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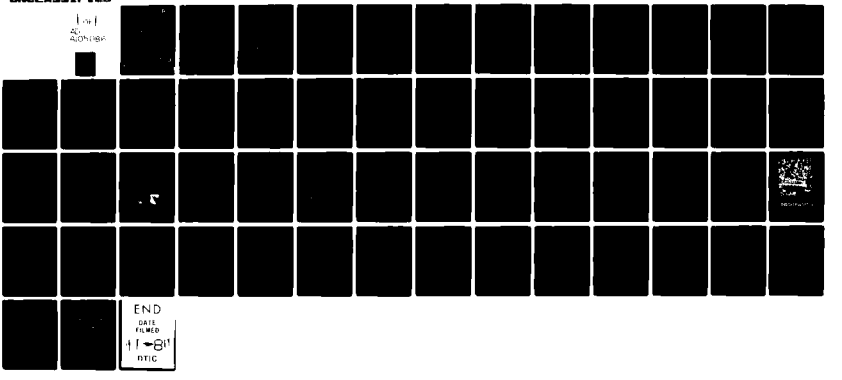

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Biological-Mathematical Modeling of Chronic Toxicity

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for the period AFOSR-76-2970-new

February 1, 1978 to May 31, 1981

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The objectives of the project "Biological-Mathematical Modeling of Chronic Toxicity" were to study the factors affecting the fate of inhaled vapors in the body and to develop a mathematical model to describe their effects on uptake, distribution and elimination. The main accomplishments of the research are: 1) A general pharmacokinetic model for inhalation administration, based on physiological parameters of the exposed subject and on physical

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and chemical properties of the inhaled substance, was defined. Mathematical theories and existing programs used in electrical engineering for solution of electric networks were suggested for solution of differential equations and specific programs were prepared. 2) Information on interspecies differences was extracted from the literature; partition coefficients of eight organic solvents were determined for eight tissues of three species (man, monkey, rat); steady state clearances calculated from pulmonary uptake, and intrinsic clearance determined form vapor distribuiton in rats were used in the model as elimination rate constants. 3) The models were used to evaluate the effects of the following parameters on uptake, distribution and elimination of inhaled vapors: solubility, metabolism, body build, interspecies differences, physical exertion, exposure duration, exposure repetition, and short-term excursion limit. 4) Nonlinear dependence of pulmonary uptake on exposure concentration was observed in the animal model. 5) Reduced pulmonary uptake and quantitative and qualitative changes in elimination were observed if two vapors were inhaled simultaneously.

SUMMARY

The objectives of the project "Biological-Mathematical Modeling of Chronic Toxicity" were to study the factors affecting the fate of inhaled vapors in the body and to develop a mathematical model to describe their effects on uptake, distribution and elimination.

The main accomplishments of the research are: 1) A general pharmacokinetic model for inhalation administration, based on physiological parameters of the exposed subject and on physical and chemical properties of the inhaled substance, was defined. Mathematical theories and existing programs used in electric engineering for solution of electric networks were suggested for solution of differential equations and specific programs were prepared. 2) Information on interspecies differences was extracted from the literature; partition coefficients of eight organic solvents were determined for eight tissues of three species (man, monkey, rat); steady state clearances calculated from pulmonary uptake, and intrinsic clearance determined from vapor distribution in rat were used in the model as elimination rate constants. 3) The models were used to evaluate the effects of the following parameters on uptake, distribution and elimination of inhaled vapors: solubility, metabolism, body build, inter-species differences, physical exertion, exposure duration, exposure repetition, and short- term excursion limit. 4) Nonlinear dependence of pulmonary uptake on exposure concentration was observed in the animal model. 5) Reduced pulmonary uptake and quantitative and qualitative changes in elimination were observed if two vapors were inhaled simultaneously.

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The objectives of the project "Biological-Mathematical Modeling of Chronic Toxicity" were to study the factors affecting the fate of inhaled vapors in the body and to develop a mathematical model to describe their effects on uptake, distribution and elimination. The ultimate goal was to be able to employ the mathematical model to predict optimum exposure conditions for biological testing of chronic toxicity.

In our attempt to explore mathematical modeling in inhalation toxicology, our research took two courses: 1) Development of an animal model to generate information for the simulation model and to corroborate experimentally the predictions made by the simulation model. 2) Development of a general simulation model, based on physiological parameters, for quantitative description of uptake, distribution and elimination of inhaled vapors or gases. The general simulation model was refined in order to make possible studies of various factors which may affect the fate of inhaled vapors in the body. The general simulation model was also simplified in order to accomodate the program on a small programmable pocket calculator. The simplified model uses relatively inexpensive equipment, and the user needs no mathematical skill. The specific simplified programs are designed to be used by practicing toxicologists and hygienists. The program for evaluation of short-term excursion limits is an example.

The main accomplishments of the research are:

1) A general pharmacokinetic model for inhalation administration was defined. This model is based on physiological parameters of the exposed subject and on physical and chemical properties of the inhaled substance. The concept of compartment model was applied.

2) Information on inter-species differences in pulmonary ventilation, tissue perfusion, and body build was extracted from the literature to be available for substituting in the model.

3) Partition coefficients of eight organic solvents were determined for eight tissues of three species (man, monkey, rat). Species differences and effect of meal intake on partition coefficients were under scrutiny.

4) Steady state clearances calculated for man, dog and monkey, from pulmonary uptake rate, were used to define the over-all elimination rate constants in the model.

5) Intrinsic clearances determined from vapor distribution in rat at steady state were used in the model as elimination rate constants of individual elimination pathways.

6) Mathematical theories and existing programs used in electric engineering for solution of electric networks composed from capacitances and conductances are suggested for solution of differential equations describing uptake, distribution and elimination of inhaled vapors.

7) Specific programs were prepared, the most important being for: a) A 10-compartment model in Fortran IV, to be used in large time-shared computer Univac 1100/20. b) A 5-compartment model in basic, to be used on minicomputer Apples II Plus. c) A 2-compartment model to be used in programmable pocket calculator TI-59.

8) The models were used to evaluate the effects of the following parameters on uptake, distribution and elimination of inhaled vapors: a) solubility, b) metabolism, c) body build, d) inter-species differences, e) physical exertion, f) exposure duration, g) exposure repetition, h)short-term excursion limit.

9) Nonlinear dependence of pulmonary uptake on exposure concentration was observed in the animal model. Plateau kinetics, applicable to capacity-limited processes, is suggested for description of elimination processes in the model.

10) Reduced pulmonary upake and quantitative and qualitative changes in elimination were observed if two vapors were inhaled simultaneously.

Reports and Publications:

(Under Professional name of P.I. - FISEROVA-BERGEROVA)

Methods used in this project and obtained results were reported in detail in interim scientific reports submitted to AFOSR in March of 1979 and 1980, and progress reports submitted in October of 1978, 1979, and 1980. The final interim scientific report follows. Reprints or xerox copies of publications so far resulting from this project are enclosed.

The theories and solutions of the model and supporting data obtained during this project are being prepared for publication in "Modeling of the Uptake Metabolism and Elimination of Some Vapors and Gases", edited by V. Thomas. This monograph will be published by CRC Press in 1982. Manuscripts of four chapters dealing with data and model developed and verified under the AFOSR contract will be submitted to AFOSR in Fall 1981.

Detailed Scientific Report for period: October 1980-May 1981

The main effort was concentrated on finishing the general program for minicomputer Apple II Plus, and on preparing manuscripts for the monograph.

The program solves the general multicompartment model for simulation of inhalation administration. First order kinetics is assumed. The listing of the program is attached.

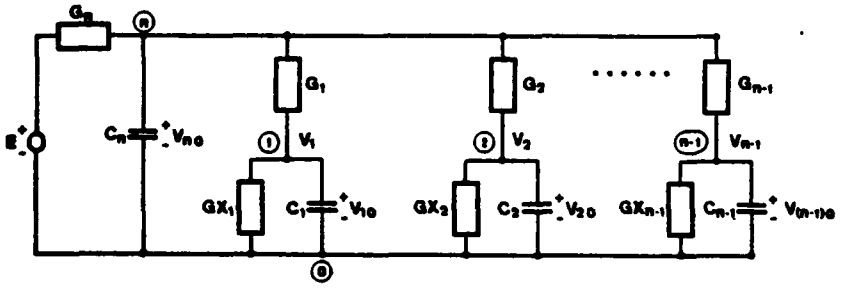
The general model denoted as LINEAR has the following options:

1) The model can simulate exposure of any subject with defined physiologic parameters to any compound for which partition coefficients and steady state clearance (or intrinsic clearance) are known. From the mathematical point of view, clear-

ance can be located in any tissue or compartment. The compartment can include one or several tissues with similar parameters. The compartments are numbered and the numbers are used as indexes, (i), of the elements in the model. The scheme of the general model is in Figure 1. The numbering of the elements (denoted by index i) is important. The last elements (i=n) always relate to respiration. ($G_{(n)}$= alveolar ventilation; $C_{(n)}$= FRC + 2/3 V_{tid} + lung tissue volume multiplied by lung-air partition coefficient + volume of arterial blood multiplied by blood-air partition coefficient; $V_{(n)}$= concentration in alveolar air = concentration in arterial blood divided by blood-air partition coefficients). It is convenient to start numbering with those organs or compartments in which elimination takes place, and to assign larger numbers to compartments without clearance. The values of the elements are defined as follows: $C_{(i)}$= tissue (or compartment) volume multiplied by tissue-air partition coefficient. $G_{(i)}$= perfusion multiplied by blood-air partition coefficient. $G_{x(i)}$= clearance multiplied by blood-air partition coefficient. If there is no clearance in the compartment, $G_{x(i)}$= 0. All partition coefficients relate to 37°C. Table 1 is designed for convenient preparation of input data (example in table 3).

FIGURE 1

General n-Compartment Simulation Model



The element GX is removed from those compartments in which no clearance takes place.

TABLE 1

Preparing Data for LINEAR

STATEMENT	READING				
50	No. of compartments, No. of clearances				
52-57	No. compartment: perfusion $x\lambda_{tis/air}$, volume $x\lambda_{bl/air}$	$F\lambda_{bl/air}$	$V\lambda_{bl/air}$		
52	1: description				
53	2: description				
54	3: description				
55	4: description				
58	n : alveolar ventilation, V_d of lung*				
60	Clearance in comp. 1,2,3,4				
62	Printer (indicate in minutes)				
64	How many exposure concentrations?				
	Indicate exposure concentration and duration time in sequence:				
66	1: Exposure conc., duration (minutes)				
67	2: " "				
68	3: " "				
69	4: " "				
70	5: " "				
.					
.					
90	n " "				

*V_d = FRC + 2/3 V_{tid} + volume of lung tissue x $\lambda_{lung/air}$ + volume of art. blood x $\lambda_{bl/air}$

TABLE 2

Comments to output commands

STATEMENT	EXPLANATION	DENOTATION	
1270	Prints times from the simulation start in minutes (Defined in statement 62).	TIME =	
1280-1289	CHOICE: Concentration in tissues divided by tissue-air partition coefficient [$x_{(i)}$]. Index (i) according to compartment number.		
1280	Example in listing	$x_{(1)}$	$x_{(2)}$
1281		$x_{(3)}$	$x_{(4)}$
⋮	add additional compartment if required		
1290-1299	CHOICE: Elimination rates [$CUR_{(i)}$]. Index (i) indicates compartment number except with the last one. The last CUR always indicates the uptake rate or exhalation rate.		
1290	Example in listing: $CUR_{(2)}$ is either uptake rate(+) or exhalation rate (-).	$CUR_{(1)}$	$CUR_{(2)}$
⋮	add additional clearances if required		
1300-1309	CHOICE: Total amounts metabolized or excreted [$CYNT_{(i)}$]. Index indicates compartment number		
1300	Example in listing	$CYNT_{(1)}$	
⋮	add additional clearances if required		
1310	Total pulmonary uptake; Total amount exhaled. The indexes do not relate to the model. They change automatically according to number of excretory pathways (defined in statement 50).		
	Example in listing: $CYNT_{(3)}$ = uptake(+), $CYNT_{(4)}$ = exhaled(-)	$CYNT_{(3)}$	$CYNT_{(4)}$

2) The model accomodates any number of changes in exposure concentration, thus enabling simulation of any kind of exposure. In the input, "number of time section" (statement 64) controls the number of changes in exposure concentrations. Information on exposure concentration and duration of exposure is presented in consecutive order in statements 66-99 (table 1).

