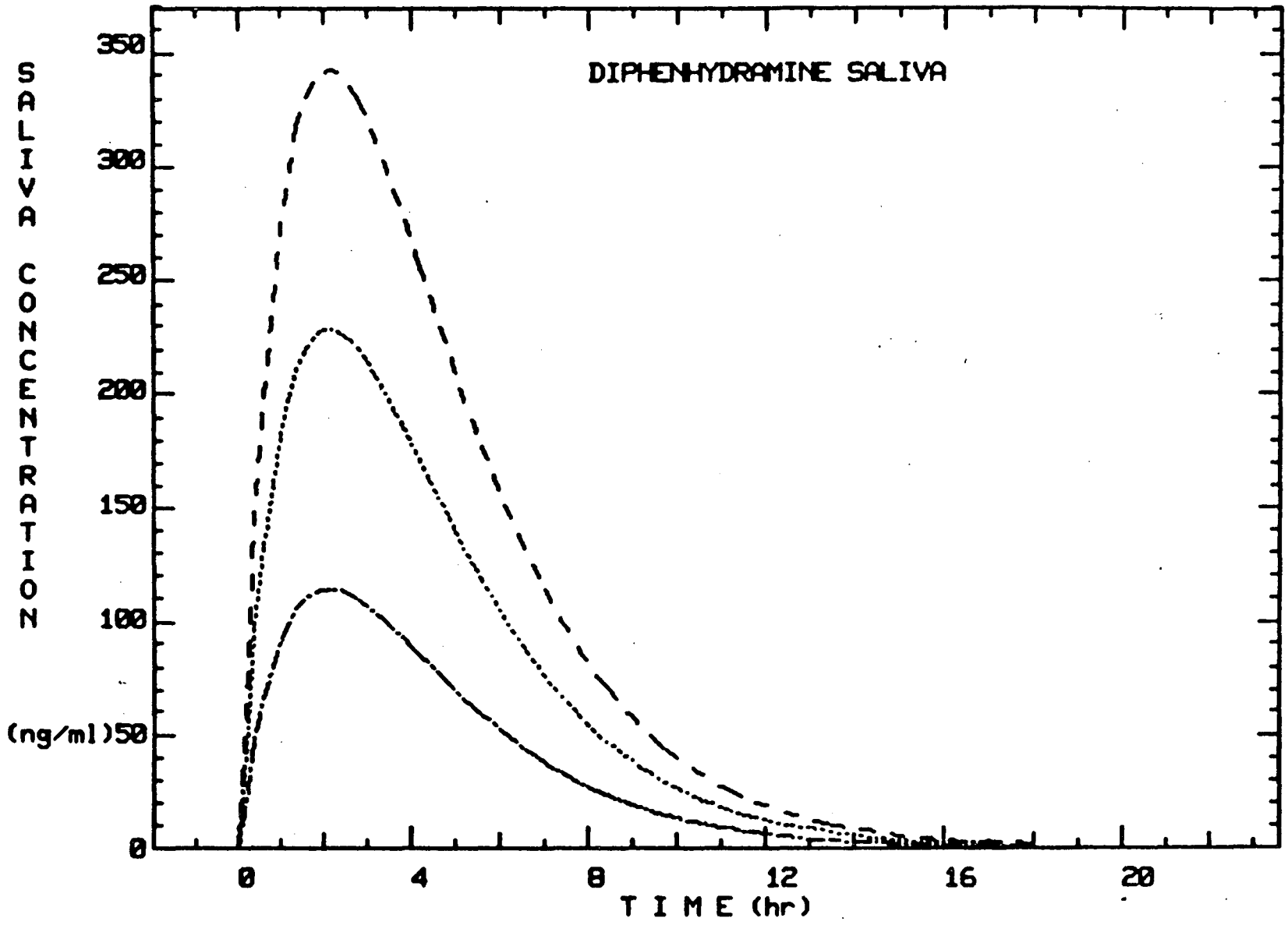


FIGURE 36 .APPROXIMATE SALIVA CONCENTRATION OF DIPHENHYDRAMINE WITH ESTIMATED RANGE FOR 24 HR AFTER AN ORAL DOSE OF 0.94 mg/kg.

