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DESCRIPTIVE SUMMARY WITH CONCLUSIONS:

Upper respiratory tract (URT) absorption of several compounds with differing water solubilities and potentials to cause lesions of the nasal mucosa was studied in rats. Uptake of propylene glycol monomethyl ether (PGME), PGME acetate ester (PGMEAc), ethyl acrylate (EA), epichlorohydrin (EPI), styrene (STY), nitroethane (NE), ethylene dibromide (EDB) and methylene chloride ($MeCl_2$) vapors by the isolated URT were compared with the uptake of these compounds by the isolated lower respiratory tract (LRT) and whole animal. Nearly all PGME, PGMEAc and 30-70% of EA, EPI, STY, NE and EDB were absorbed by the URT. Similar levels were absorbed by the LRT and whole animal except for STY (>90% absorbed). It was estimated that intact animals received between 19% ($MeCl_2$) and 47% (PGME) of its total dose via the URT. Further, the dosage per unit surface area of URT was as much as 500 times that of the LRT. This absorption was observed to be quantitatively related to the blood/air partition coefficient of these compounds. Absorption of chemical by the URT, however, did not correlate with the ability of compounds to cause lesions of the nasal mucosa. Several predictive pharmacokinetic models were developed for uptake of chemicals by various regions of the respiratory tract.

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THE COMPARATIVE ABSORPTION AND EXCRETION OF CHEMICAL VAPORS BY THE UPPER, LOWER AND INTACT RESPIRATORY TRACTS OF RATS

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ABSTRACT

Upper respiratory tract (URT) absorption of several compounds with differing water solubilities and potentials to cause lesions of the nasal mucosa was studied in rats. Uptake of propylene glycol monomethyl ether (PGME), PGME acetate ester (PGMEAc), ethyl acrylate (EA), epichlorohydrin (EPI), styrene (STY), nitroethane (NE), ethylene dibromide (EDB) and methylene chloride ($MeCl_2$) vapors by the isolated URT were compared with the uptake of these compounds by the isolated lower respiratory tract (LRT) and whole animal. Nearly all PGME, PGMEAc and 30-70% of EA, EPI, STY, NE and EDB were absorbed by the URT. Similar levels were absorbed by the LRT and whole animal except for STY (>90% absorbed). It was estimated that intact animals received between 19% ($MeCl_2$) and 47% (PGME) of its total dose via the URT. Further, the dosage per unit surface area of URT was as much as 500 times that of the LRT. This absorption was observed to be quantitatively related to the blood/air partition coefficient of these compounds. Absorption of chemical by the URT, however, did not correlate with the ability of compounds to cause lesions of the nasal mucosa. Several predictive pharmacokinetic models were developed for uptake of chemicals by various regions of the respiratory tract.

INTRODUCTION

The mucosa of the upper respiratory tract (URT) of rodents has been observed to be a frequent target tissue of inhaled chemicals. Compounds fall into two general categories; those causing a nonspecific degeneration of epithelium (e.g., ethylene dibromide), and those causing primarily lesions of the olfactory neuroepithelium (e.g., ethyl acrylate) (Nitschke et al., 1981; Miller et al., 1980). Unlike the lesions produced by several nonspecific nasal mucosal toxicants (e.g. formaldehyde), lesions of the olfactory epithelium have not been observed to progress to neoplasia.

The URT functions as a first line of defense in preventing potentially harmful chemical vapors from reaching the lower respiratory tract (LRT). Described by Brain (1970) as an efficient "scrubbing tower", the URT directs inhaled air into close contact with a mucosa richly supplied with fenestrated capillaries (Swindle, 1935; Proctor and Swift, 1977). Not surprisingly, the URT has been observed to absorb large amounts of respiratory irritants such as ozone, formaldehyde, mustard gas, acrolein, hydrogen fluoride and sulfur dioxide (Brain, 1970; Feron et al., 1978; Giddens and Fairchild, 1972; Cameron et al., 1946; Aharonson et al., 1974; Spiezer and Frank, 1966; Egle, 1972; Morris and Smith, 1982). This absorption is generally believed to be related to the water solubility and reactivity of the inhaled compounds (Aharonson et al., 1974; Morgan and Frank, 1977).

In order to better assess the potential human risk of exposure to compounds causing lesions of the URT mucosa in obligate nasal breathing rodents, there is a need for additional information regarding; 1) potential

physicochemical factors controlling chemical absorption by the URT, 2) the relationship of chemical absorption to the development of specific lesions of the URT mucosa, and 3) the role the URT plays relative to the LRT in the absorption of chemicals by the entire respiratory tract. The purpose of the present study was to provide this information in rats for several compounds of differing water solubilities and potential to cause lesions of the URT (Table 1).

METHODS AND MATERIALS

Chemicals.

Ethyl acrylate (EA; Lot #EJS 11-9-77; >99% pure) was obtained from Rohm and Haas Co., Philadelphia, PA, nitroethane (NE; Lot #8020-513; >97% pure) was obtained from International Minerals Co., Terre Haute, IN, and methylene chloride ($MeCl_2$; Lot #AE411; >99% pure) was obtained from Burdick and Jackson Laboratories Inc., Muskegon, MI. Styrene (STY; Lot #11-30-81), epichlorohydrin (EPI; Lot #TP-073k), ethylene dibromide (EDB; production grade), propylene glycol monomethyl ether (PGME; Lot #810310-25) and its acetate ester (PGMEAC; Lot #DPC 203-23) were all obtained from the Dow Chemical Company, Midland, MI, and were >99% pure.

Animals.

Male Fischer 344 rats (200-260 g), obtained from Charles River Breeding Laboratories (Portage, MI) were utilized in all experiments. Animals were pair housed in environmentally controlled rooms (23±2°C, 50±15% relative humidity, 12 hour photoperiod), fed Purina Certified Rodent Chow (Ralston Purina, St. Louis, MO) and given water ad libitum, and acclimated at least 7 days prior to use.

For all experiments rats were anesthetized (60 mg/kg sodium pentobarbital, ip.), were shorn of facial hair, and had their mouths sealed using surgical clips. The level of anesthesia maintained throughout experiments (approximately stage 3, level 2) resulted in respiratory minute volumes of 53±3 ml/min as determined by plethysmography (Landry et al., 1982).

Procedures.

Atmospheres of 75 ppm EDB, 100 ppm EPI, 200 ppm STY, 225 ppm EA, 500 ppm $MeCl_2$, 1000 ppm NE, 1000 ppm PGME and 1000 ppm PGMEAc were used in all experiments. These exposure levels represented those reportedly causing URT lesions in rat bioassays (where applicable) and were absorbed by intact animals at rates directly proportional to exposure levels. Concentrations of these compounds were quantitated using appropriate standards with a Varian Model 1500 gas chromatograph (GC) (Palo Alto, CA) equipped with a 1 ml loop injector, a 1 foot SS 1/8 in. ID column packed with 10% Carbowax 1500 on Chromasorb WH-P (Supelco, Inc., Bellefonte, PA) (column temperature varied between compounds) and a flame ionization detector (20 ml/min He carrier gas at 180°C). Rates of absorption or excretion of the inhalant by an animal were determined upon reaching a constant level using equations (1) or (2) respectively: (a = moles chemical/mole effluent gas; b = moles chemical/mole test atmosphere; c = l/min flow rate; d = 24.45 l/mole).

$$\text{moles/min absorbed} = \frac{(b-a)(c)}{d} \qquad (1)$$

$$\text{moles/min excreted} = \frac{(a)(c)}{d} \qquad (2)$$

Absorption of inhaled compounds by the intact respiratory tract was investigated by exposing individual anesthetized rats in a small, nose-only chamber equipped with a tight fitting polyvinyl chloride (PVC) cuff which was fastened around the animal's snout. Test atmospheres were pumped (Fluid Metering Inc., Oyster Bay, NY) through the nose-only apparatus at a rate of 150 ml/min and then through a flow meter (Gilmont Inc., Great Neck, NY) and to the GC.

Absorption and excretion of inhaled chemicals by the isolated URT or LRT of rats were investigated in double tracheostomized, anesthetized rats much as has been described by Morris and Smith (1982) (Dia. 1). The caudal endotracheal tube (PE 200; Clay Adams, New York, NY) extended out of the trachea approximately 1.5 cm, ending inside a 1/8 inch I.D. Y-intersection. A gas flow of 150 ml/min was maintained through this intersection into the GC via Teflon tubing (1/8 in ID). For LRT absorption studies, the gas intake line was attached to a Saran gas bag containing the desired atmosphere. To determine LRT excretion of compounds this end was left open to room air.