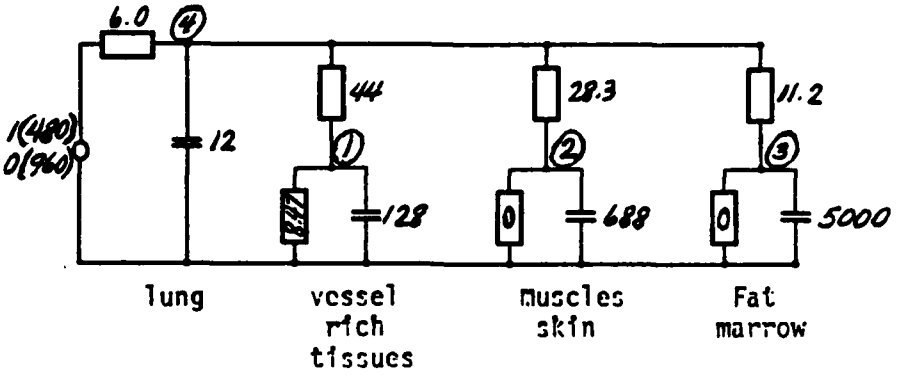
3) The output offers the following information (tables 2 and 4): a) Asymptotic values. Asymptotic values, multiplied by appropriate tissue-air partition coefficient, represent tissue concentrations reached at steady state for exposure concentration equal to 1. b) Time constants and rate constants, which are hybrid constants related to all distribution and elimination processes. These rate constants equal exponent constants in Laplace transform. c) For time intervals, scheduled in minutes (controlled by STEP in statement 62), information is displayed in the following order: First, concentration in all compartments (for i = 1 to n), divided by partition coefficients. Second, excretion rates, or metabolic rates, related to clearance $G_{x(i)}$ (for i = 1 to n-1), followed by pulmonary uptake rate (during saturation, positive sign) or exhalation rate (during desaturation, negative sign). Last, the total amounts excreted or metabolized via clearance denoted $G_{x(i)}$, followed by total pulmonary uptake and total amount exhaled.

4) The output data is displayed on the screen. On command, the output can also be printed or filed on the disk. The data file is arranged so that it can be used as input in the Appleplot program for graphic display.

Arrangement of input data and output data is shown in a simple example. Four compartment model should be used to simulate eight-hour exposure of a resting man to typical organic solvent (1 mg/ℓ), followed by 16 hour exposure to zero concentration. The data for each eight hours should be printed. The simulation model is pictured in Figure 2. The input data is prepared in table 3 and the printout with commentary is in table 4. The input data is also part of listing of the program (framed statements in listing).

FIGURE 2

Simulation Model for 8-Hour Exposure to Organic Solvents



Data refers to tables 3-4. Compartment numbers are circled.

TABLE 3

Preparing Data for LINEAR

Simulation of 8-Hour Exposure to Organic Solvent*

STATEMENT	READING				
50	No. of compartments, No. of clearances			4	1
52-57	No. compartment: perfusion $x\lambda_{tis/air}$, volume $x\lambda_{bl/air}$	$F\lambda_{bl/air}$	$V\lambda_{bl/air}$		
52	1: description 4.4x10 ; 6.4 x 20	44	128		
53	2: description 2.83 x 10 ; 34.4 x 20	28.3	688		
54	3: description 1.12 x 10 ; 12.5 x 400	11.2	5000		
55	4: description —	---	—		
58	n : alveolar ventilation, V_d of lung* n = 4			6	12
60	Clearance in comp. ①2,3,4 0.847 x 10	8.47	0	0	0
62	Printer (indicate in minutes)			480	
64	How many exposure concentrations?			2	
	Indicate exposure concentration and duration time in sequence:				
66	1: Exposure conc., duration (minutes)			1	480
67	2: " "			0	960
68	3: " "				
69	4: " "				
70	5: " "				
.					
.					
90	n " "				

*V_d = FRC + 2/3 V_{tid} . + volume of lung tissue x $\lambda_{lung/air}$ + volume of art. blood x $\lambda_{bl/air}$

*Data are in the listing of program (example).

TABLE 4

Print out for 8-hour exposure to 1 mg/ℓ of an organic solvent.

(Input data in program listing)

```
ASYMPTOTIC VALUES FOR UNIT EXPOSURE
      CONCENTRATION
(1)              .384 Vessel rich tissue (elimination!)
(2)              .45792 muscle, skin
(3)              .45792 fat, marrow
(4)              .45792 alveolar air or arterial blood
```

To obtain steady state concentration in tissue (mg/ℓ), the assymptotic values must be multiplied by appropriate tissue-air partition coefficients.

```
STEP=              480
# OF TIME SECTIONS=                2
CONCENTR. mg/ℓ  TIME IN MIN
1                  480
0                  960

EXPONENT          TIME CONST.   minute
-1.16583694E-03   857.752884
-.0187986412      53.1953343
-.246105268       4.06330188
-7.64555918       .130794881
```

SATURATION

```
                TIME=480  min after start of simulation
concentrations* in (1) .274469211    (2) .323863796
                   (3) .186312692    (4) .327670372
metabolic rate     (1) 2.32475422    (4) 4.03397777 uptake rate
total metabolized  (1) 911.673557
total uptake       (4) 2105.08547    (4) 0          total exhaled
```

DESATURATION

```
                TIME=960  min after start of simulation
concentrations* in (1) .0469573777   (2) .0574781799
                   (3) .116414466    (4) .0558367587
metabolic rate     (1) .397728989    (4) -.335020552 exhalation rate
total metabolized  (1) 1220.2008
total uptake       (4) 2105.08547    (4) -256.65618  total exhaled

                TIME=1440
                .0268251847          .0328285721
                .0665243045          .0318980546
                .227209315           -.191388328 exhalation rate
                1366.36337
                2105.08547           -379.78012
```

*To obtain concentrations in tissues (mg/ℓ) the values must be multiplied by appropriate tissue-air partition coefficients.

The circled numbers match compartment numbers in Table 3 and Figure 2.

GENERAL DISCUSSION

Toxic effect is related to the concentration of the substance in the target organ and to the interaction of the substance with receptors. The concentration in the target organ is different from exposure concentration and changes with exposure duration in a predictable way. The interaction with receptors is less predictable. The receptor can be any constituent in the body, usually macromolecules including enzymes which intermediate the metabolism of the inhaled substance. The simulation by our mathematical model predicts quantitatively how the volatile substance gets from the environment to the tissues, but provides no information on interaction with receptor on biotransformation, or on toxic action mechanism.

Modern computer technology and mathematical theories enable solution of multicompartment models with simultaneous elimination processes. Pharmacokineticists proposed numerous models for dosing and elimination of drugs administered intravenously or orally. Anesthesiologists offered a model for uptake of inert inhalation anesthetics administered at constant alveolar concentration. We proposed the first multicompartment model for simulation of exposure to metabolized (or excreted) vapors and gases (Fiserova-Bergerova,V.,Vlach, J.,Singhal,K.,Simulation and prediction of uptake, distribution, and exhalation of organic solvents, Br.J.Ind.Med., 31, 45, 1974). Since then, we refined the model and searched for experimental designs suitable for obtaining input data for the model. Obtaining input data is nowadays a more difficult task than mathematical solution of the model. The following information and methods were missing, or were inadequate, when we prepared the general simulation model: Methodology for determination of individual elimination rate constants in vivo is not fully developed; diffusion constants are known for a very limited number of compounds; information on partition coefficients is scattered; a non-invasive method for determination of cardiac output and its distribution is not commonly available; the significance of extrahepatic metabolism has only recent-

ly been appreciated; no attempt has been made to quantitatively evaluate adsorption and desorbtion of vapors in respiratory airways. We were able to fill some of these gaps, such as developing animal models for determination of clearance, or obtaining data on clearance and partition coefficients of some substance. But for information on other factors, such as diffusion and perfusion, we relied only on the literature. Some new factors affecting uptake and distribution of inhaled vapors we recognized during the process of model development. Because of lack of time and unavailability of data, we were not able to include these factors in the model. Our observation concerns three particulars:

1) Nonlinear elimination processes. The nonlinear dependence of pulmonary uptake on exposure concentration was observed and was attributed to capacity limited metabolism or excretion. Methods for measuring some parameters describing nonlinearity were developed, and a limited amount of information was obtained in our laboratory and elsewhere (*Toxicology Research Laboratory* of Dow Chemical Co.;Toxic Hazards Research Unit Department of the Air Force). Mathematical theories suitable for solving the nonlinearity of elimination processes were scrutinized.

2) Additional factors affecting pulmonary gas exchange. We observed that the values of pulmonary uptake rate obtained from the difference between concentrations in ambient air and mixed exhaled air multiplied by minute ventilation were in some instances smaller than the values obtained from the difference between concentrations in ambient air and end exhaled air multiplied by alveolar ventilation. We found three possible explanations: metabolism of vapor in lung tissue; adsorbtion and desorbtion of vapors in respiratory airways; and slow diffusion accross alveolar membranes. The first possibility is supported by a recently published review of drug metabolism in lungs. (Brandenburger Brown, E.A., The localization, metabolism, and effects of drugs and toxicants in lung, Drug Metabolism Reviews, 3, 33, 1974; Chiou, W.L., Potential pitfalls in the conventional pharmaco-

kinetic studies: effects of the initial mixing of drug in blood and the pulmonary first-pass elimination, Journal of Pharmacokinetics and Biopharmaceutics, 7, 527, 1979; Welch, R.M., Cavallito, J., Loh, A., Effect of exposure to cigarette smoke on the metabolism of benzo(a)pyrene and acetophenetidin by lung and intestine of rats, Toxicol. Appl. Pharmacol., 23, 749, 1972). The second possibility is also supported by the literature (Fiserova-Bergerova, V., Teisinger, J., Pulmonary styrene vapor retention, Industrial Medicine and Surgery, 34, 620, 1965; Bardodej, Z., The value and use of exposure tests XIL. Mercury exposure test, Ceskoslovenska Hygiena, 8, 157, 1963; Landahl, H.D., Hermann, R.G., Retention of vapors and gases in the human nose and lungs, Archives of Industrial Hygiene and Occupational Medicine, 1, 36, 1950). However, quantitative description of adsorbtion and desorbtion in respiratory airways is lacking. We were attempting to fill this gap. The third possibility, the limitation of uptake rate by diffusion, is supported by older literature (Kety, S.S., The theory and applications of the exchange of inert gas at the lungs and tissues, Pharmacological Reviews, 3, 1, 1951; Hunter, A.R., The group pharmacology of anaesthetic agents. I:The adsorbtion-elimination of inhaled drugs, Brit.J.Anaesth., 28, 244, 1956). However, diffusion is not our priority concern, since there was no systematic deviation of the ratio of concentrations in arterial blood and alveolar air from blood-air partition coefficient.