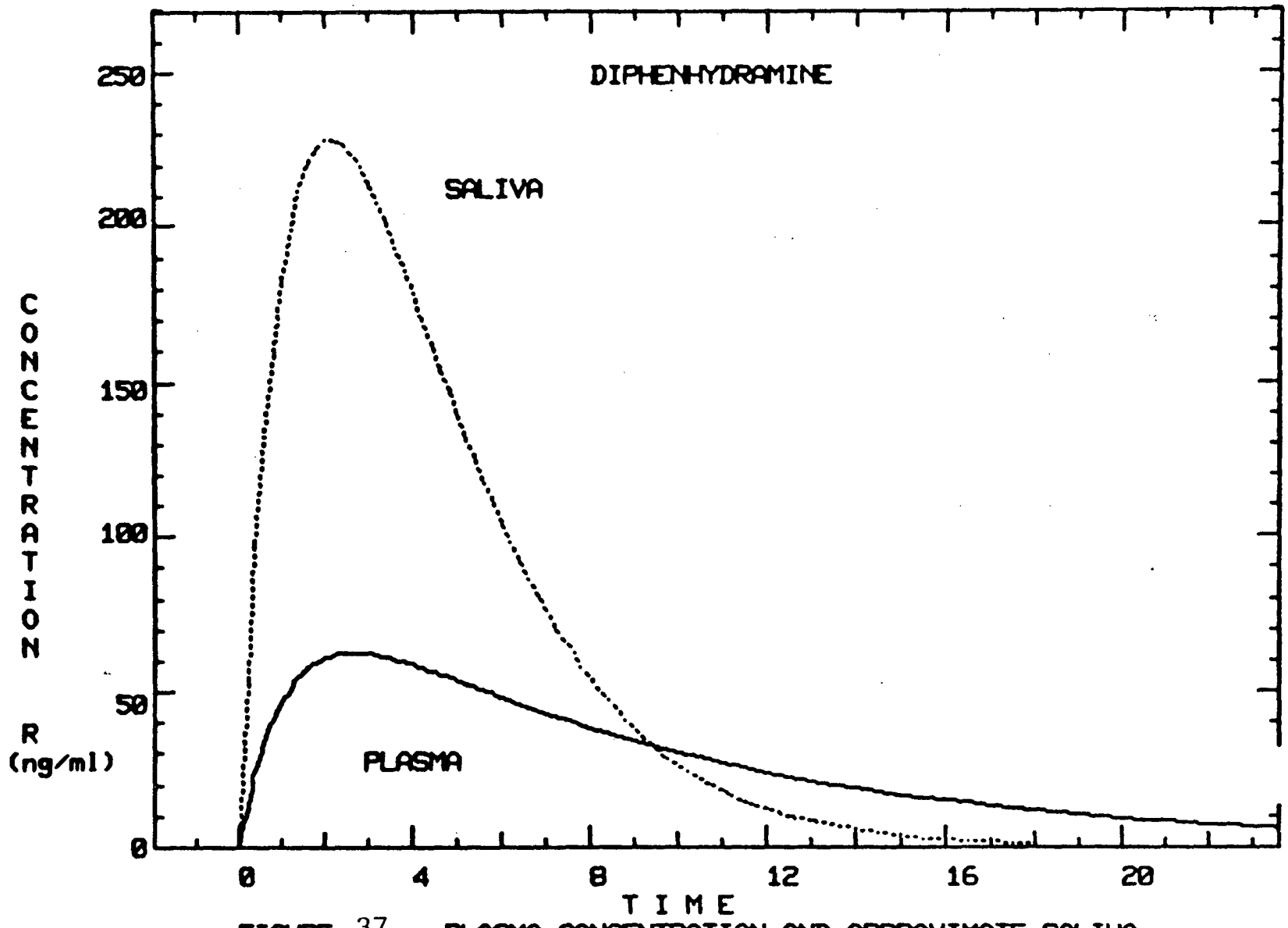


FIGURE 37. PLASMA CONCENTRATION AND APPROXIMATE SALIVA CONCENTRATION OF DIPHENHYDRAMINE FOR 24 HR AFTER AN ORAL DOSE OF 0.94 mg/kg.