To determine URT absorption of compounds, the cephalad endotracheal tube (PE 160) was attached to the GC via a flow meter and pump (Dia. 1). A unidirectional 50-60 ml/min or 100-110 ml/min gas stream was thus maintained from the nares (mouth clipped shut) to the trachea. A PVC cuff was firmly secured about the animals snout on one end and attached to a Saran gas bag containing the test atmosphere on the other. To measure excretion

of chemicals by the URT the same gas flow was maintained but in the opposite direction (trachea to nares), the intake was of room air and the outflow to the GC was via a Teflon line in place of the gas bag at one end of the PVC cuff.

Using these data, the "dose" of chemical received by the animal via the URT and LRT was estimated using equations (3) and (4) respectively (e = moles absorbed by URT/t; f = moles passing into animal/t; g = fraction absorbed; t=time). In the normal animal, exposure of the URT to test atmosphere occurs primarily during inhalation (i.e. approximately one-half the time of exposure), thus the URT "dose" was multiplied times 0.5t. The dose received by the whole animal was also calculated (equation 5):

$$\text{moles absorbed by URT} = (f)\,(g)\,(0.5t) \qquad (3)$$

$$\text{moles absorbed by LRT} = (f-e)\,(g)\,(t) \qquad (4)$$

$$\text{moles absorbed by whole animal} = (f)\,(g)\,(t) \qquad (5)$$

To better understand the factors controlling URT absorption of chemical vapors, as well as the interrelationship of the isolated URT, LRT and the intact respiratory system, a kinetic model was constructed to simulate

the absorption and excretion rates observed in these experiments. The model was based on partitioning of the chemical between blood and air, and the partition coefficient for a given chemical was considered to be identical in the URT, LRT and intact respiratory system. When compound instabilities prohibited measurement of blood/air partition coefficients, water/air values were substituted (Table 1).

In the intact system, absorption of an inhaled chemical by the URT may take place during inhalation and to a less extent during exhalation, thus the model depicting the intact animal (Dia. 2) contained a "nasal cavity" for each situation (URTI and URTE). Inhaled atmospheres were passed through the URTI first, then the lungs and exited through the URTE. Models describing the uptake and excretion of inhalants by the URT and LRT contained only one URT with both the URT and LRT being independently ventilated, one with test atmosphere (absorption) and the other with air (excretion) (Dia. 3).

The rest of the body (eg. muscle, fat, liver) were lumped into a single compartment equivalent to the volume of distribution of the chemical in rats. Nonrespiratory elimination of absorbed chemicals was defined to be equivalent to their central compartment elimination rate constants observed in rats. Physiological constants included; a total cardiac output in pentobarbital anesthetized rats of 14.8 l/hour•kg (Blood et al., 1950) of which 1.5% was estimated to perfuse the URT (Stott et al., 1982) and 98.5% the central compartment; a URT capillary blood volume of 0.052 ml (10% of a

measured total URT blood volume in rats); an estimation of 0.34 ml of capillary blood in pulmonary tissues (Weibel, 1963); and an effective ventilation of the respiratory tract (minus anatomical dead space) of 0.7 x 53.2 ml/min. All other constants were maintained as in the intact system. The constants used and computer programs with their differential equations are shown in Appendices I-III. In addition, i.v. blood curves of PGME, PGMEAc, NE and EA are shown in Appendices IV-VII.

RESULTS

Absorption of chemical vapors by the URT, LRT and intact respiratory tracts of pentobarbital anesthetized rats reached an apparent plateau within 10 to 20 minutes and remained relatively constant for the duration of exposure. As shown in Table 2, the isolated URT was observed to absorb over 90% of PGME and PGMEAc and between 50 to 70% of EA, EPI, STY, NE or EDB when these vapors were passed through the URT at a flow rate equivalent to the animals respiratory minute volume (50-60 ml/min). In contrast, $MeCl_2$ was only poorly absorbed (17%) by the URT. Similar rates of absorption were observed to occur with the LRT and the intact respiratory tract, with the exception of STY and $MeCl_2$ which were more readily absorbed (>90% and >36% respectively) than in the URT.

In general, only a small percentage (<5%) of LRT absorbed compounds were simultanelously excreted via the URT. Likewise, little of the compounds absorbed by the URT were simultaneously excreted by the LRT (<3%) (Table 2). $MeCl_2$ was an exception to this rule, as virtually all $MeCl_2$ absorbed by the URT was excreted by the LRT. A constant rate of excretion by the URT and LRT was also observed even though it was doubtful that steady-state blood levels had been attained. Indeed, this was observed in preliminary experiments on PGME excretion, in which pulmonary excretion appeared to remain constant over the same time period in which blood levels of PGME doubled. An explanation of this may be the inability to detect small absolute changes in chemical vapor concentrations of effluents.

An increased URT ventilation rate (100-110 ml/min) was observed to result in less than a 5% decrease in the absorption of PGME, PGMEAc and EPI. A larger decrease (25 to 40%) in the absorption of vapors was noted for EA, STY, NE, EDB and $MeCl_2$ (Table 3). Despite this decrease in percent absorption, the rate of URT uptake of chemicals was observed to increase for most of the compounds tested. PGME, PGMEAc and EPI were absorbed at rates equivalent to 1.9 to 2.0 times, and EA, STY, $MeCl_2$ and EDB at rates 1.2 to 1.5 times, the rates observed at the slower URT ventilation rate.

URT absorbed material was estimated to contribute from 19% ($MeCl_2$) to 47% (PGME) of the total dose of test chemicals received by exposed intact rats (Fig. 1). These estimates were obtained using the URT % absorption data obtained at two times the respiratory minute volumes of these animals, thus approximating the residence times of chemicals passing through the URT. The calculated total dose of a given chemical received by rats (i.e. sum of the isolated URT and LRT doses) was well within the potential experimental error for that calculated from actual whole animal exposure data. These results, when normalized for a uniform exposure concentration and exposure time, are displayed in Fig. 1.

A comparison of the rates of chemical absorption predicted by kinetic models for the three experimental preparations are presented in Table 4. In general, there was good agreement between predicted values and the experimentally observed results shown in Table 2. Notable exceptions were

the absorption of $MeCl_2$ by the LRT and intact animals, in which the models overpredicted uptake, and the absorption of EA, EPI and EDB by the isolated URT, in which the model considerably underpredicted absorption. Predicted URT and LRT excretion values were within the range of experimentally observed values (data not shown).

DISCUSSION

The results of the present study demonstrate that the URT plays a significant role in the absorption a variety of chemical vapors by rodents. The isolated, ventillated URT of anesthetized Fischer-344 rats was observed to absorb nearly all PGME and PGMEAc vapors, and 30-70% of EA, EPI, NE, EDB, and STY vapors passed through them at a ventilation rate equivalent to 1 or 2 times the respiratory minute volume (53 ml/min). The URT appears to play a relatively minor role in the absorption of $MeCl_2$ and in the excretion of all these chemicals, once absorbed into the blood stream.

To obtain these data, the bidirectional, alternating ventilation of the URT in the intact animal was replaced by the unidirectional, constant ventilation of the isolated URT. Thus, gradients of vapor concentrations which normally exist between the URT and LRT were disrupted. However, considerable evidence suggests that these data do approximate normal URT function. Unidirectional air flow prevents the loss of absorbed chemicals from the nasal mucous due to solute backpressure normally occurring during exhalation. However, significant backpressure would be expected only with high concentrations of compounds (eg. >1%) with high vapor pressures and low water solubilities, circumstances quite different from those employed here. Preliminary experiments established that there were no appreciable differences in URT blood flow between the exposed isolated URT and the URT of exposed intact animals, and that no trigeminal nerve reflex mediated changes in respiratory rates occurred in these anesthetized rats. And finally, there was good agreement between the total amounts of chemicals absorbed when calculated as a sum of the isolated parts of the respiratory system and the intact system (Fig. 1).

The influence of flow rate on absorption of chemical vapors by the isolated URT was also evaluated. As shown in Table 3, a two-fold increase in the flow rate from 53 to 105 ml/min resulted in up to a 40% decrease in the absorption of chemicals. The former URT ventilaton rate utilized represented the respiratory minute volumes of these animals thus maintaining an equivalent net mass transfer of chemicals in each of the animal preparations. The later flow rate resulted in roughly equivalent residence times of vapors in the isolted URT as occurred in the URT of exposed whole animals. A similar relationship of URT flow rate and chemical absorption has been discussed by Brain (1970) and Aharonson et al. (1974).