3) Interference of simultaneously administered xenobiotics. We observed that if two vapors are inhaled simultaneously, the one reduces pulmonary uptake of the other. We expressed the hypothesis that reduced uptake is caused by competitive inhibition of metabolism. Experiments corroborating this hypothesis are underway, but so far no data suitable to application for modeling was obtained.

Significance:

With progressing technology, toxicologists and hygienists confront the problem of securing safe exposure to an increasing number of air pollutants. The adverse

biological effect of pollutants, like the therapeutic effect of drugs, is related to blood concentration and/or time integral of concentration in the target organs. Passage of pollutants from the environment to the target organ has the same significance as migration of drugs from site of administration to the target organ. Pharmacokinetics describing the transport of drugs in the body is a potent tool for designing dosage regimens of optimum therapeutic effect. We employed similar methods to propose exposure regimens with equivalent adverse effect. The evaluation is based on comparison of concentrations reached in arterial blood. Two of our observations deserve special attention: 1) The first observation was made while using the program for simulation of short-term increase of exposure concentration. It was calculated that the rising of vapor concentration in tissues depends on the solubility and elimination of the substance. It was demonstrated that if, during the first four hours of an eight hour exposure, the exposure concentration rises for a short period (15 minutes) two or three times, tissue concentrations of well soluble vapors at the end of excursion are smaller than at the end of exposure. Based on this simulation, we suggested to the Threshold Limited Value Airborne Contaminants Committee of American Conference for Industrial Hygienists that short-term excursion limits for industrial pollutants (STEL) should be based on solubility of the vapor, rather than on the average concentration (TWA), as is the current practice. Similar suggestion is made by Japanese investigators (Koizumi,A., Sekiguchi, T., Konno, M., Ikeda, M., Evaluation of the time weighted average of air contaminants with special references to concentration fluctuation and biological half-time, American Industrial Hygiene Association Journal, 41, 693, 1980).

2) The second important observation - the nonlinear dependence of biological effect on exposure concentration - concerns the extrapolation of toxicological data. The observed limited capacity of elimination process can affect the elimination not only quantitatively but also qualitatively. Gehring and Blau discussed mechanism of carcinogenesis with regard to dose dependent changes in metabolic pathways

of inhaled carcinogens (Gehring, P.J., Blau, G.E., Mechanisms of carcinogenesis: dose response, Journal of Environmental Pathology and Toxicology, 1, 163, 1977). We are showing in our experiments with halothane that similar changes in metabolic pathways can be induced if the vapor is inhaled simultaneously with another vapor. The studies show that, in addition to enhancing secondary elimination pathways, the saturation of the major elimination pathways results in the rapid rising of vapor concentration in tissues. The quantitative and qualitative changes introduced by capacity limited processes render dubious the extrapolation of safe exposure concentration from toxicological studies performed at higher exposure concentrations or from studies in which other than inhalation administration was used. In order to prevent an unexpected reaction in the presence of additional xenobiotics (including drugs) exposure concentrations below those which saturate detoxifying mechanisms should be recommended whenever determining the safety limit for occupational or environmental exposure.

It is highly desirable to continue to study the parameters defining nonlinear elimination, and to prepare a eneral simulation model which accomodates capacity limited processes.

Program LINEAR (also POMOC)

General Linear model for 5 compartments

```
]LIST
1  REM  SEQUENCE OF READING
2  REM  N,NGX
3  REM  G(I),C(I),I=1...N
4  REM  GX(I),I=1...NGX
5  REM  (IF NGX=0,NO GX(I) IS READ)
6  REM  STEP
7  REM  NUMBER OF TIME SECTIONS,NUMSEC
8  REM  E(I),TIMEND(I),I=1...NUMSEC
50  DATA  4,1
52  DATA  44,128
53  DATA  28.3,688
54  DATA  11.2,5000
58  DATA  6,12
60  DATA  8.47
62  DATA  480
64  DATA  2
66  DATA  1,480
68  DATA  0,960
100  DIM A(6,6),B(6,6,7),C(6),CC(7)
110  DIM G(6),GX(6),XT(6),XYNT(6),CUR(6)
120  DIM CYNT(8),TD(30),MSTE(30),E(30)
130  DIM X(6),RR(6),XM(6)
135  DIM W(6)
140  DIM BB(7),H(7),D(11),Z(200)
150  DIM TS(100),NAP(100,6)
160  DIM PROUD(100,6),WZ(100,8)
170  READ N,NGX
180  PRINT "N=",N
181  PRINT "NGX=",NGX
190 N1 = N + 1
200 N2 = N - 1
210 N5 = NGX + 1
220 N6 = NGX + 2
230 N7 = NGX + 3
231 NM1 = N - 1
240  REM  INITIALIZATION
250  FOR I = 1 TO N
260 XM(I) = 0
270 XYNT(I) = 0
280 X(I) = 0
285 W(I) = 0
290 GX(I) = 0
300  NEXT I
305  PRINT
```

TABLE 1

```
310  REM  READ ELEMENTS
311  PRINT "G(I)              C(I)"
320  FOR I = 1 TO N
330  READ G(I),C(I)
340  PRINT G(I),C(I)
350  NEXT
360  IF NGX = 0 GOTO 420
361  PRINT
362  PRINT "NGX(I)"
370  FOR I = 1 TO NGX
380  READ GX(I)
390  PRINT I,GX(I)
400  NEXT I
402  REM  START PRINTER
404  INPUT "WANT PRINTER? (Y/N)";R$
406  IF R$ = "Y" THEN  PR# 1
410  REM  CALCULATE ASYMPTOTS
420  GOSUB 5000
425 W(N) = G(N)
426  PRINT
430  GOSUB 5500
431  PRINT "ASYMPTOTIC VALUES FOR UNIT
432  PRINT ".       CONCENTRATION"
440  FOR I = 1 TO N
450  PRINT I,X(I)
460  NEXT I
470  FOR I = 1 TO N
480 X(I) = 0
490 W(I) = 0
510  NEXT I
610  PRINT
615  REM  SIMULATION INFORMATION
620  READ SEP
630  PRINT "STEP=",SEP
640  READ NUS
650  PRINT "# OF TIME SECTIONS=",NUS
654  PRINT
655  PRINT "CONCENTR.       TIME IN MIN"
660  FOR I = 1 TO NUS
670  READ E(I),TD(I)
680  PRINT E(I),TD(I)
690  NEXT I
700 FAN = G(N) / C(N)
710  GOSUB 3000
720  GOSUB 3160
730  GOSUB 3890
740 T = 0
750 IT = 0
760 UOLD = 0
770 FZ = 0
780  FOR I = 1 TO NUS
790 MSTE(I) = TD(I) / SEP
800  NEXT I
810  PRINT
```

```
820  REM  START OF SIMULATION
830  FOR JJ = 1 TO NUS
840 MM = MSTE(JJ)
850 FOT = E(JJ)
860  FOR JK = 1 TO MM
870 FZ = FZ + FOT * SEP
880 T = T + SEP
890 IT = IT + 1
900 TS(IT) = T
910  REM     CALCULATE X(I),XYNT(I) - CONCENTRATIONS
920  FOR L = 1 TO N
930 S1 = 0
940 S2 = 0
950  FOR M = 1 TO N
960 S1 = S1 + A(L,M) * X(M)
970 S2 = S2 + B(L,M,N1) * X(M)
980  NEXT M
990 XT(L) = S1 + C(L) * FOT
1000 U = S2 + CC(L) * FOT
1010 XYNT(L) = U + XM(L)
1020  NEXT L
1030  REM  TRANSFER X(I),XYNT(I).
1040  FOR L = 1 TO N
1050 XM(L) = XYNT(L)
1060 X(L) = XT(L)
1070 NAP(IT,L) = X(L)
1080  NEXT L
1090  REM    CALCULATE CUR(I),CYNT(I) - RATES AND AMOUNTS
1100  IF NGX = 0 THEN  GOTO 1170
1110  FOR I = 1 TO NGX
1120 CUR(I) = GX(I) * X(I)
1130 PROUD(IT,I) = CUR(I)
1140 CYNT(I) = GX(I) * XYNT(I)
1150 WZ(IT,I) = CYNT(I)
1160  NEXT I
1170 CUR(N5) = G(N) * (FOT - X(N))
1180 PROUD(IT,N5) = CUR(N5)
1190 CYNT(N5) = G(N) * (FZ - XYNT(N))
1200 WZ(IT,N5) = CYNT(N5)
1210 U = CYNT(N5) - UOLD
1220  IF U > 0 THEN CYNT(N6) = CYNT(N6) + U
1230  IF U < 0 THEN CYNT(N7) = CYNT(N7) + U
1240 UOLD = CYNT(N5)
1250 WZ(IT,N6) = CYNT(N6)
1260 WZ(IT,N7) = CYNT(N7)
1265  REM  DISPLAY DATA (SEE OUTPUT TABLE)
1269  PRINT
1270  PRINT "TIME="T
1280  PRINT X(1),X(2)
1281  PRINT X(3),X(4)
1290  PRINT CUR(1),CUR(2)
1300  PRINT CYNT(1)
1310  PRINT CYNT(3),CYNT(4)
1320  NEXT JK
1330  NEXT JJ
```