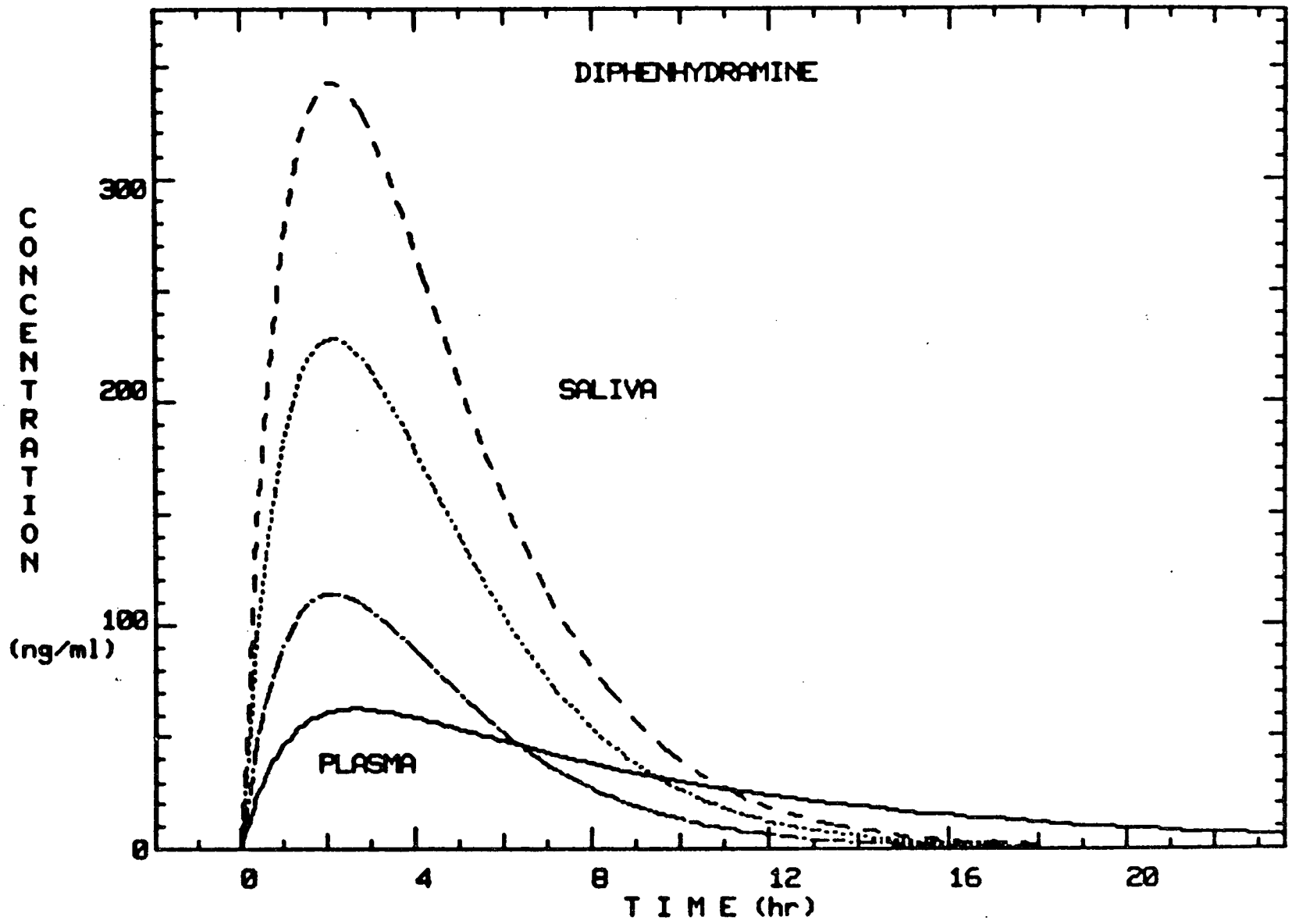


FIGURE 38 .PLASMA CONCENTRATION AND APPROXIMATE SALIVA CONCENTRATION AND SALIVA RANGE FOR 24 HR AFTER AN ORAL DOSE OF 0.94 mg/kg OF DIPHENHYDRAMIN.