Based upon the above considerations, the chemical dose of PGME, PGMEAc, EA, STY, EPI, EDB and NE absorbed by animals via the URT appears to be quite substantial relative to that absorbed by the LRT in the intact respiratory system, even though the URT is only exposed primarily during the inhalation phase of the breathing cycle (Fig. 1). Furthermore, when absorption is expressed in terms of surface area (Chang et al., 1982; Bevin et al., 1979), the dose received by the URT is as much as 500 times greater than that of the LRT. Thus, it is not surprising that the reactive compounds EDB and EPI were observed to effect the respiratory epithelium of the nasal cavity before that of the LRT (Nitschke et al., 1981; Quast et al., 1979). In these cases the protective role of the nasal mucosa is well illustrated.

Simple chemical vapor absorption itself however, does not correlate with the production of morphologic lesions of the URT mucosa. PGME was readily absorbed by the isolated URT yet does not cause these lesions in exposed rats (Miller et al., 1981a). Likewise, the potential site of activity within the URT mucosa of exposed rats does not appear to be related to their URT absorption. Compounds causing primarily lesions of the olfactory epithelium (NE, EA, PGMEAc) were absorbed by the isolated URT at rates greater or equivalent to those compounds which cause primarily lesions of the respiratory epithelium (EPI, EDB) (Gushow et al., 1982; Miller et al., 1980, 1981b; Nitschke et al., 1981; Quast et al., 1979).

The kinetic models utilized to predict chemical absorption by the URT, LRT and intact respiratory tract correctly reflected the dynamics of chemical vapor uptake in the exposed rat. Uptake was related to the blood/air partitioning of compounds, but only when used in conjunction with the distribution and excretion kinetics of the chemicals. Likewise, a simple correlation between uptake and water solubilities was not evident. Differences in observed and predicted values of chemical vapor absorption were mostly inconsequential and not attributable to any single variable. The large underestimations of URT absorption of EA, EPI and EDB made by the model were not surprising. EA has been observed to be readily hydrolyzed by nasal cavity area esterases in vitro (Stott and Young, 1982), while EPI and EDB are known to undergo metabolic activation and to bind with tissue macromolecules (Rannug, 1980; Fishbein, 1976; Jones et al., 1969). Indeed,

the nasal mucosa is well supplied with xenobiotic metabolizing enzyme systems (Dahl et al., 1980; Brittebo et al., 1981). Thus, substantial amounts of these three chemicals may be removed in the URT at a rate faster than physical blood/air partitioning would account for. The overprediction of $MeCl_2$ absorption by the LRT and intact animal models may reflect a more serious error in the physical and biological constants used or a particular sensitivity to some experimental effect.

The data reported here emphasize the role the URT may play in protecting the lungs from exposure to high concentrations of potentially harmful chemical vapors. However, extensive absorption of vapors by the URT does not indicate that a compound is a respiratory tract toxicant or that it causes lesions of the URT mucosa. It is expected that mouth breathing by exposed nonobligate nasal breathing animals, including humans, will circumvent this protective role thereby decreasing the dose of chemical received by the URT relative to the LRT. In this situation, compounds causing generalized lesions of the respiratory epithelium would be expected to have a greater effect on the LRT epithelium. For example, pulmonary effects have been observed by Amdur (1959) to occur in tracheostomized guinea pigs but not in normal guinea pigs exposed to formaldehyde vapors. However, for those compounds causing primarily lesions of the URT olfactory neuroepithelium, a significant bypassing of the URT in these animals would result in a decrease in the severity of mucosal lesions.

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TITLE OF STUDY: THE COMPARATIVE ABSORPTION AND EXCRETION OF CHEMICAL VAPORS BY THE UPPER, LOWER AND INTACT RESPIRATORY TRACTS OF RATS - HET T2.8-1-13-(2)

In compliance with Good Laboratory Practice Regulations, the study phases were inspected by the Quality Assurance Unit and the results of these inspections reported to Management and the Study Director on the dates listed below. The report accurately reflects the data generated in accordance with the regulations and Standard Operating Procedures of the laboratory. All data and the reports are located at the submitting laboratory.

Study Started:	21 Dec. 1981	Report Issued Date:	28 October 1982
Dates of Inspection:	21 Dec. 1981	Date of Report:	21 Dec. 1981
	19 Feb. 1982		23 Feb. 1982
	8 March 1982		8 March 1982
	13 October 1982		14 October 1982

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TABLE 1

Physical and Biological Data

Compound	Water Solubility (ppm)	Partition Coefficient[a] (Blood or Water/Air)	Central Compartment Excretion Constant[b] (hr^{-1})	Volume Distribution[b] (ℓ)	Reported Lesions of the URT Mucosa of Exposed Rats
PGME		403 (B)	0.23	0.91	No Visible Lesions (Miller et al., 1981a)
PGMEAc	200,000	141 (W)	4.9	1.01	Degeneration Olfactory Epithelium (Miller et al., 1981b)
EA	2,000	2.3 (W)	15.8	0.36	Degeneration Olfactory Epithelium (Miller et al., 1980)
EPI	60,000	11 (W)	0.16[c]	0.35[c]	Degeneration Respiratory Epithelium (Quast et al., 1979)
STY	330	39 (B)[d]	2.7[d]	1.15[d]	No Visible Lesions (Jersey et al., 1978)
NE	110	21 (B)	1.7	0.16	Degeneration Olfactory Epithelium (Gushow et al., 1982)
EDB	4,000	3.9 (B)	1.8[e]	0.23[e]	Degeneration Respiratory Epithelium (Nitschke et al., 1981; Reznik et al., 1980)
$MeCl_2$	13,250	9.7 (B)[f]	10.6[g]	0.30[g]	No Visible Lesions (Rampy et al., 1979)

[a]Determined experimentally at 37°C in a 100 ml sealed vial containing 5 ml whole heparinized blood or distilled water unless noted by footnote. (B) = blood; (W) = water.
[b]Determined experimentally upon i.v. administration to rats (blood concentration curve analysis) unless noted by footnote.
[c]Smith (1982).
[d]Ramsey and Young (1978). The rate constant is based on the rapid (α) distributive phase.
[e]Watanabe and Fox (personal communication).
[f]Sato and Nakajima (1979).
[g]McKenna (1979).

TABLE 2

Absorption and Excretion of Chemical Vapors by the Isolated URT, LRT and by the Intact Respiratory Tract of Rats[a]

Compound	% Absorption[b]			% Excretion[c]	
	URT	LRT	Intact	URT	LRT
PGME	94	106	87	0.2	0.5
	0.05	7.3	6.8	0.1	0.6
PGMEAc	92	99	85	3.8	2.8
	0.41	38	12	3.6	0.2
EA	68	61	65	1.7	1.8
	5.9	8.6	7.3	0.2	0.8
EPI	65	73	51	ND	ND
	9.1	8.6	7.7		
STY	62	94	92	4.5	0.9
	8.2	3.6	9.5	5.0	0.4
NE	62	71	58	2.8	2.0
	5.9	5.0	12	2.0	0.4
EDB	50	51	58	ND	ND
	1.8	17	9.1		
$MeCl_2$	17	37	44	4.8	100
	1.8	4.1	10	3.8	16

[a]Average ± standard deviations of 4-8 animals.

[b]Absorption expressed as a % of chemical available for absorption at a ventillation rate of 53 ml/min.

[c]Excretion expressed as a % of absorbed chemical.

ND = None Detected.

TABLE 3

Absorption of Chemical Vapors by the Isolated URT at 1 and 2 Times the Respiratory Minute Volumes in Rats[a]

Compound	% Absorption[b] 50-60 ml/min flow	100-110 ml/min flow	Ratio[c]
PGME	100 0.05	100 0.05	1.0
PGMEAc	99 0.5	97 2.3	0.98
EA	68 6.4	42 11	0.62
EPI	54 6.4	51 4.5	0.94
STY	52 1.8	33 5.0	0.63
NE	70 1.8	52 1.4	0.74
EDB	48 3.2	32 5.0	0.67
$MeCl_2$	10 2.3	6 2.7	0.60

[a]Average ± standard deviations of 3 rats.

[b]Absorption expressed as a % of chemical available for absorption.

[c]Percent absorption at 110-110 ml/min divided by percent absorption at 50-60 ml/min.