TABLE 2

```
1335  REM  FILE DATA
1339   PRINT
1340   INPUT "WANT FILE? (Y/N)";R$
1345   IF R$ = "N" THEN  END
1350 F$ = "RESULT"
1360 D$ =  CHR$ (4)
1370   PRINT D$;"OPEN";F$
1380   PRINT D$;"DELETE";F$
1390   PRINT D$;"OPEN";F$
1400   PRINT D$;"WRITE";F$
1410   PRINT N
1420   PRINT N5
1430   PRINT N7
1440   PRINT IT
1450   FOR I = 1 TO IT
1460   PRINT TS(I)
1470   FOR J = 1 TO N
1480   PRINT NAP(I,J)
1490   NEXT J
1500   FOR J = 1 TO N5
1510   PRINT PROUD(I,J)
1520   NEXT J
1530   FOR J = 1 TO N7
1540   PRINT WZ(I,J)
1550   NEXT J
1560   NEXT I
1570   PRINT D$;"CLOSE";F$
1575  REM  ORGANISE DATA
1590 Z(0) = IT
1600 Z(1) = 0
1610   FOR JM = 1 TO 3
1620   IF JM = 1 THEN NK = N
1630   IF JM = 2 THEN NK = N5
1640   IF JM = 3 THEN NK = N7
1650   FOR J = 1 TO NK
1660   IF JM = 1 THEN  GOSUB 4670
1670   IF JM = 2 THEN  GOSUB 4740
1680   IF JM = 3 THEN  GOSUB 4810
1690   FOR I = 1 TO IT
1700 MM = 2 * I
1710 Z(MM) = TS(I)
1720 MM = MM + 1
1730   IF JM = 1 THEN Z(MM) = NAP(I,J)
1740   IF JM = 2 THEN Z(MM) = PROUD(I,J)
1750   IF JM = 3 THEN Z(MM) = WZ(I,J)
1760   NEXT I
1770   GOSUB 4560
1780   NEXT J
1790   NEXT JM
1800   END
```

```
3000  REM  FORMULATION OF THE SYSTEM MATRIX
3010  FOR I = 1 TO N
3020  FOR J = 1 TO N
3030 A(I,J) = 0
3040  NEXT J
3050  NEXT I
3060 N2 = N - 1
3070 S1 = 0
3080  FOR I = 1 TO N2
3090 A(I,I) =  - (G(I) + GX(I)) / C(I)
3100 A(N,I) = G(I) / C(N)
3110 A(I,N) = G(I) / C(I)
3120 S1 = S1 + G(I)
3130  NEXT I
3140 A(N,N) =  - (S1 + G(N)) / C(N)
3150  RETURN
3160  REM  SUBROUTINE LEVER
3170  FOR K = 1 TO N1
3180  FOR I = 1 TO N
3190  FOR J = 1 TO N
3200 B(I,J,K) = 0
3210  NEXT J
3220  NEXT I
3230  NEXT K
3240  FOR I = 1 TO N
3250 B(I,I,1) = 1
3260  NEXT I
3270 L = 2
3280 LM = L - 1
3290  FOR I = 1 TO N
3300  FOR J = 1 TO N
3310 S1 = B(I,J,L)
3320  FOR K = 1 TO N
3330 S1 = S1 + A(I,K) * B(K,J,LM)
3340  NEXT K
3350 B(I,J,L) = S1
3360  NEXT J
3370  NEXT I
3380  REM  CALCULATE TRACE
3390 S1 = 0
3400  FOR I = 1 TO N
3410 S1 = S1 + B(I,I,L)
3420  NEXT I
3430 C(LM) =  - S1 / LM
3440  FOR I = 1 TO N
3450 B(I,I,L) = B(I,I,L) + C(LM)
3460  NEXT I
3470  IF L > N GOTO 3500
3480 L = L + 1
3490  GOTO 3280
3500  FOR I = 1 TO N
3510 CC(I + 1) = C(I)
3520  NEXT I
3530 CC(1) = 1
```

```
3540  REM  CALCULATE THE EXPONENTS
3550 EPS = 1E - 16
3560 LIM = 100
3570  GOSUB 4120
3580  REM  CALCULATE THE RESIDUES
3590  FOR L = 1 TO N
3600 RL = RR(L)
3610 PROD = 1
3620  FOR K = 1 TO N
3630  IF L = K GOTO 3650
3640 PROD = PROD * (RL - RR(K))
3650  NEXT K
3660 C(L) = PROD
3670  NEXT L
3680  FOR I = 1 TO N
3690  FOR J = 1 TO N
3700  FOR K = 1 TO N
3710 CC(K) = B(I,J,K)
3720  NEXT K
3730  FOR L = 1 TO N
3740 RL = RR(L)
3750 PUA = CC(1)
3760  FOR K = 2 TO N
3770 PUA = PUA * RL + CC(K)
3780  NEXT K
3790 B(I,J,L) = PUA / C(L)
3800  NEXT L
3810  NEXT J
3820  NEXT I
3825  PRINT
3826  PRINT "EXPONENT          TIME CONST."
3830  FOR L = 1 TO N
3835 U =  - 1 / RR(L)
3840  PRINT RR(L),U
3850  FOR I = 1 TO N
3860  NEXT I
3870  NEXT L
3880  RETURN
3890  REM  CALCULATE EXPONENTIALS AND INTEGRALS
3900  FOR I = 1 TO N
3910 CC(I) = 0
3920 C(I) = 0
3930  FOR J = 1 TO N
3940 A(I,J) = 0
3950 B(I,J,N1) = 0
3960  NEXT J
3970  NEXT I
3980  FOR K = 1 TO N
3990 EU =  EXP (RR(K) * SEP)
4000 EU = (EU - 1) / RR(K)
4010 EW = (EU - SEP) / RR(K)
4020  FOR I = 1 TO N
4030 C(I) = C(I) + B(I,N,K) * EU + FAN
4040 CC(I) = CC(I) + B(I,N,K) * EW + FAN
4050  FOR J = 1 TO N
4060 A(I,J) = A(I,J) + B(I,J,K) * EU
4070 B(I,J,N1) = B(I,J,N1) + B(I,J,K) * EU
4080  NEXT J
4090  NEXT I
4100  NEXT K
4110  RETURN
```

```
4120  REM  ROOT-FINDING STEERING ROUTINE
4130  FOR I = 1 TO N1
4140 BB(I) = CC(I)
4150  NEXT I
4160 XX = 0
4170 NO = N
4180 NP = N1
4190  FOR IROOT = 1 TO N
4200 ITER = 0
4210  GOSUB 4420
4220 ITER = ITER + 1
4230  IF ITER < LIM GOTO 4260
4240  PRINT "ITERATIONS EXCEEDED"
4250  END
4260 DX =  - FU / DN
4270 XX = XX + DX
4280 U =  ABS (DX)
4290  IF U > EPS THEN  GOTO 4210
4300 RR(IROOT) = XX
4310  GOSUB 4360
4320 NO = NO - 1
4330 NP = NP - 1
4340  NEXT IRROT
4350  RETURN
4360  REM  DEFLATION OF THE POLYNOMIAL
4370  IF NP < 2 THEN  GOTO 4410
4380  FOR K = 2 TO NP
4390 BB(K) = BB(K) + BB(K - 1) * XX
4400  NEXT K
4410  RETURN
4420  REM  POLYNOMIAL EVALUATION
4430  FOR I = 1 TO NP
4440 H(I) = BB(I)
4450  NEXT I
4460  FOR I = 2 TO NP
4470 H(I) = H(I) + XX * H(I - 1)
4480  NEXT I
4490 FU = H(NP)
4500  IF NO = 1 THEN  GOTO 4540
4510  FOR I = 2 TO NO
4520 H(I) = H(I) + XX * H(I - 1)
4530  NEXT I
4540 DN = H(NO)
4550  RETURN
```

```
4555  REM  FILE ORGANISED DATA
4560 D$ = CHR$ (4)
4570  PRINT D$;"OPEN";F$
4580  PRINT D$;"DELETE";F$
4590  PRINT D$;"OPEN";F$
4600  PRINT D$;"WRITE";F$
4610 ML = 2 * IT + 1
4620  FOR I = 0 TO ML
4630  PRINT Z(I)
4640  NEXT I
4650  PRINT D$;"CLOSE";F$
4660  RETURN
4670  IF J = 1 THEN F$ = "NAP1"
4680  IF J = 2 THEN F$ = "NAP2"
4690  IF J = 3 THEN F$ = "NAP3"
4700  IF J = 4 THEN F$ = "NAP4"
4710  IF J = 5 THEN F$ = "NAP5"
4720  IF J = 6 THEN F$ = "NAP6"
4730  RETURN
4740  IF J = 1 THEN F$ = "PROUD1"
4750  IF J = 2 THEN F$ = "PROUD2"
4760  IF J = 3 THEN F$ = "PROUD3"
4770  IF J = 4 THEN F$ = "PROUD4"
4780  IF J = 5 THEN F$ = "PROUD5"
4790  IF J = 6 THEN F$ = "PROUD6"
4800  RETURN
4810  IF J = 1 THEN F$ = "INGR1"
4820  IF J = 2 THEN F$ = "INGR2"
4830  IF J = 3 THEN F$ = "INGR3
4840  IF J = 4 THEN F$ = "INGR4"
4850  IF J = 5 THEN F$ = "INGR5"
4860  IF J = 6 THEN F$ = "INGR6"
4870  IF J = 7 THEN F$ = "INGR7"
4880  IF J = 8 THEN F$ = "INGR8"
4890  RETURN
5000  REM  LU FACTORIZATION
5010 D(N) = 0
5020  FOR I = 1 TO NM1
5030 D(I) = G(I) + GX(I)
5040 L = N + I
5050 D(L) =  - G(I) / D(I)
5060 D(N) = D(N) + G(I) * (1 + D(L))
5070  NEXT I
5080 D(N) = D(N) + G(N)
5090  RETURN
5500  REM  SUBROUTINE LUSOL
5520 Z(N) = W(N)
5530  FOR I = 1 TO NM1
5535 Z(N) = Z(N) + Z(I) * G(I)
5540 Z(I) = W(I) / D(I)
5550  NEXT I
5560 Z(N) = Z(N) / D(N)
5570 U = Z(N)
5580  FOR I = 1 TO NM1
5590 L = N + I
5600 X(I) = Z(I) - D(L) * U
5610  NEXT I
5620 X(N) = U
5630  RETURN
```

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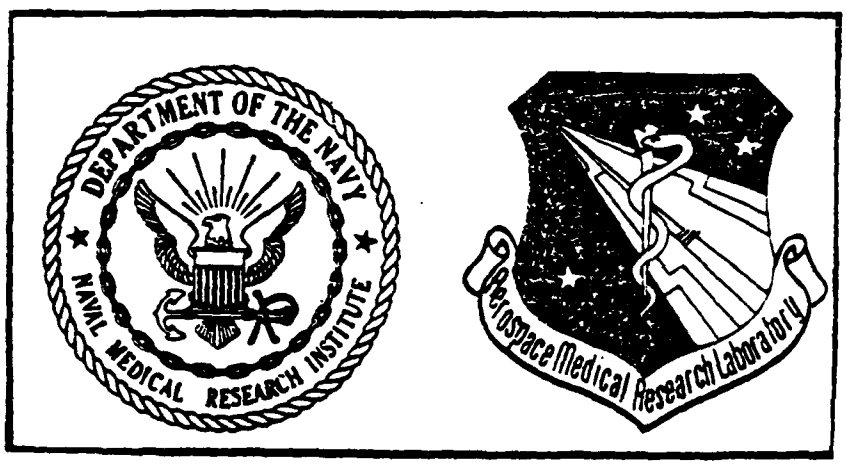
APRIL 1980



AIR FORCE AEROSPACE MEDICAL RESEARCH LABORATORY
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PAPER NO. 5

DETERMINATION OF KINETIC CONSTANTS FROM PULMONARY UPTAKE

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The adverse biological effect of an air pollutant is related to its concentration and/or time integral of concentration in the target organ. The passage of pollutant from the environment to the target organ is a dynamic process, determined by the physical and chemical properties of the pollutant and by the physiological parameters of the exposed subject (Eger, 1963). Inhaled, nonwater soluble vapors are removed from the body by pulmonary and metabolic clearance. Since pulmonary clearance takes place only after the end of exposure (or when exposure concentration decreases), the vapor is removed during exposure only by metabolic clearance (Fiserova-Bergerova et al., 1974).

Metabolic clearance in vivo is usually defined by the half-time of disappearance of the xenobiotic from plasma after bolus administration, or as the half-time of urinary excretion of xenobiotic metabolites. The determination of plasma clearance requires frequent blood sampling, which imposes stress on subjects. The urinary excretion of metabolites is affected by a variety of factors, such as distribution of metabolites in the body, binding, and renal clearance.

Inhalation administration makes possible a noninvasive, accurate measurement of the rate of overall metabolism of inhaled vapors (Teisinger and Soucek, 1952).

The pulmonary uptake rate, $\dot{u}$, is the sum of retention rates of vapor in tissues, $\dot{u}_{tis}$, and the rate of overall metabolism, $\dot{u}_m$:

$$\dot{u} = \dot{u}_{tis} + \dot{u}_m \qquad (1)$$

The pulmonary uptake can be determined from the difference between vapor concentrations in inhaled and mixed-exhaled air multiplied by minute ventilation:

$$\dot{u} = (C_{inh} - C_{exh})\,\dot{V} \qquad (2)$$

where C_{inh} and C_{exh} are vapor concentrations (mg/liter) in inhaled air and in mixed-exhaled air, and $\dot{V}$ is minute ventilation (liter/minute).