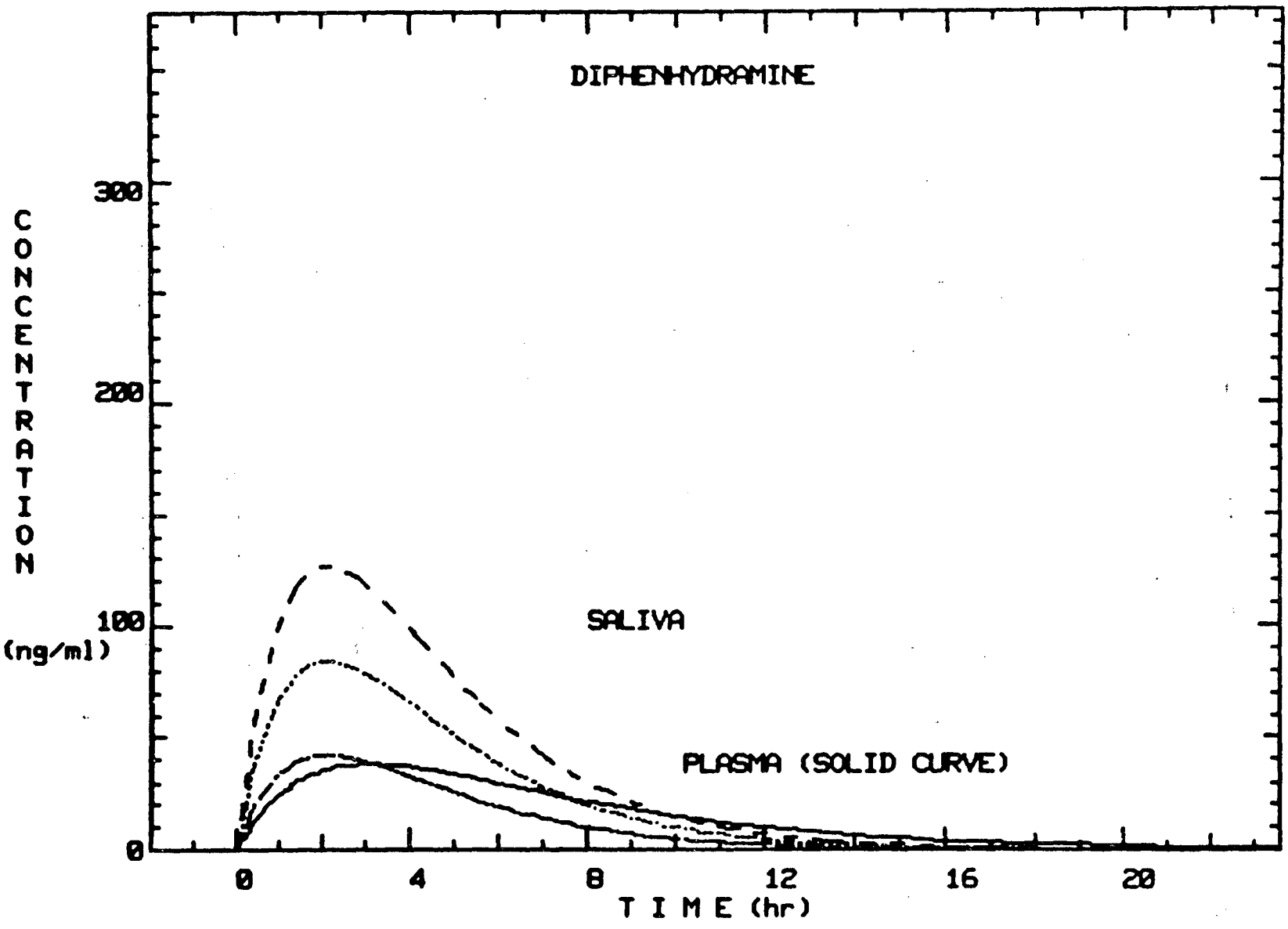


FIGURE 39 .PLASMA CONCENTRATION AND APPROXIMATE SALIVA CONCENTRATION AND SALIVE RANGE FOR 24 HR AFTER AN ORAL DOSE OF 0.63 mg/kg OF DIPHENHYDRAMINE.