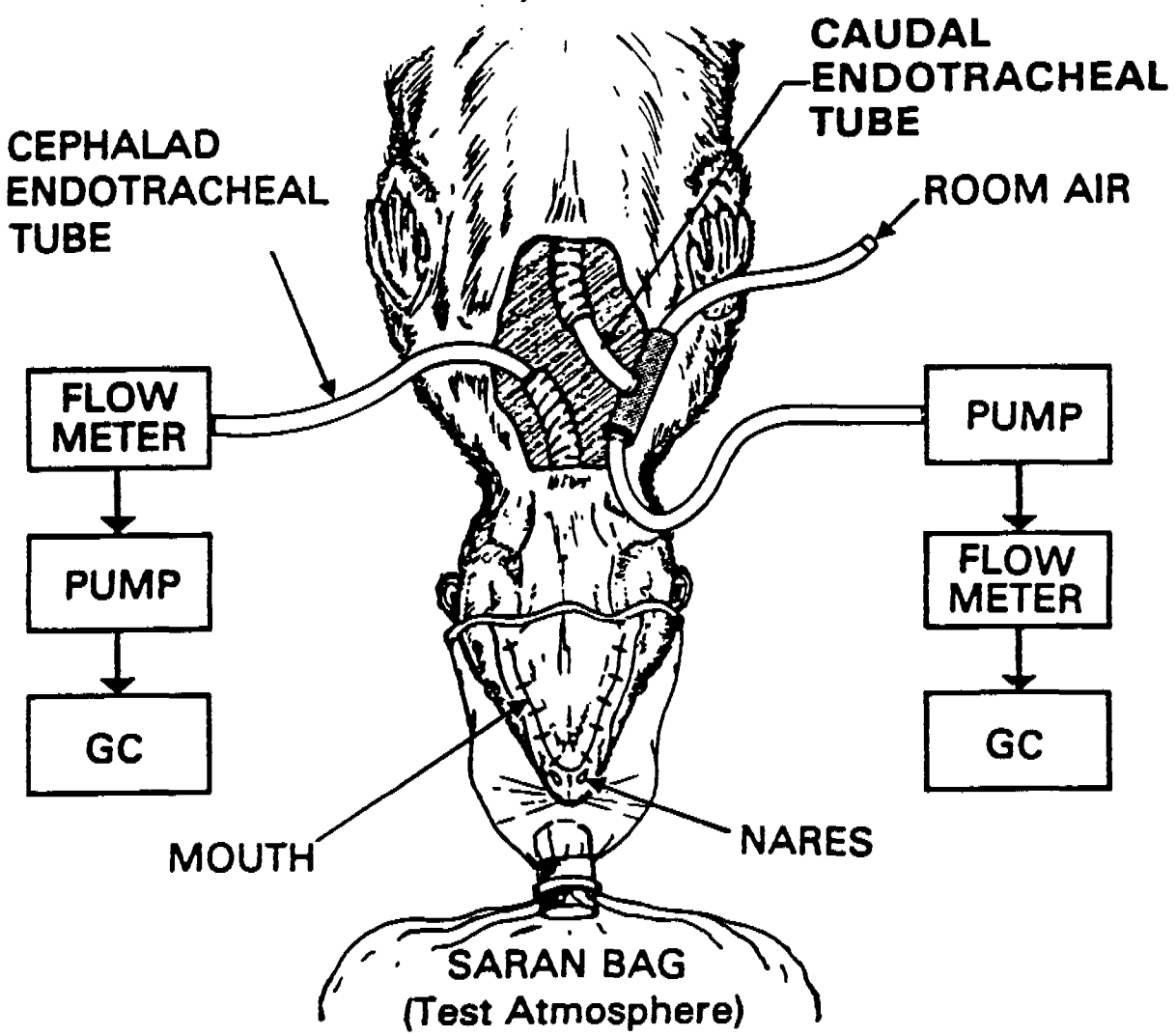
TABLE 4

Predicted vs. Observed Values for Chemical Absorption in Rats[a]

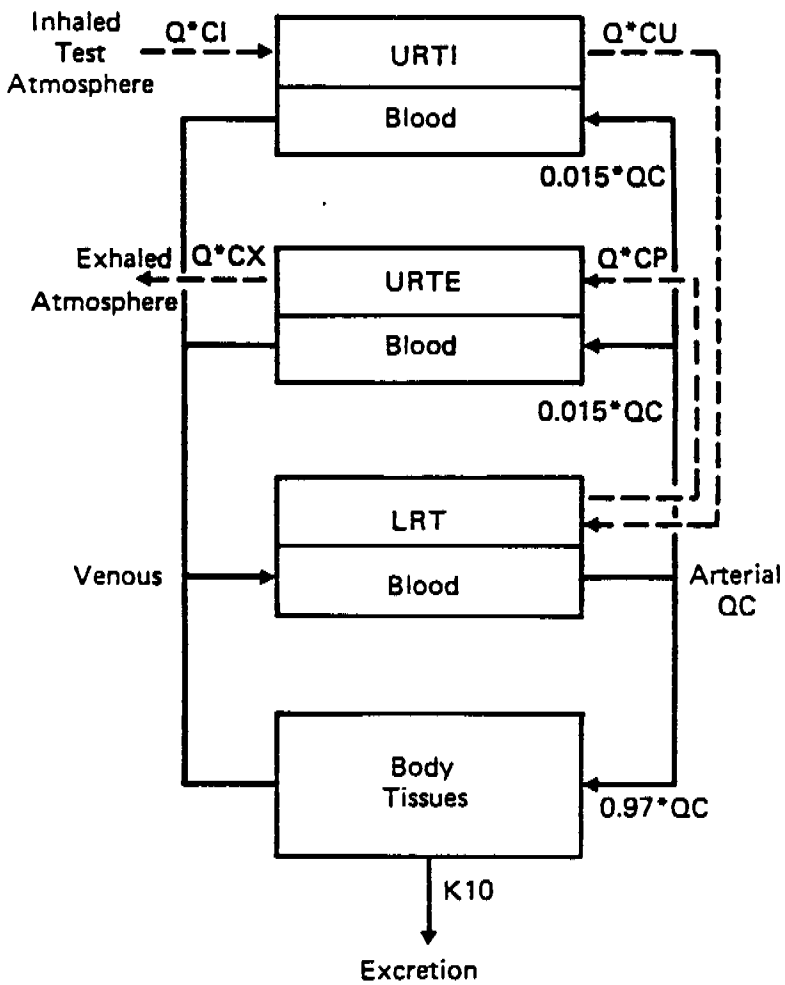
Compound	Percent of Experimental Value		
	URT	LRT	Intact Respiratory Tract
PGME	99	94	115
PGMEAc	85	100	116
EA	7.3	113	106
EPI	29	80	111
STY	77	104	105
NE	50	104	123
EDB	16	81	66
$MeCl_2$	111	240	198

[a]Values are presented as a % of experimental values = $\frac{\text{predicted} \times 100}{\text{observed}}$

Dia. 1. Ventral view of animal preparation used to determine absorption of chemical vapors by the URT and simultaneous excretion of absorbed compounds by the LRT.



Dia. 2. Schematic of kinetic model of uptake of chemical vapors by the whole animal. Abbreviations: Q, respiratory minute volume; QC, total cardiac output; CI, concentration of chemical vapor going to LRT; CP, concentration of chemical vapor exiting LRT; CX, concentration of chemical vapor in exhaled atmosphere; K10, central compartment excretion constant.



Dia. 3. Schematic of computer model of URT and LRT absorption and simultaneous excretion of chemical vapors. Abbreviations are as in Dia. 2 plus; CIP, concentration of chemical vapors entering the LRT. For URT absorption and LRT excretion of chemical vapors CI = test atmosphere and CIP = room air. For LRT absorption and URT excretion of chemical vapors CI = room air and CIP = test atmosphere.