We have presented a compartmental model which can be used to determine the retention rate of inhaled vapor in tissues. Using three compartments (VRG - vessel rich tissues, MG - muscles and skin, FG - fat and fat marrow), the retention rate:

$$\dot{u}_{tis} = C_{alv} \left[F_{VRG} \lambda_{bl/air} \exp \left(- \frac{F_{VRG}}{V_{VRG} \lambda_{VRG/bl}} t \right) \right.$$

$$+ F_{MG} \lambda_{bl/air} \exp \left(- \frac{F_{MG}}{V_{MG} \lambda_{MG/bl}} t \right) \qquad (3)$$

$$\left. + F_{FG} \lambda_{bl/air} \exp \left(- \frac{F_{FG}}{V_{FG} \lambda_{FG/bl}} t \right) \right]$$

where F's are blood flows (liter/minute) through the compartments, V's (l) are their volume. λ's are the corresponding partition coefficients of inhaled vapor at 37°C, C_{alv} is the vapor concentration (mg/liter) in alveolar air, and exp is the natural logarithm.

Substituting from Equations 2 and 3 in Equation 1, the rate of overall metabolism can be determined. Since the retention of vapor in tissues is an exponential function, the retention rate diminishes with exposure duration. This determination is most accurate during apparent steady state, when retention by tissues is small ($\dot{u}_m >> \dot{u}_{tis}$).

We demonstrated the effect of metabolism on pulmonary uptake in an informed volunteer patient who was anesthetized with fluroxene (CH_2:CH.O.CH_2.CF_3) in the presence of a small concentration of non-metabolized isoflurane (CHF_2.).CHCl.CF_3) (Fiserova-Bergerova and Holaday, 1979). The amount of metabolites accounts for less than 1% of isoflurane uptake (Holaday et al., 1975), and about 45% of fluroxene uptake (Gion et al., 1974).

During anesthesia, samples of inhaled gas and end-exhaled gas were drawn during the appropriate phase of respiration via a nylon cannula inserted in the endotracheal tube at 4 to 10 minute intervals. Mixed-exhaled gas was obtained at the same time at the outlet of a mixing chamber interposed in the expiratory breathing tube. Gas samples were collected in 20 ml glass syringes. At the same time,

minute ventilation was measured with a Wright respirometer. The cumulative uptake D was determined: (1) from the amount of anesthetics delivered by syringe in the closed anesthetic circuit, and (2) from the sum of the differences between concentrations of inhaled and mixed-exhaled air multiplied by minute ventilation, and time intervals between sampling (t in minutes)

$$D = \Sigma \dot{V} t (C_{inh} - C_{exh}) \qquad (4)$$

The cumulative uptake predicted by integration of Equation 3 as retention in tissues correlates with the measured uptake of isoflurane (calculated by Equation 4), but the measured fluroxene uptake greatly exceeds the calculated fluroxene retention in tissues (Figure 1). The difference accounts for fluroxene metabolism.

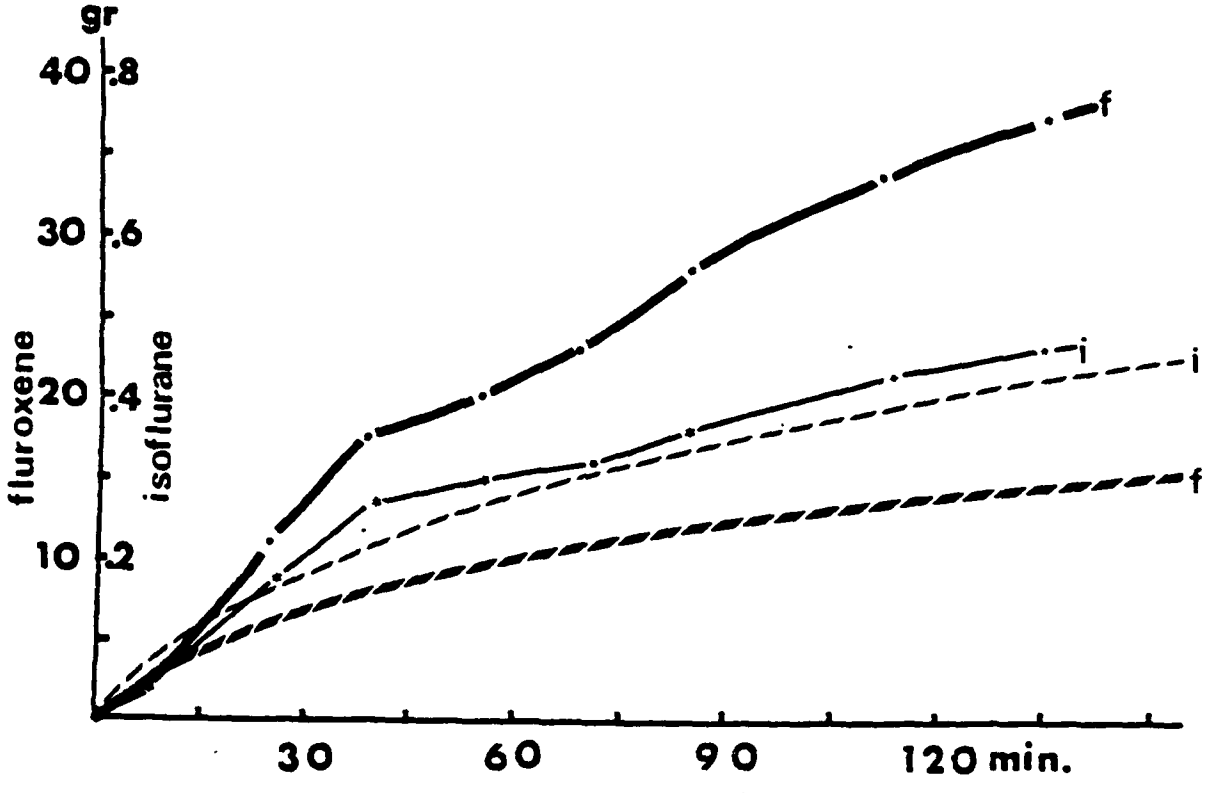

Figure 1. Cumulative uptake of isoflurane (i) and fluroxene (f) administered simultaneously to a surgical patient. Cumulative uptake is plotted against the time after the start of anesthesia. The dashed lines are uptake curves predicted by integration of Equation 3 for alveolar concentrations of fluroxene (154 mg/liter) and isoflurane (3 mg/liter).

To study the effect of exposure concentration on pulmonary uptake, the following assumptions were made: (1) the retention of vapor in tissue is a first order process, which means its rate constant is concentration independent; and (2) metabolic clearance is a limited-capacity process described by Michaelis-Menten kinetics.

To determine the Michaelis-Menten constants in vivo, we exposed male rhesus monkeys (approximately 3 kg) consecutively to three concentrations of one of the following compounds: benzene, halothane (CF_3·CHClBr), methylene chloride, or trichloroethylene. Concentrations were in the range of TLV during the first exposure; equal to five times TLV during the second exposure; and equal to 25 TLV during the third exposure. In order to reach apparent steady state, each exposure lasted approximately two and one-half hours. Vapors were administered in light sernylane anesthesia via endotracheal tube. The following parameters were measured: (1) vapor concentrations in inhaled air (C_{exp}), mixed-exhaled air (C_{exh}), and end-exhaled (C_{alv}) and arterial blood(C_{art}); (2) blood-gas partition coefficients ($\lambda bl/air$); (3) minute ventilation; (4) blood pressure and pulse rate; and (5) blood gases and PCO_2 in mixed-exhaled air. Uptake rate, metabolic rate, and alveolar ventilation were calculated from the measured data. Apparent Michaelis-Menten constants of overall metabolism in vivo (K_m) were calculated from double reciprocal plots of metabolic rate versus C_{alv}, C_{exp}, or $C_{art}/\lambda bl/air$ (measured at a steady state), and versus calculated concentrations in tissues.

In Figure 2, the double reciprocal plots from benzene and methylene chloride are presented. K_m values related to the concentrations in alveolar air at steady state for all four studied compounds are in Table 1.

Figures 3 and 4 demonstrate double reciprocal plots of metabolic rates of trichloroethylene and halothane versus exposure concentration, alveolar concentration, arterial concentration, and tissue concentration. The data indicate that K_m values depend on the site in which the concentration is measured, but the maximum metabolic rate (V_{max}) is the same regardless of whether it is derived from concentration in inhaled air, alveolar air, arterial blood, or tissue.

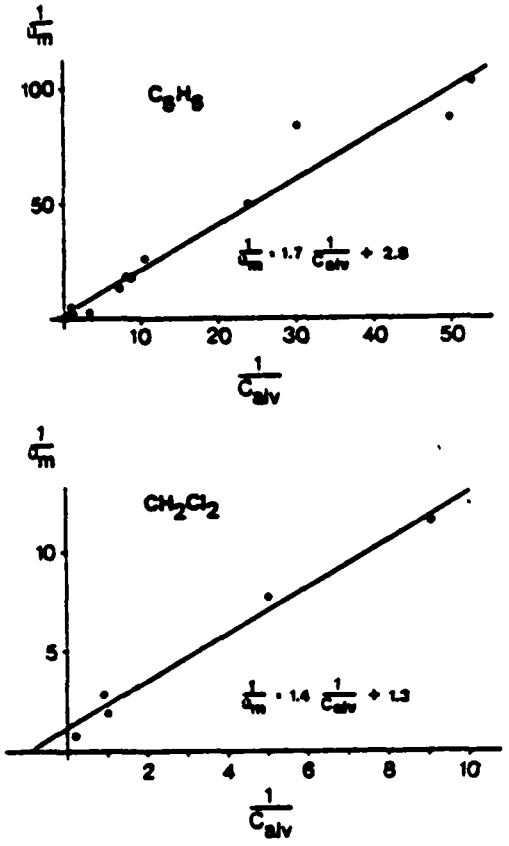

Figure 2. Double reciprocal plot of uptake rates of benzene and methylene chloride versus alveolar concentration. The lines represent optimum fit to experimental data obtained in rhesus monkeys (3 kg males).