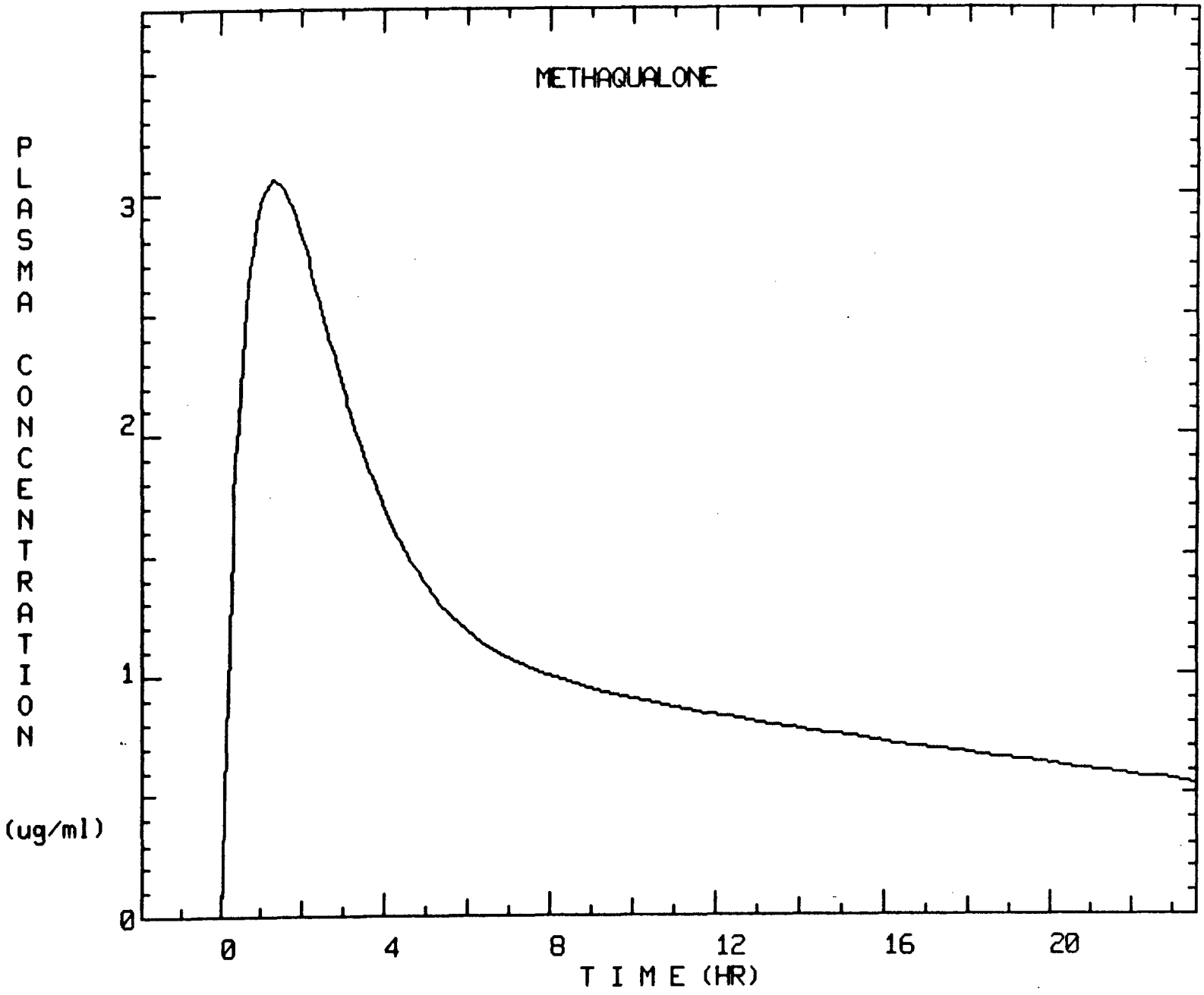


FIGURE 40 .PLASMA CONCENTRATION OF METHAQUALONE FOR 24 HR AFTER AN ORAL DOSE OF 300 mg.