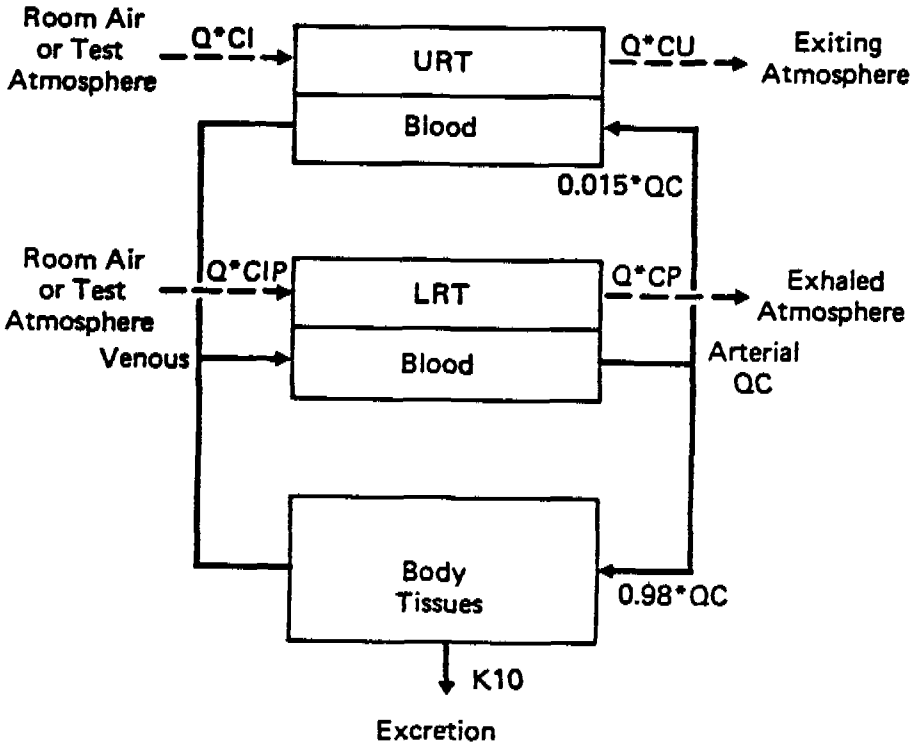
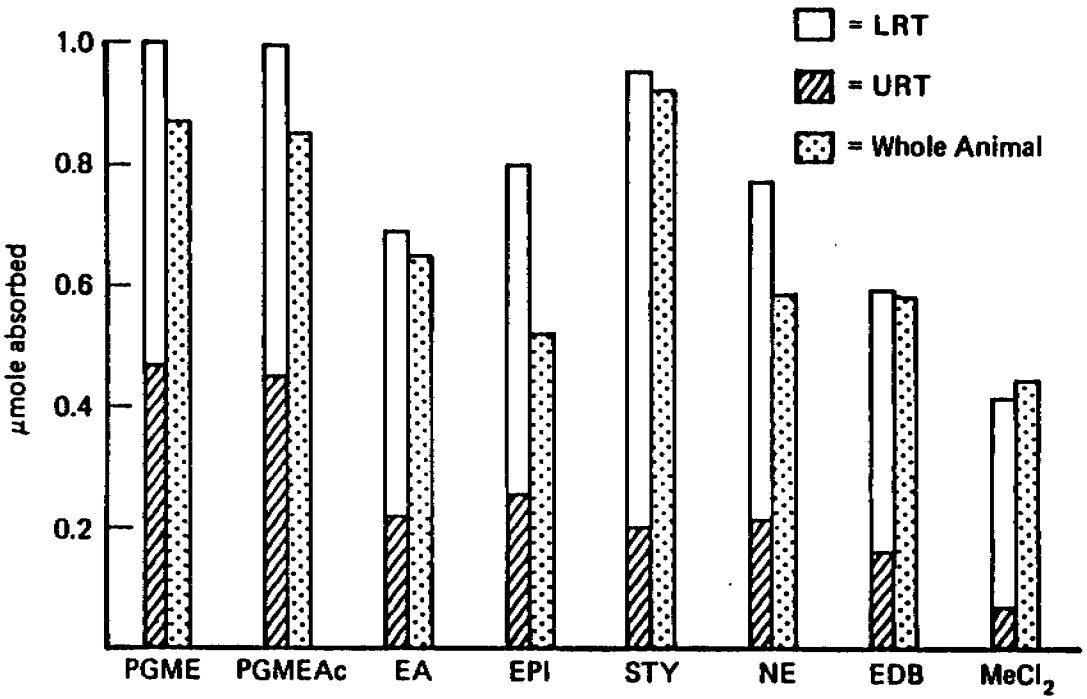


Fig. 1. Comparison of calculated doses of chemicals received via the isolated URT, LRT and intact respiratory system. All data were normalized to a 1 μmole/min equal time exposure.



APPENDIX I. Computer program used to estimate uptake of chemical vapors by the whole animal.

```
00000010 PROGRAM:  GRETAC.ACSL;DYNAMIC GAS EXCHANGE MODEL WITH SATURABLE
00000011 '         METABOLISM AND TISSUE UPTAKE - INHAL EQUILIBRATION    '
00000012 '         MODEL  -  WHOLE ANIMAL EXPOSSURE - RATS               '
00000013 '
00000061
00000062 INITIAL
00000063
00000064            'QI = TOTAL AIR FLOW RATE (L/HR)'
00000065 CONSTANT    QI = 9.0
00000066
00000067            'QMV = MINVOL'
00000068 CONSTANT  QMV = 3.192
00000069
00000070
00000071            'Q = ALVEOLAR VENTILATION RATE (L/HR)'
00000072 CONSTANT    Q = 2.234
00000073
00000074            'QC = CARDIAC  OUTPUT (L/HR)'
00000075 CONSTANT    QC = 3.4
00000076
00000077            'QU = CARD OUTPUT AT 1.5%QC'
00000078 CONSTANT    QU =0.051
00000079
00000080            'QR = CARD OUTPUT RESERV'
00000081 CONSTANT    QR = 3.298
00000085
00000086            'VR = VOL RESERVOIR'
00000087 CONSTANT    VR =.001
00000088
00000089            'K = 1ST ORDER RATE K'
00000090 CONSTANT     K = .001
00000091            'VBP= VOLUME OF CAPILLARY BLOOD IN LUNGS (L)'
00000092 CONSTANT    VBP= 0.00034
00000100
00000110            'VBU = VOL BLOOD IN URT (L)'
00000111 CONSTANT    VBU=0.000052
00000112
00000113            'PB = BLOOD-TO-AIR PARTITION COEFFICIENT'
00000114 CONSTANT    PB = .001
00000115
00000130
00000200          'CONC = CONCENTRATION IN CHAMBER AIR (MG/L)'
00000300 CONSTANT  CONC = 0.001
00000310
00000500 'TIMING COMMANDS'
00000600
00000610 CONSTANT  TCHNG =   6.0
00000700 CONSTANT  TSTOP =   2.0
00000800 CONSTANT POINTS = 120.0
00000900            CINT = TSTOP/POINTS
00001000
00001100 END      $'END OF INITIAL'
00001200
00001300 DYNAMIC
00001400
00001410 ALGORITHM IALG = 2
00001411 DERIVATIVE                                          DO 136496
00001412                                                     CONFIDENTIAL
00001413          'CY = MEASURED AIR CONCENTRATION (MG/L)'
00001414           CY = (CX*QMV+CI*(QT - QMV))/QI
00001415
00001416          'CI = CONCENTRATION IN INHALED AIR (MG/L)'
```

```
00001417          CI = CONC*(1.0 - STEP(TCHNG))
00001418
00001505        TMASS = ABP+ABUE+ABUI+AR+AX+AM
00001506       'TMASS = MASS BALANCE (MG)'
00001509
00001510
00001511         'CV POOLING'
00001512          CV =(QR*CVR + QU*CVUI + QU*CVUE)/QC
00001513
00001514
00001515          DIF = AI- TMASS
00001516
00001517
00001518        'DOSE = NET AMOUNT ABSORBED (MG)'
00001519         DOSE = AI - AX
00001530
00001540
00001550         'ABUI = AMT IN BLOOD URT INSPIRATION'
00001560         RABUI = Q*(CI-CVUI/PB) + QU*(CA-CVUI)
00001570          ABUI = INTEG(RABUI, 0.0)
00001580            CU = CVUI/PB
00001590          CVUI= ABUI/VBU
00001600
00001700         'ABP  = AMT IN BL LUNG '
00001800         RABP  = Q*(CU - CA/PB) + QC*(CV-CA)
00001900          ABP  = INTEG(RABP, 0.0)
00002000            CP  = CA/PB
00002001            CA  = ABP/VBP
00002002
00002003         'ABUE = AMT IN BL URT EXHALATION'
00002004         RABUE = Q*(CP-CVUE/PB) +QU*(CA-CVUE)
00002005          ABUE = INTEG(RABUE, 0.0)
00002007            CX = CVUE/PB
00002008          CVUE= ABUE/VBU
00002010
00002300
00002941
00002942         'AM = AMOUNT METAB (MG)'
00002943         RAM = K * AR
00002944          AM = INTEG (RAM, 0.0)
00002945
00002946        'RAR = RATE AMT CHANGE IN RESERVOIR'
00002947         RAR = QR*(CA - CVR)- RAM
00002948          AR = INTEG  (RAR, 0.0)
00002949          CVR= AR/VR
00002950
00002960         'AX = AMOUNT EXHALED (MG)'
00002970         RAX = Q*CX
00002980          AX = INTEG(RAX, 0.0)
00003200
00004000
00004100         'AI = AMT INH TO URT'
00004200         RAI = Q*CI
00004300          AI = INTEG (RAI, 0.0)
00004310
00004900
00005000
00005300 TERMT(T.GT.TSTOP)
00005310
00005320 PREPAR(T,CY,CI,RABUI,ABUI,CU,CV,RABUE,...
00005330 ABUE,CX,CA,RABP,ABP,CP,RAM,AM,RAR,AR,...
00005400 RAX,AX,RAI,AI,TMASS,DOSE,CVR,PB,QMV,...
```