TABLE 1. APPARENT MICHAELIS-MENTEN CONSTANTS IN VIVO (3 KG MALE RHESUS MONKEY)

Compound	V_{max} (mg/min)	K_m* (mg/liter)	TLV** (mg/liter)
Benzene	0.3	0.6	0.03
Trichloroethylene	0.7	1.0	0.27
Methylene Chloride	0.7	1.1	0.36
Halothane	1.2	7.4	0.40

*Related to C_{alv}

**Threshold limit values recommended by ACGIH in 1979 as TWA.

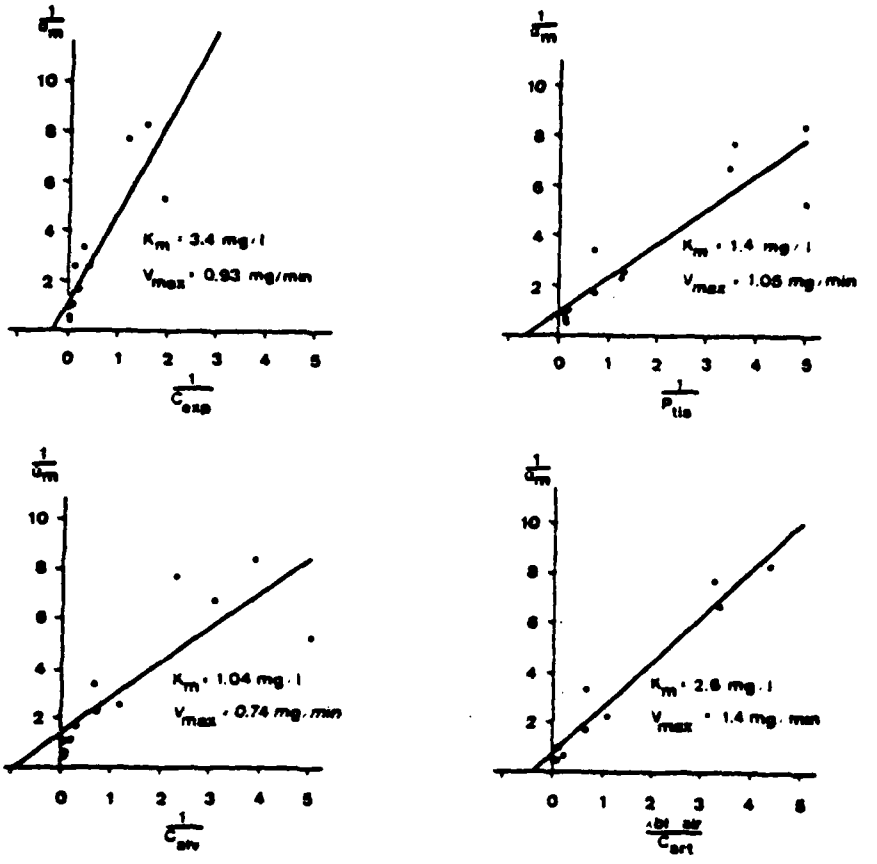

Figure 3. Double reciprocal plot of uptake rates of trichloroethylene versus measured concentrations in inhaled air (C_{exp}), end-exhaled air (C_{alv}), arterial blood (C_{art}), and calculated concentrations in tissues.

$$P_{tis} = \frac{C_{tis}}{\lambda tis/air} = \left(- \frac{\dot{u}_m}{F_{VRG}} + C_{art}\right) \frac{1}{\lambda bl/air}$$

The lines represent optimum fit to experimental data obtained in rhesus monkeys (3 kg males).

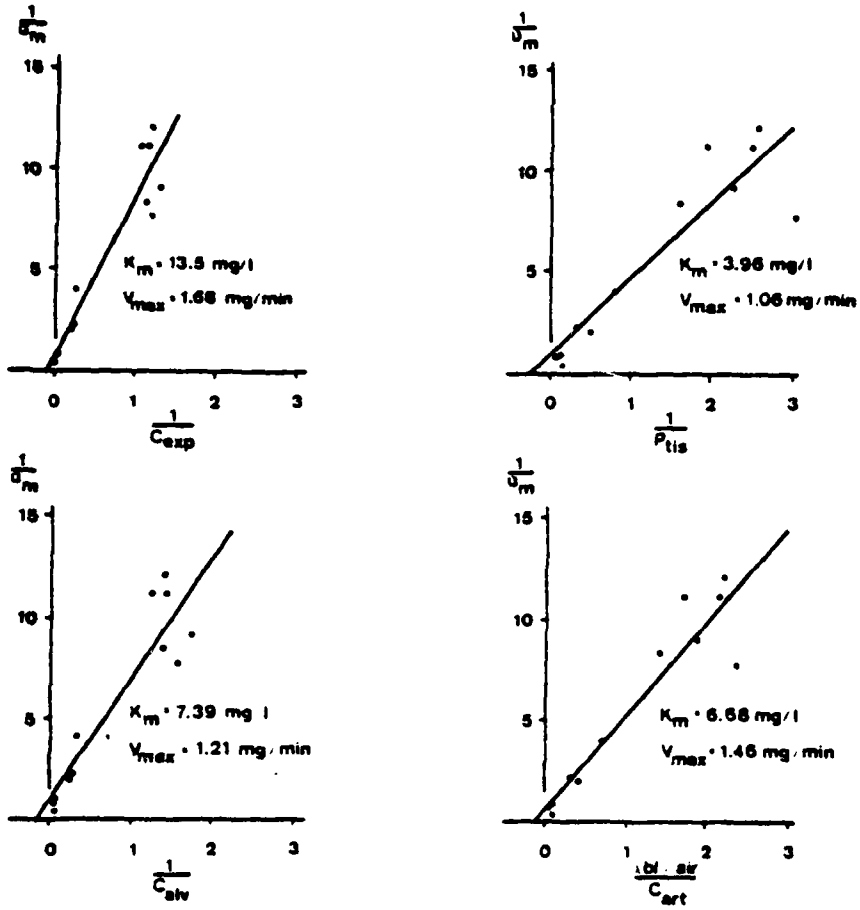

Figure 4. Double reciprocal plot of uptake rates of halothane versus measured concentrations in inhaled air (C_{exp}), end-exhaled air (C_{alv}), arterial blood (C_{art}), and calculated concentrations in tissues.

$$P_{tis} = \frac{C_{tis}}{\lambda tis/air} = (- \frac{\dot{u}_m}{F_{VRG}} + C_{art}) \frac{1}{\lambda bl/air}$$

The lines represent optimum fit to experimental data obtained in rhesus monkeys (3 kg males).

The differences in K_m values might be explained by the three concentration gradients on the pathway of the vapor from the environment to the metabolic site: (1) Vapor concentration entering the lung with each breath is smaller than the exposure concentration because of the dilution by alveolar air from deadspace; (2) When the air reaches the alveoli, the partial pressures in alveolar air and arterial blood are readily equilibrated. Uptake of vapor by arterial blood reduces the concentration further. The concentration decreases, depending on the cardiac output and alveolar ventilation, on the solubility of vapor in blood, and on the concentration of vapor in mixed-venous blood; (3) Arterial blood transfers the vapor to the tissues, where it is retained to the extent that partial pressures in tissue and venous blood are equilibrated. The concentration gradient C_{art}/C_{ven} in blood which supplies metabolic sites is further increased by metabolic clearance.

At steady state, the partial pressures of nonmetabolized vapor equilibrate, and the vapor concentrations in tissues equal the exposure concentration multiplied by the appropriate partition coefficient. If the vapor is metabolized, the concentrations are reduced.

Employing our nonlinear model (Fiserova-Bergerova et al., in preparation), we examined the conditions under which this method for K_m and V_{max} is applicable, and found the following limitations:

(1) Metabolism must be concentration dependent. According to Michaelis-Menten kinetics, this requirement is met if substrate concentrations are smaller than 10 K_m. This means that the studies must be performed in the range of exposure concentrations which are smaller than 10 K_m.

$$C_{exp} < 10\ K_m$$

(2) The system cannot be flow-limited. This requires that transportation rate of vapor from environment to the metabolic site is larger than metabolic rate. This condition is met if:

$$\frac{V_{max}}{K_m} < \frac{F\ \lambda bl/air\ \dot{V}_{alv}}{\dot{V}_{alv} + F\ \lambda bl/air}$$

This expression can be rearranged:

$$\frac{V_{max}}{K_m} < F\ \lambda bl/air\ \frac{1}{1 + \frac{F}{\dot{V}_{alv}}\ \lambda bl/air}$$

Optimum conditions for determination are: (a) the vapor is highly susceptible to biotransformation, and (b) the metabolite sites are well perfused or the vapor is well soluble in blood.

We analyzed the tissues of rats and monkeys exposed to different concentrations of halothane and trichloroethylene to determine the effect of exposure concentrations on concentrations of these vapors in tissues. When exposure concentrations were larger than K_m, the metabolic clearance diminished and the concentration ratios C_{exp}/C_{tis} increased (Fiserova-Bergerova, unpublished data). The same conclusions were drawn using our nonlinear mathematical model (Fiserova-Bergerova et al., in preparation).

The determination of metabolic rate from pulmonary uptake is also suitable for studying the effect of modifiers on metabolism of inhaled vapors. In experiments similar to those described above, we administered two vapors simultaneously to monkeys. One vapor was administered at a low constant concentration; the concentration of the other vapor - the modifier - was increased in three steps. Data from these experiments are in Figure 5. As the concentration of modifier increased, the pulmonary uptake of the studied vapor decreased. The decrease is probably caused by competitive inhibition of metabolism of the inhaled vapors.

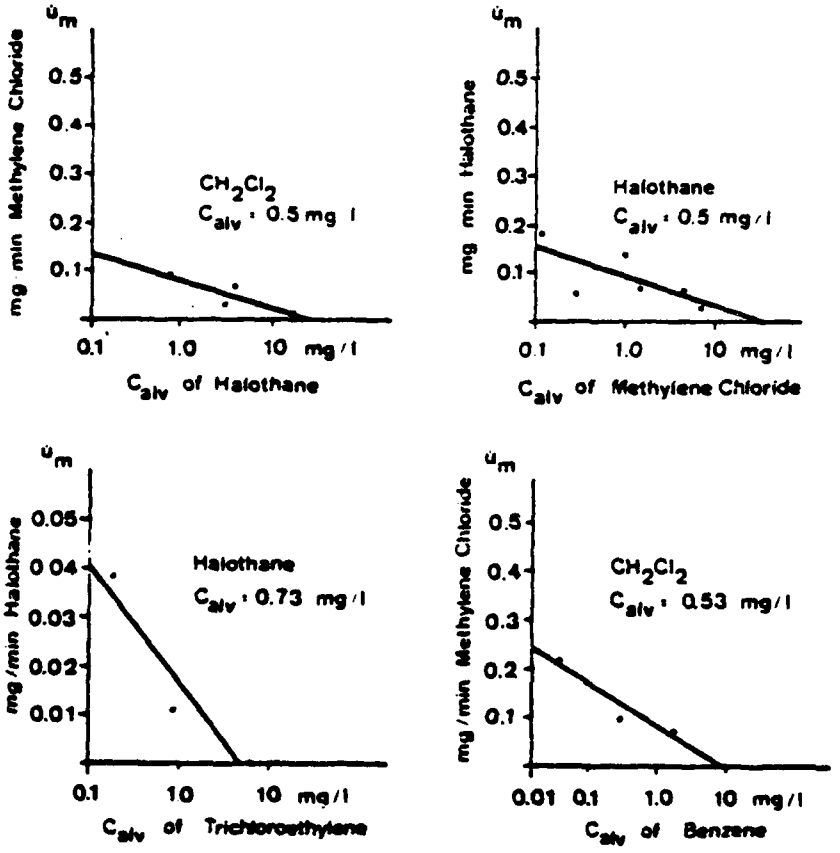

Figure 5. Effect of increasing exposure concentration of vapor-modifier (abcissa) on metabolic rate of the vapor inhaled at constant concentration.

CONCLUSIONS

We have presented rationales for the determination of metabolic constants in vivo from pulmonary uptake rate, and briefly described the procedures and some applications.

The determination of the extent of vapor metabolism from the uptake rate has an advantage over making this determination from excreted metabolites, in that the effect of metabolite distribution and binding in the body, and the effect of renal clearance, are eliminated. Since air sampling is a noninvasive procedure, samples can be collected continuously, or as frequently as needed.