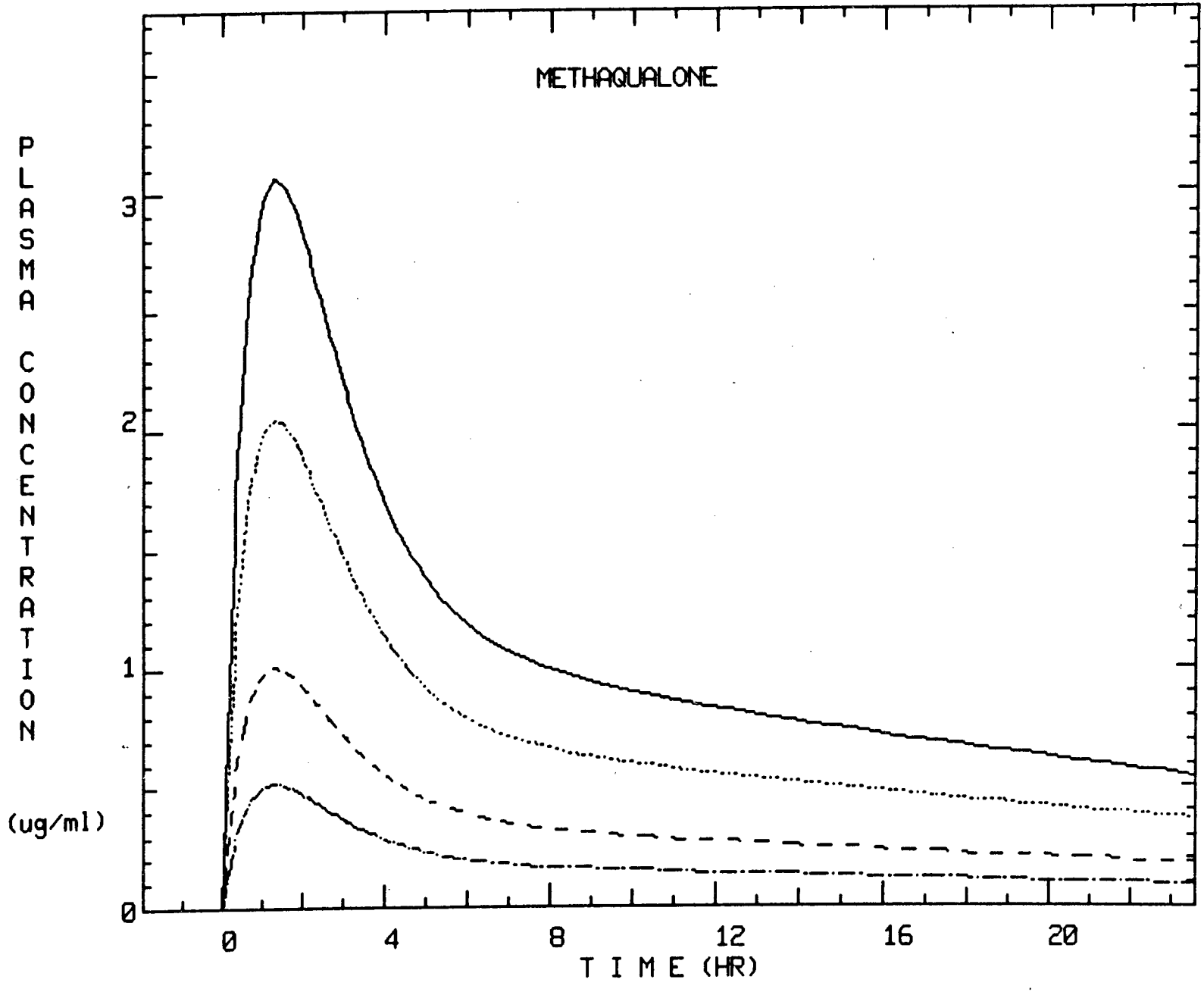


FIGURE 41. PLASMA CONCENTRATION OF METHAQUALONE FOR 24 HR AFTER AN ORAL DOSE OF 300 mg, 200 mg, 100 mg, 50 mg FOR CURVES FROM TOP TO BOTTOM RESPECTIVELY.