DO 136497
CONFIDENTIAL

```
00005410 CVUI,CVUE,DIF)
00005500 END      $'END OF DERIVATIVE'
00005510
00005600
00005700 END      $'END OF DYNAMIC'
00005800
00005900 END      $'END OF PROGRAM'
```

APPENDIX II. Computer program used to estimate URT uptake and LRT excretion of chemical vapors.

```
00000010 PROGRAM:  GBETAD.ACSL;DYNAMIC GAS EXCHANGE MODEL WITH SATURABLE
00000011 '         METABOLISM AND TISSUE UPTAKE - INHAL EQUILIBRATION    '
00000012 '         MODEL  -  URT ABSOPTION / LRT EXCRETION IN RATS       '
00000013 '
00000061
00000062 INITIAL
00000063
00000064            'QI = TOTAL AIR FLOW RATE (L/HR)'
00000065 CONSTANT    QI = 9.0
00000066
00000067            'QMV=MIN VOL'
00000068 CONSTANT    QMV= 3.192
00000069
00000070            'Q =  VENTILATION RATE (L/HR)'
00000071 CONSTANT    Q = 2.234
00000072
00000073            'QC = CARDIAC  OUTPUT (L/HR)'
00000074 CONSTANT    QC = 3.4
00000075
00000076            'QR = CARDIAC OUTPUT TO RESERVOIR'
00000077 CONSTANT    QR = 3.349
00000078
00000079            'QU = CARD OUTPUT AT 1.5%QC'
00000080 CONSTANT    QU = .051
00000085
00000086            'VR = VOL RESERVOIR'
00000087 CONSTANT    VR = .001
00000088
00000089            'K = 1ST ORDER RATE K'
00000090 CONSTANT     K = .001
00000091            'VBP= VOLUME OF CAPILLARY BLOOD IN LUNGS (L)'
00000092 CONSTANT    VBP= 0.00034
00000100
00000110            'VBU = VOL BLOOD IN URT (L)'
00000111 CONSTANT    VBU=0.000052
00000112
00000113            'PB = BLOOD-TO-AIR PARTITION COEFFICIENT'
00000114 CONSTANT    PB = .001
00000115
00000130
00000200          'CONC = CONCENTRATION IN CHAMBER AIR (MG/L)'
00000300 CONSTANT  CONC = 0.001
00000310
00000500 'TIMING COMMANDS'
00000600
00000610 CONSTANT  TCHNG =   6.0
00000700 CONSTANT  TSTOP =   2.0
00000800 CONSTANT POINTS = 120.0
00000900            CINT = TSTOP/POINTS
00001000
00001100 END      $'END OF INITIAL'
00001200
00001300 DYNAMIC
00001400
00001410 ALGORITHM IALG = 2
00001411                                                    DO 136500
00001412 DERIVATIVE                                         CONFIDENTIAL
00001414
00001415          'CY=MEAS CONC AT 0.15 LPM'
00001416           CY =(QMV*CP+ CIP*(QI-QMV))/QI
00001417
00001419         'CI= CONCENTRATION IN INHALED AIR (MG/L
```

DOW CONFIDENTIAL

```
00001419          CI= CONC*(1.0 - STEP(TCHNG))
00001420
00001438
00001439
00001444       TMASS = ABP+ABU+AR+AXP+AM+AXU
00001445      'TMASS = MASS BALANCE (MG)'
00001446
00001447
00001448       'DOSE = NET AMOUNT ABSORBED (MG)'
00001449        DOSE = AI+AIP-AXP-AXU
00001450
00001460
00001510
00001540
00001550         'ABU = AMT IN BLOOD URT '
00001560         RABU=Q*(CI-CVU/PB) + QU*(CA-CVU)
00001570          ABU = INTEG(RABU, 0.0)
00001580            CU = CVU/PB
00001590           CVU= ABU/VBU
00001600
00001700         'ABP  = AMT IN BL LUNG '
00001800         RABP  = Q*(CIP - CA/PB) + QC*(CV-CA)
00001900          ABP  = INTEG(RABP, 0.0)
00002000           CP  = CA/PB
00002001           CA  = ABP/VBP
00002002
00002003           'POOLING OF CV'
00002004           CV  = (QR*CVR + QU*CVU)/QC
00002010
00002300
00002941
00002942         'AM = AMOUNT METAB (MG)'
00002943         RAM = K * AR
00002944          AM = INTEG (RAM, 0.0)
00002945
00002946        'AR =  AMT IN RESERVOIR'
00002947         RAR = QR*(CA -CVR) - KA
00002948          AR = INTEG  (RAR, 0.0)
00002949         CVR = AR/VR
00002950
00003200
00003300         'AXU = AMT EXH FROM URT'
00003400         RAXU=Q*CU
00003500          AXU = INTEG (RAXU, 0.0)
00003600
00003700         'AXP = AMT EXH PULM'
00003800         RAXP = Q*CP
00003900          AXP = INTEG (RAXP, 0.0)
00004000
00004100         'AI = AMT INH TO URT'
00004200         RAI=Q*CI
00004300          AI = INTEG (RAI, 0.0)
00004310
00004320         'AIP = AMT INH TO PULM'
00004330         RAIP = Q*CIP
00004340          AIP = INTEG(RAIP, 0.0)
00004341          CIP= 0.00000000001
00004350
00004800
00005000 TERMT(T.GT.TSTOP)
00005310
00005320 PREPAR(T,CI,RABU,CV,ABU,CU,CVR,CIP,DOSE,...
```

DO 136501
CONFIDENTIAL

```
00005330 CA,RABP,ABP,CP,RAM,AM,RAR,AR,...
00005400 RAI,AI,TMASS,DOSE,CY,PB,QMV,...
00005410 RAXU,AXU,RAXP,AXP,RAIP,AIP,CVU)
00005500 END      $'END OF DERIVATIVE'
00005510
00005600
00005700 END      $'END OF DYNAMIC'
00005800
00005900 END      $'END OF PROGRAM'
```

APPENDIX III. Computer program used to estimate LRT uptake and URT excretion of chemical vapors.

```
00C00010 PROGRAM:  GBETA.ACSL; DYNAMIC GAS EXCHANGE MODEL WITH SATURABLE
00000011 '         METABOLISM AND TISSUE UPTAKE - INHAL EQUILIBRATION
00000012 '         MODEL  -  LRT ABSORPTION / URT EXCRETION -  RATS
00000013 '
00000061
00000062 INITIAL
00000063
00000064            'QI = TOTAL AIR FLOW RATE (L/HR)'
00000065 CONSTANT    QI = 9.0
00000066
00000067            'QMV=MIN VOL'
00000068 CONSTANT    QMV= 3.192
00000069
00000070            'Q =  VENTILATION RATE (L/HR)'
00000071 CONSTANT    Q = 2.234
00000072
00000073            'QC = CARDIAC  OUTPUT (L/HR)'
00000074 CONSTANT    QC = 3.4
00000075
00000076            'QR = CARDIAC OUTPUT TO RESERVOIR'
00000077 CONSTANT    QR = 3.349
00000078
00000079            'QU = CARD OUTPUT AT 1.5%QC'
00000080 CONSTANT    QU = .051
00000085
00000086            'VR = VOL RESERVOIR'
00000087 CONSTANT    VR = .001
00000088
00000089            'K = 1ST ORDER RATE K'
00000090 CONSTANT     K = .001
00000091            'VBP= VOLUME OF CAPILLARY BLOOD IN LUNGS (L)'
00000092 CONSTANT    VBP= 0.00034
00000100
00000110            'VBU = VOL BLOOD IN URT (L)'
00000111 CONSTANT    VBU=0.000052
00000112
00000113            'PB = BLOOD-TO-AIR PARTITION COEFFICIENT'
00000114 CONSTANT    PB = .001
00000115
00000130
00000200          'CONC = CONCENTRATION IN CHAMBER AIR (MG/L)'
00000300 CONSTANT  CONC = 0.001
00000310
00000500 'TIMING COMMANDS'
00000600
00000610 CONSTANT  TSTART =   0.0
         CONSTANT  TSTOP =    2.0
         CONSTANT  POINTS =  120.0
00000700             CINT = TSTOP/POINTS
00001000
00001100 END      $'END OF INITIAL'
00001200
00001300 DYNAMIC
00001400
00001410 ALGORITHM IALG = 2
00001411                                                    DO 136504
00001412 DERIVATIVE                                         CONFIDENTIAL
00001414
00001415
00001416          'CY=MEAS CONC AT 0.15LPM'
00001417           CY=(QMV*CP + CIP*(QI-QMV))/QI
00001418
```