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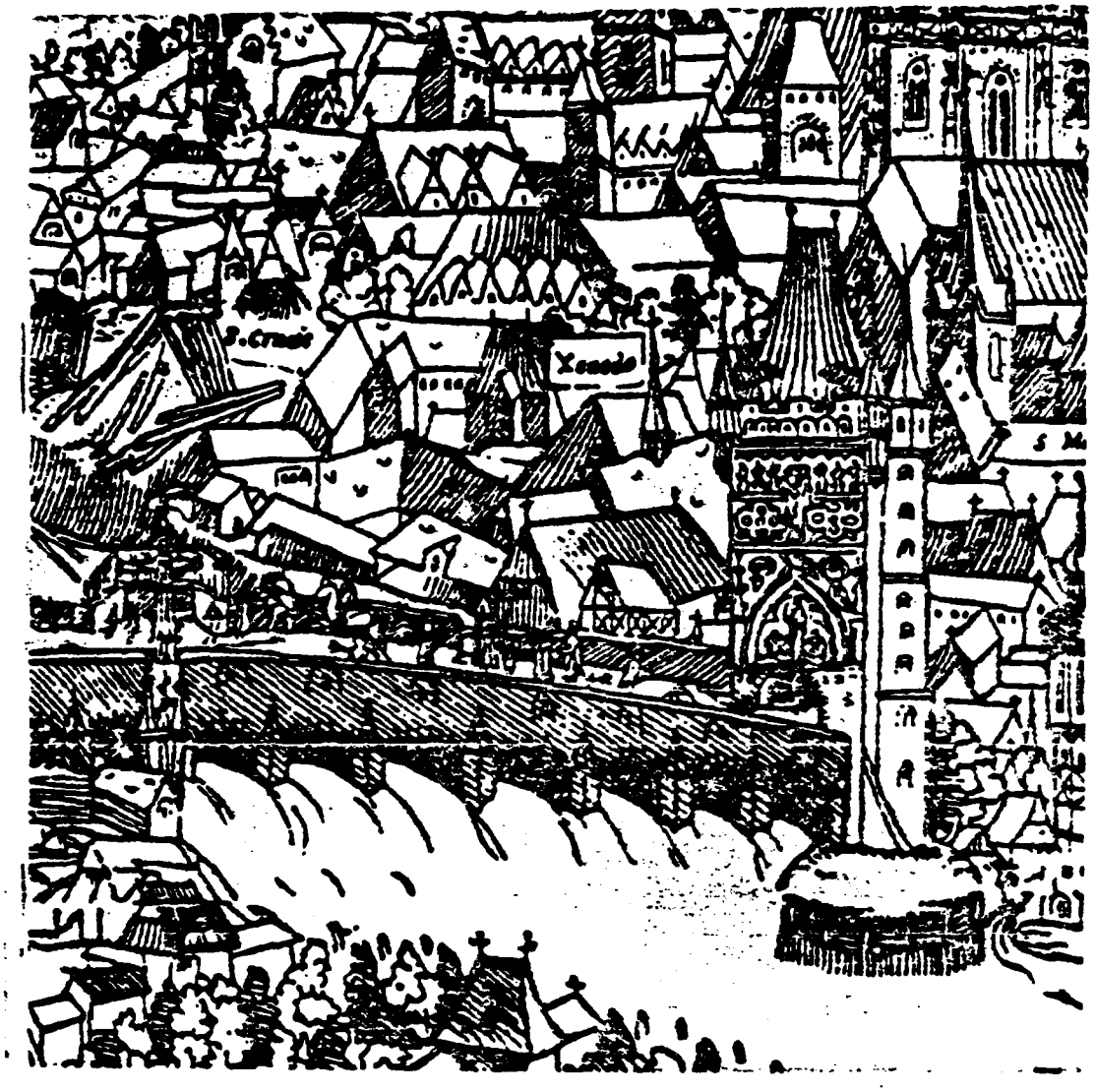

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MODELING OF UPTAKE AND CLEARANCE OF INHALED VAPORS AND GASES

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With progressing technology, toxicologists and hygienists confront the problem of securing safe exposure to an increasing number of air pollutants. The adverse biological effect of pollutants, like the therapeutic effect of drugs, is related to blood concentration and/or time integral of concentration in the target organs. Passage of pollutants from the environment to the target organ has the same significance as migration of drugs from the site of administration to the target organ. Pharmacokinetics describing the transport of drugs in the body is a potent tool for designing dosage regimens of optimum therapeutic effect.[1] Methods similar to those used by pharmacokineticists can be employed to design exposures with minimal undesirable biological effects.

Inhalation administration has some specific characteristics: Equilibration of partial pressures of inhaled vapor in the body and in ambient air is the driving force determining uptake.[2,3] The equilibration rate depends on pulmonary ventilation, tissue perfusion, and on solubility and clearance of inhaled vapor. The concentration in tissues depends on exposure concentration, exposure duration, and equilibration rate.

Since solubility of inhaled vapor varies for different tissues according to water and lipid content, and since cardiac output is not equally distributed, a multi-compartmental model is needed to describe uptake, distribution, and elimination of inhaled vapors (Figure 1).

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In the model, tissues are assigned to the compartment according to perfusion, ability to metabolize the inhaled substance, and solubility of the substance in the tissue.[4,5] Lung tissue, functional residual air, and arterial blood form the central compartment 'LG', in which pulmonary uptake and clearance take place. The partial pressure of inhaled vapor equilibrates with four peripheral compartments. Well perfused tissues form two peripheral compartments: BR-compartment includes brain, which lacks capability to metabolize most xenobiotics, and is treated as a separate compartment because of its biological importance and the toxic effect of many vapors and gases on CNS. VRG-compartment includes vessel rich tissues with sites of vapor metabolism such as liver, kidney, glands, heart, and tissues of the gastrointestinal tract. Less perfused tissues are also pooled in two peripheral compartments, according to lipid content: Muscles and skin form compartment 'MG', and adipose tissue and white marrow form compartment 'FG'. It is important to treat the FG-compartment separately, since dumping of lipid soluble vapors in this compartment has a smoothing effect on concentration variation in other tissues, caused by changes in exposure concentration, minute ventilation, and exposure duration. This model is described by a set of five first-order differential equations linear to the first approximation.[5]

Mathematical solution of this model is available if the model is pictured as an electric network composed of conductances and capacitances.[4-9] In figure 2 'Z' stands for exposure concentration. The values of capacitances 'C' are derived from capacity of tissues to retain the vapor, that is, tissue volumes multiplied by appropriate tissue-air partition coefficients 'λ' at 37°C. The values of conductances G_{BR}, G_{VRG} , G_{MG} and G_{FG} are derived from transportation rates of vapor from the lung to the tissues, that is, blood blow times blood-air partition coefficient (37°C). Alveolar ventilation was substituted for G_{LG}. 'G_x'stands for clearance by metabolism. All parameters required by the model can be defined: Physiological parameters can be found in the literature.[2,3,10-14] Partition coefficients can be

easily measured. Metabolic clearance can be determined from pulmonary uptake during steady state[10,15-17]

The determination of metabolic rate from the uptake rate has an advantage over making this determination from excreted metabolites,[18] in that the effect of metabolite distribution and binding in the body, and the effect of renal clearance, are eliminated.

After sufficiently long exposure, the steady state is reached and pulmonary uptake rate equals clearance rate. If clearance does not take place, uptake equals zero and ratios of tissue concentrations to the exposure concentration equal the corresponding partition coefficients. If the vapor is excreted or metabolized during exposure, the ratio of concentrations in alveolar air and in tissue to exposure concentration is smaller than corresponding partition coefficients. The deviation from partition coefficient is directly related to clearance and indirectly related to the flow of vapor to the site of metabolism.

The uptake rate '$\dot{u}$' can be determined from difference of exposure concentration 'C_{exp}' and vapor concentration in mixed exhaled air 'C_{exh}', alveolar air 'C_{alv}' or arterial blood 'C_{art}'.

$$\dot{u} = (C_{exp} - C_{exh})\ \dot{V} \qquad (1)$$

$$\dot{u} = (C_{exp} - C_{alv})\ \dot{V}_{alv} \qquad (2)$$

$$\dot{u} = \left(C_{exp} - \frac{C_{art}}{\lambda_{bl/air}}\right) \dot{V}_{alv} \qquad (3)$$

where '$\dot{V}$' is minute ventilation, '$\dot{V}_{alv}$' is alveolar ventilation ($\dot{V}_{alv} \doteq 2/3\dot{V}$) and '$\lambda$' is partition coefficient.

Determination of uptake rate by analysis of air samples (equations 1 and 2) has the advantage that sampling of mixed exhaled air as well as of end exhaled air (alveolar air) can be done frequently without imposing stress on the subject. However, this method is limited to "cooperative subjects", such as men[15,19-22] or animals which tolerate a face mask.[10,16] Sampling of arterial blood (equation 3) is more suitable for small experimental animals.[23] Anesthesia or any drug administered to subjects undergoing the exposure, might affect the metabolism of inhaled vapor.

For organic solvents, metabolism is the main excretory pathway, and therefore during steady state, metabolic rate $\dot{u}_m = \dot{u}$. If flow rate of the vapor to the site of metabolism is much larger than metabolic rate, the measured clearance is intrinsic clearance and

$$G_x = \frac{\dot{u}_m}{C_{exp}} \qquad (4)$$

However, for most vapors, pulmonary ventilation and tissue perfusion ('F') affects the metabolic rate, and G_x must be calculated:

$$\frac{1}{G_x} = \frac{C_{exp}}{\dot{u}} - \frac{1}{V_{alv}} - \frac{1}{F\,\lambda_{bl/air}} \qquad (5)$$

or

$$\frac{1}{G_x} = \frac{C_{alv}}{\dot{u}} - \frac{1}{F\,\lambda_{bl/air}} \qquad (6)$$

or

$$\frac{1}{G_x} = \frac{1}{\lambda_{bl/air}}\left(\frac{C_{art}}{\dot{u}} - \frac{1}{F}\right) \qquad (7)$$

G_x can be calculated most accurately if vapor concentration in metabolizing tissue during steady state is known:

$$G_x = \lambda_{tis/air} \quad \frac{\dot{u}_m}{C_{tis}} \tag{8}$$

Perfusion of metabolic rate 'F' can be calculated by subtracting equation 8 from equation 5, 6 or 7 (making $\dot{u} = \dot{u}_m$)

G_x is a constant if metabolism follows first order kinetics (low exposure concentration). However, metabolism, like all enzymatic reactions, is a capacity limited process. Therefore G_x becomes a dependent variable of tissue concentration, and of exposure duration.[24] G_x can be calculated by substituting for '$\dot{u}_m$' in equation 8 from Michaelis-Menten equation:

$$G_x = \frac{\lambda_{tis/air}}{C_{tis}} \cdot \frac{V_{max}\ C_{tis}}{K_m + C_{tis}} = \frac{V_{max}\ \lambda_{tis/air}}{K_m + C_{tis}} \tag{9}$$

K_m and V_{max} can be determined from double reciprocal plot of uptake versus tissue concentration measured during steady state in subjects exposed to different concentrations.

The non-linear element G_x describing metabolism of limited capacity further complicated the mathematical solution of the model. However, there is a solution for electric network with non-linear element [25,26] and computer programs are available.[4-8,24] The programs calculate time course of voltages in capacitors and currents in resistors. The voltages 'V' are directly related to tissue concentrations ($C_{tis} = V\ \lambda_{tis/air}$). Currents are equivalent to uptake rates (or to pulmonary clearance rate) (in G_{LG}), metabolic clearance rates (in G_x), and retention rates (in G_{BR}, G_{VRG}, G_{MG}, G_{FG}). Integrated currents represent amounts retained, metabolized or exhaled.

Examples of the application of modeling to problems of industrial toxicology are in Figures 3 to 7.