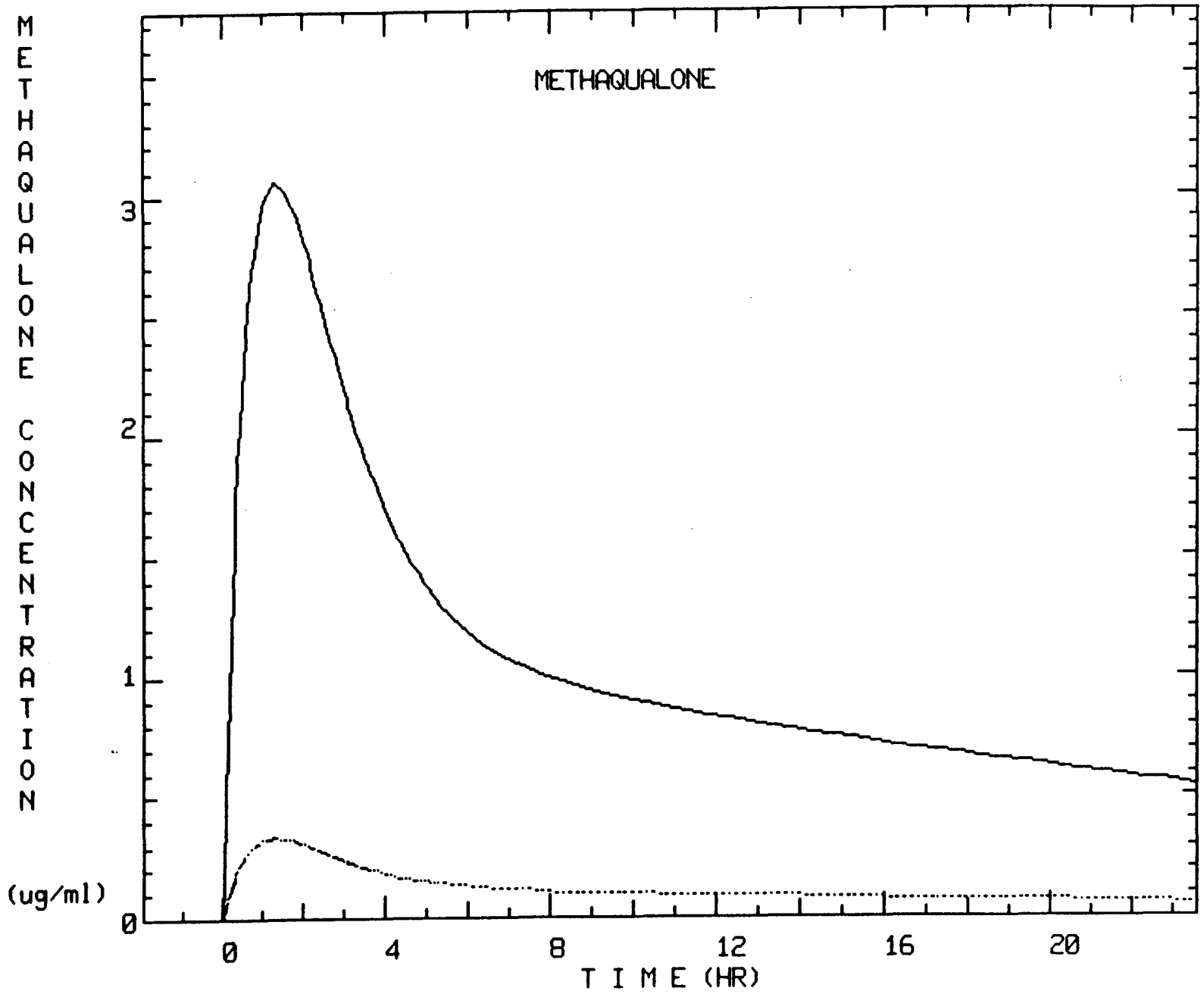


FIGURE 42. CONCENTRATION OF METHAQUALONE IN PLASMA (TOP CURVE) AND SALIVA (BOTTOM CURVE) FOR 24 HR AFTER AN ORAL DOSE OF 300 mg.

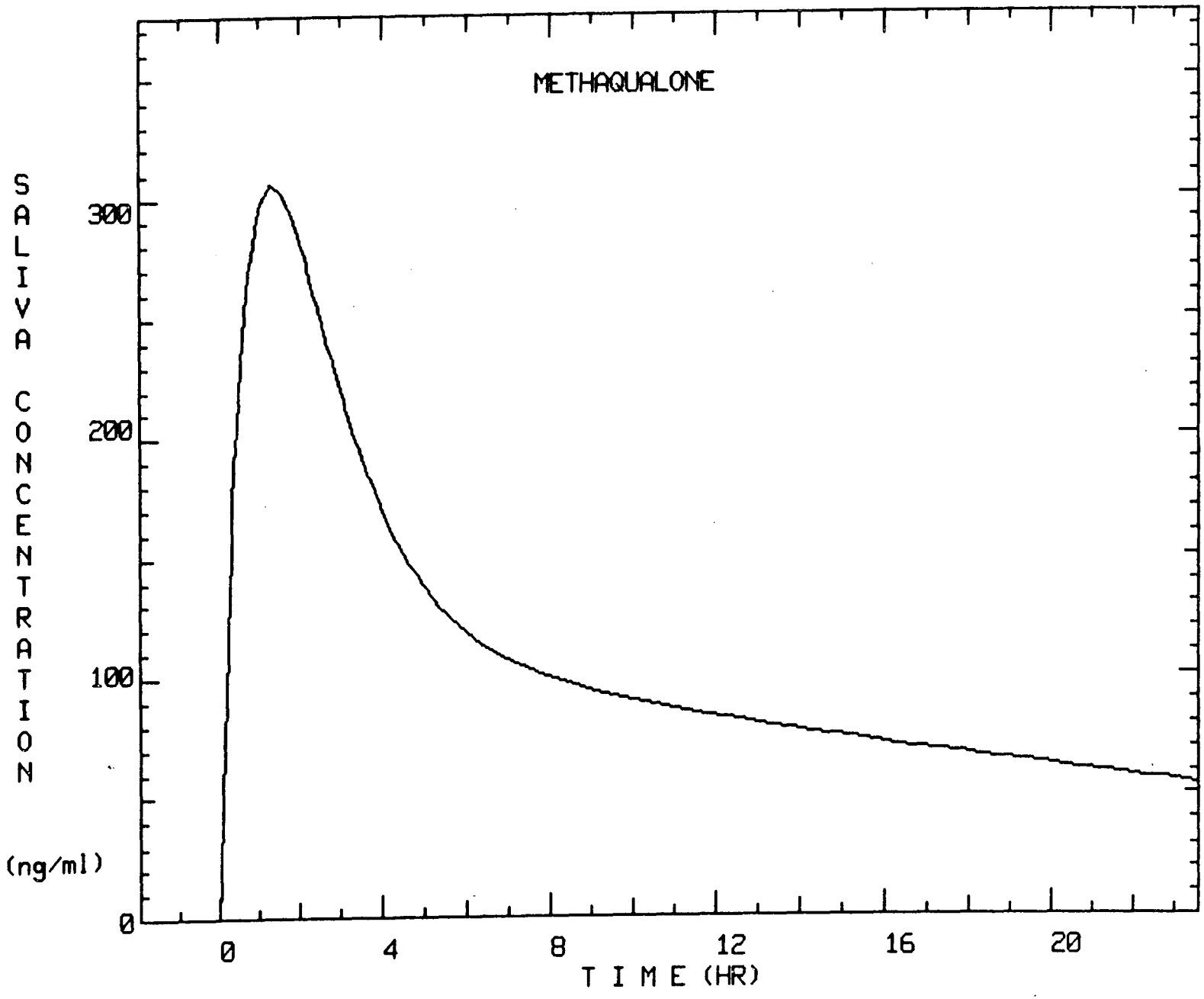


FIGURE 43. SALIVA CONCENTRATION OF METHAQUALONE FOR 24 HR AFTER AN ORAL DOSE OF 300 mg.