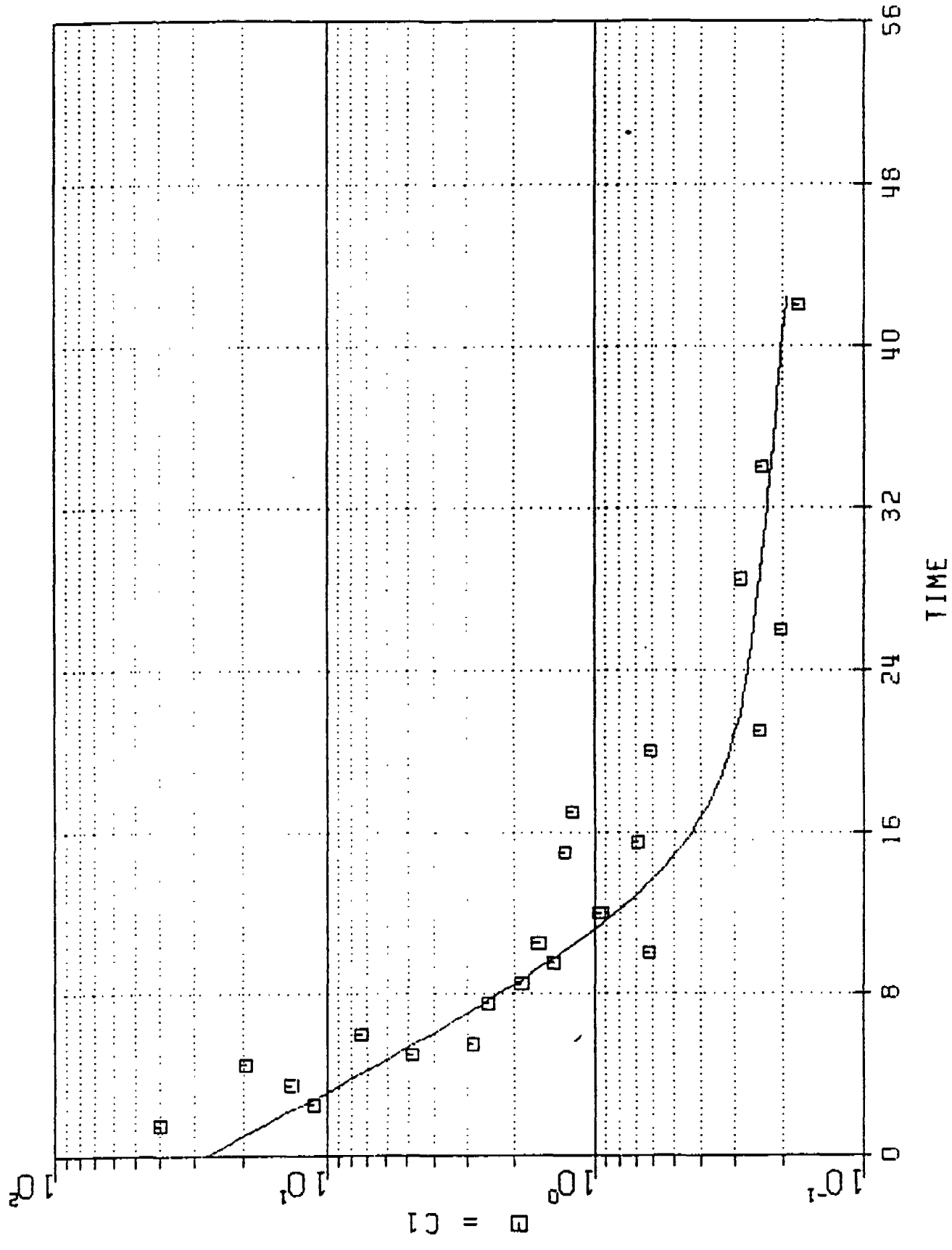
```
00001419          'CIP= CONCENTRATION IN INHALED AIR (MG/L)'
00001420           CIP= CONC*(1.0 - STEP(TCHNG))
00001430
00001438
00001439
00001444        TMASS = ABP+ABU+AR+AXP+AM+AXU
00001445       'TMASS = MASS BALANCE (MG)'
00001446
00001447
00001448        'DOSE = NET AMOUNT ABSORBED (MG)'
00001449         DOSE = AI+AIP-AXP-AXU
00001450
00001460
00001510
00001540
00001550          'ABU = AMT IN BLOOD URT '
00001560         RABU = Q*(CI-CVU/PB) + QU*(CA-CVU)
00001570          ABU = INTEG(RABU, 0.0)
00001580            CU = CVU/PB
00001590           CVU= ABU/VBU
00001600
00001700          'ABP  = AMT IN BL LUNG '
00001800         RABP  = Q*(CIP - CA/PB) + QC*(CV-CA)
00001900          ABP  = INTEG(RABP, 0.0)
00002000           CP  = CA/PB
00002001           CA  = ABP/VBP
00002002
00002003           'POOLING OF CV'
00002004           CV  = (QR*CVR + QU*CVU)/QC
00002010
00002300
00002941
00002942          'AM = AMOUNT METAB (MG)'
00002943         RAM = K * AR
00002944          AM = INTEG (RAM, 0.0)
00002945
00002946        'AR =  AMT IN RESERVOIR'
00002947         RAR = QR*(CA -CVR) - RAM
00002948          AR = INTEG  (RAR, 0.0)
00002949         CVR = AR/VR
00002950
00003200
00003300          'AXU = AMT EXH FROM URT'
00003400         RAXU = Q*CU
00003500          AXU = INTEG (RAXU, 0.0)
00003600
00003700          'AXP = AMT EXH PULM'
00003800         RAXP = Q*CP
00003900          AXP = INTEG (RAXP, 0.0)
00004000
00004100          'AI = AMT INH TO URT'
00004200         RAI = Q*CI
00004300          AI = INTEG (RAI, 0.0)
00004301          CI = 0.00000000001
00004310
00004320          'AIP = AMT INH TO PULM'
00004330         RAIP = Q*CIP
00004340          AIP = INTEG(RAIP, 0.0)
00004350
00004800
00005300 TERMT(T.GT.TSTOP)
00005310
```