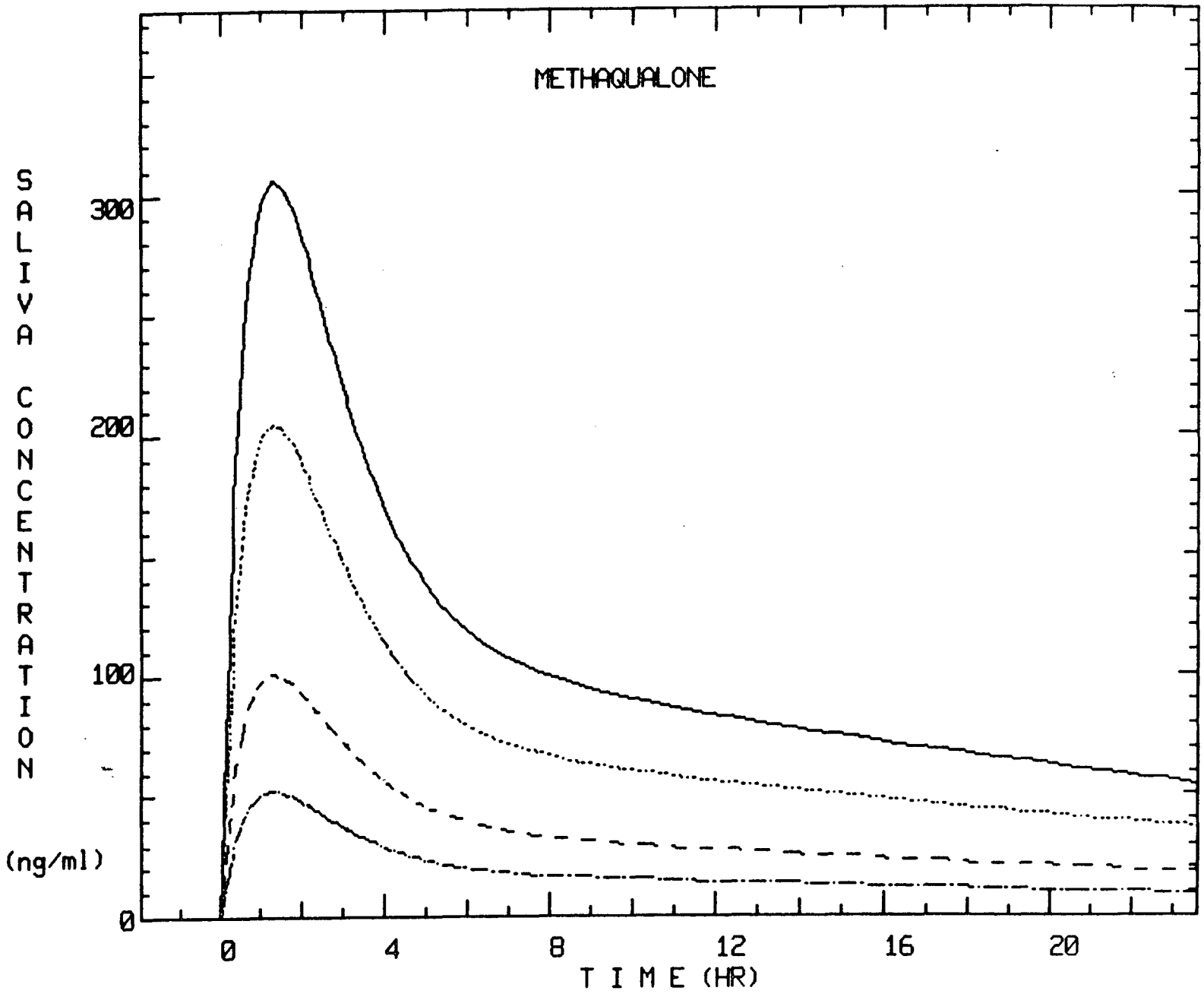


FIGURE 44. SALIVA CONCENTRATION OF METHAQUALONE FOR 24 HR AFTER AN ORAL DOSE OF 300 mg, 200 mg, 100 mg, 50 mg FOR CURVES FROM TOP TO BOTTOM RESPECTIVELY.