DO 136505
CONFIDENTIAL

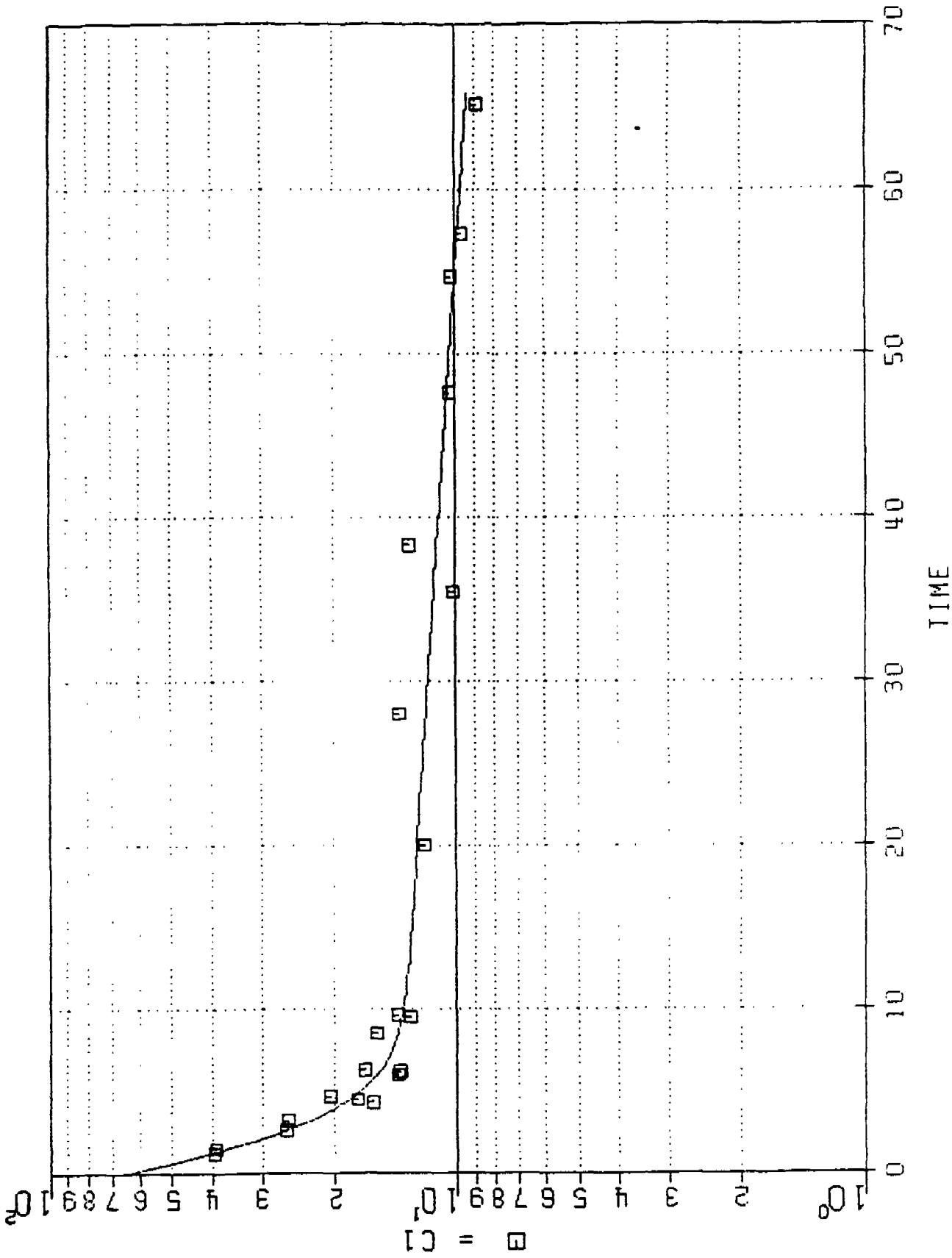
DOW CONFIDENTIAL

```
00005320 PREPAR(T,CI,RABU,CV,ABU,CU,CVR,CIP,DOSE,...
00005330 CA,RABP,ABP,CP,RAM,AM,RAR,AR,...
00005400 RAI,AI,TMASS,DOSE,CY,PB,QMV,...
00005410 RAXU,AXU,RAXP,AXP,RAIP,AIP,CVU)
00005500 END      $'END OF DERIVATIVE'
00005510
00005600
00005700 END      $'END OF DYNAMIC'
00005800
00005900 END      $'END OF PROGRAM'
```

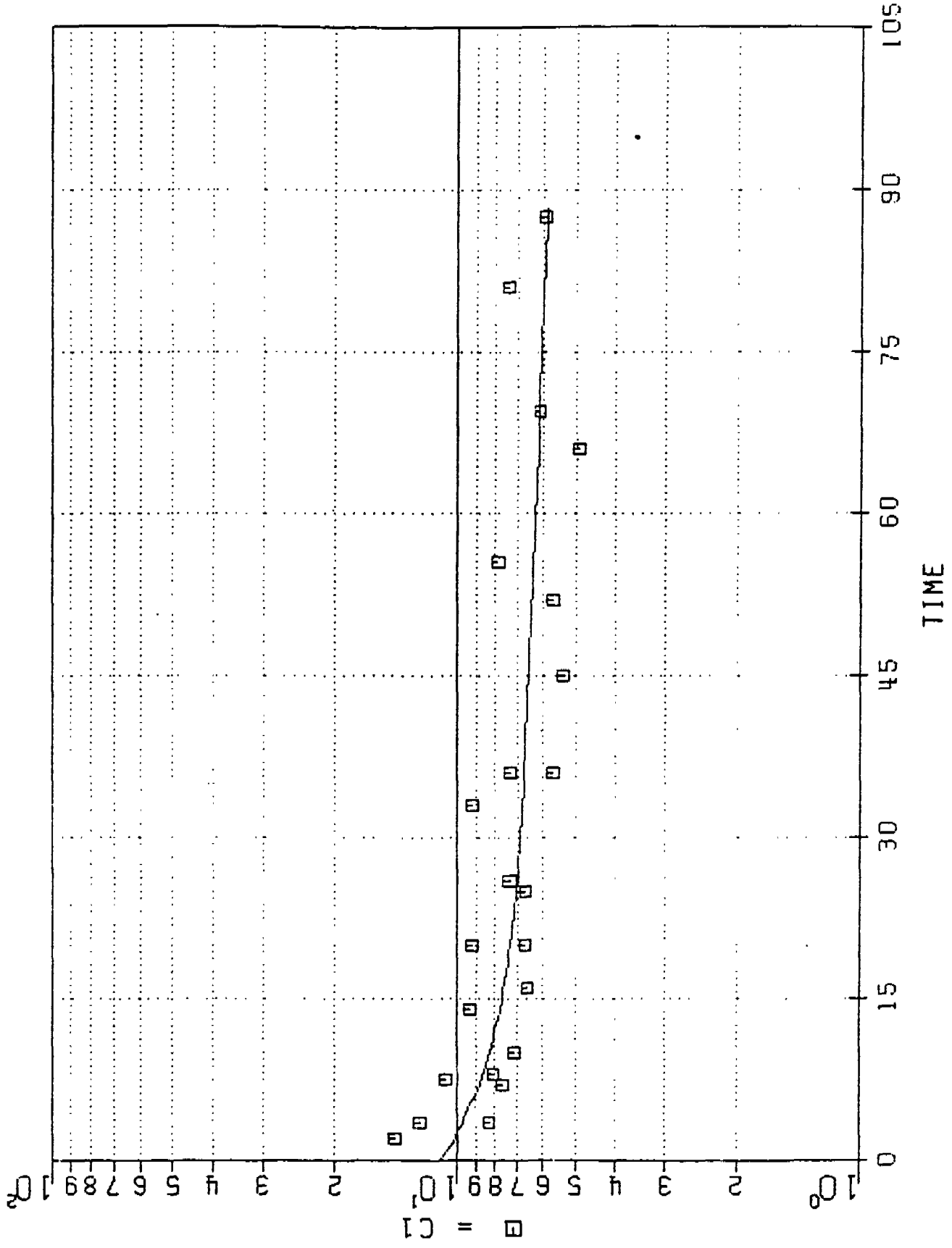
APPENDIX IV. Plasma decay curve of 10 mg/kg EA administered intravenously in rats. Calculated constants were: volume distribution = 363 ml; K10 = 0.259/min; K12 = 0.0657/min; K21 = 0.0204/min; t 1/2 alpha = 2.10 min; t 1/2 beta = 43.1 min.



APPENDIX V. Plasma decay curve of 10 mg/kg NE administered intravenously in rats. Calculated constants were: volume distribution = 155 ml; K10 = 0.0278/min; K12 = 0.393/min; K21 = 0.123/min; t 1/2 alpha = 1.29 min; t 1/2 beta = 109 min.



APENDIX VI. Plasma decay curve of 10 mg/kg PGME administered intravenously in rats. Calculated constants were volume distirbution = 907 ml; K10 = 0.00384/min; K12 = 0.0376/min; K21 = 0.0824/min; t 1/2 alpha = 5.72 min; t 1/2 beta = 266 min.



APPENDIX VII. Plasma decay curve of 50 mg/kg PGMEAc administered intravenously in rats. Calculated constants were: volume distribution = 1011 ml; K10 = 0.0810/min; K12 = 0.213/min; K21 = 0.0289/min; t 1/2 alpha = 2.20 min; t 1/2 beta = 93 min.