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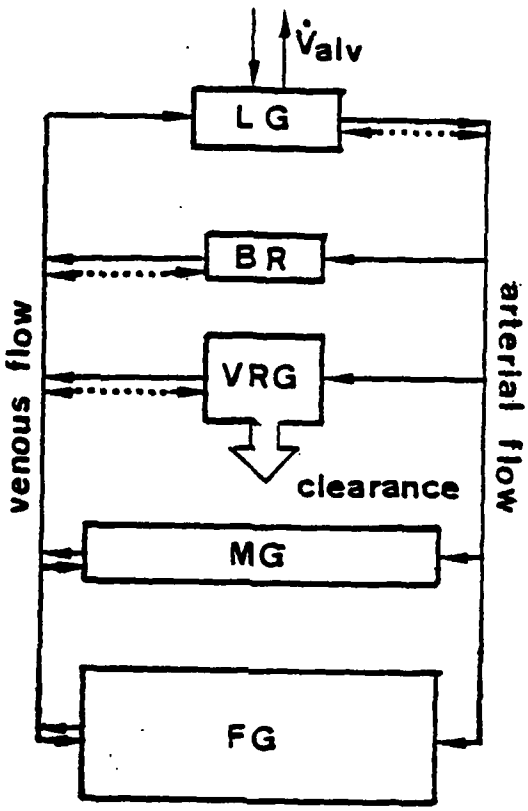
KEY WORDS:

Clearance - of inhaled vapors
Concentration excursion
Compartmental model
Distribution-of inhaled vapors
Electric analogue
Gases - low soluble
Kinetics
Metabolism - first order kinetics
capacity limited
Model - compartmental
mathematical
physiological
Modeling
Perfusion
Solubility
Vapors - lipid soluble
Ventilation - alveolar
pulmonary
Steady state
Uptake - of inhaled vapors

FIGURE 1

FIVE COMPARTMENTAL MODEL WITH METABOLISM
IN VESSEL RICH COMPARTMENT



The unbroken arrows indicate blood flow.
The broken arrows indicate partial pressure equilibration.

FIGURE 2

FIVE COMPARTMENTAL MODEL PICTURED AS ELECTRIC NETWORK.

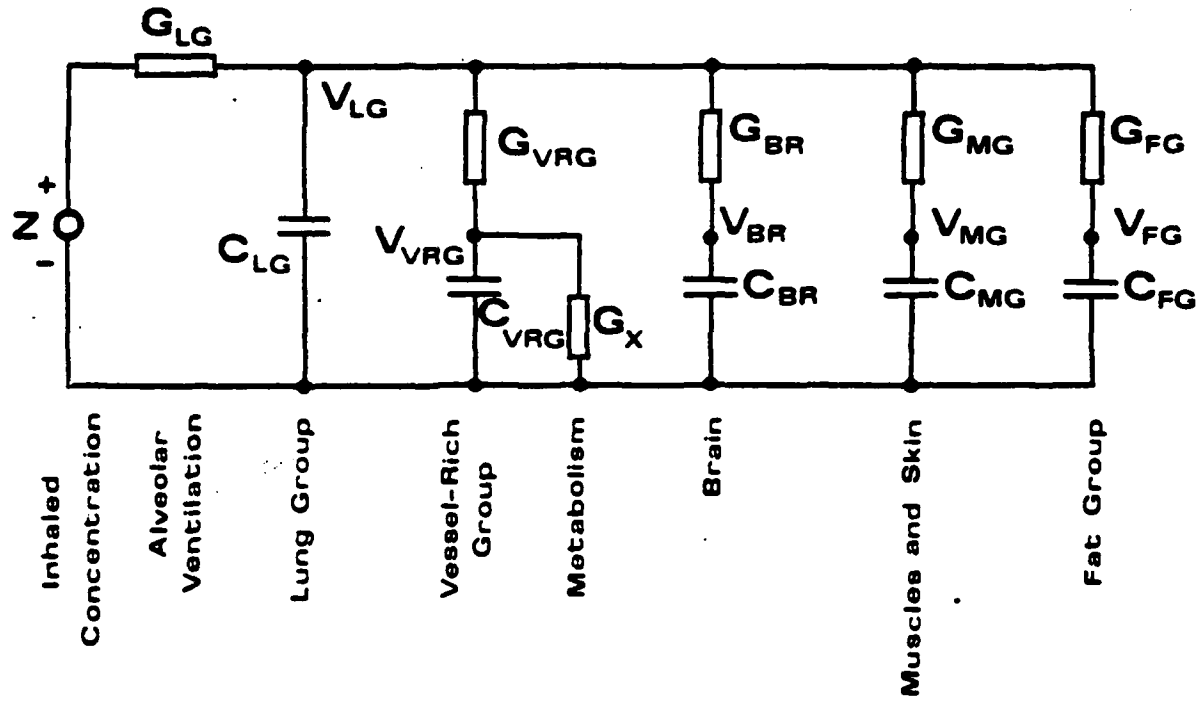
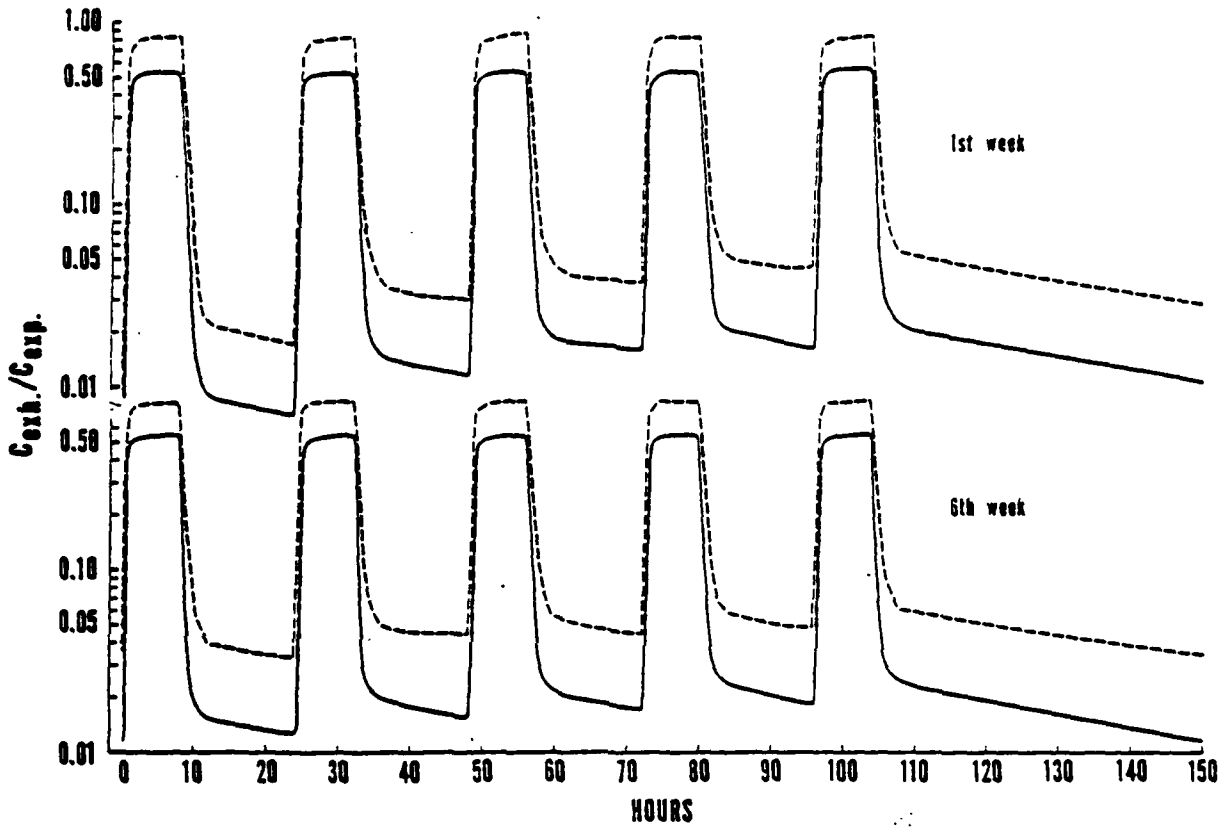


FIGURE 3

PREDICTED CONCENTRATIONS OF BENZENE IN EXHALED AIR (C_{EXH}) OF A PERSON EXPOSED TO BENZENE (8 HRS/DAY, 5 DAYS/WEEK) FOR 6 WEEKS



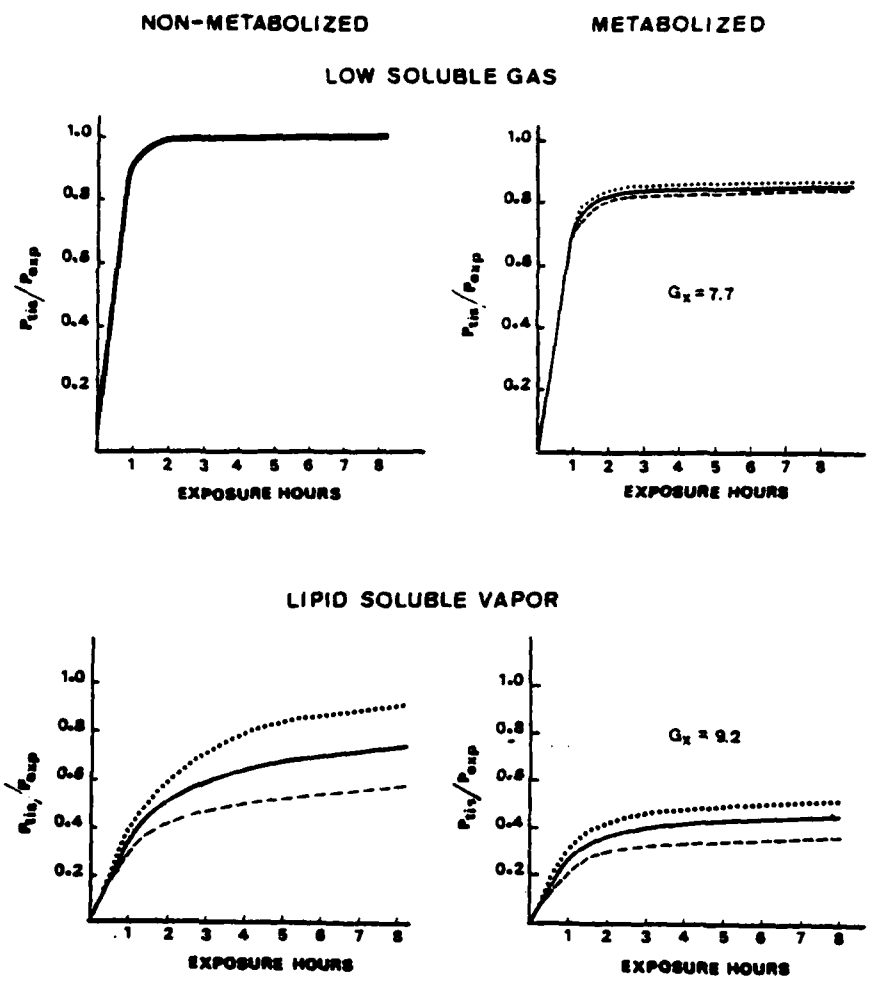
The non-broken line counts with metabolic clearance = 3.6 l/min (15, 27), the broken line represents the hypothetical situation if benzene is not metabolized.

Conclusion: Metabolism reduces benzene concentrations in exhaled air. The concentrations at the end of the week are larger than at the beginning of the week, and for five weeks, rise slightly; on the sixth week, the steady state is reached.

(Reproduced from reference 4)

FIGURE 4

EFFECT OF BODY BUILD ON EQUILIBRATION OF PARTIAL PRESSURES OF INHALED VAPORS IN BRAIN WITH EXPOSURE CONCENTRATION DURING 8-HOUR EXPOSURE



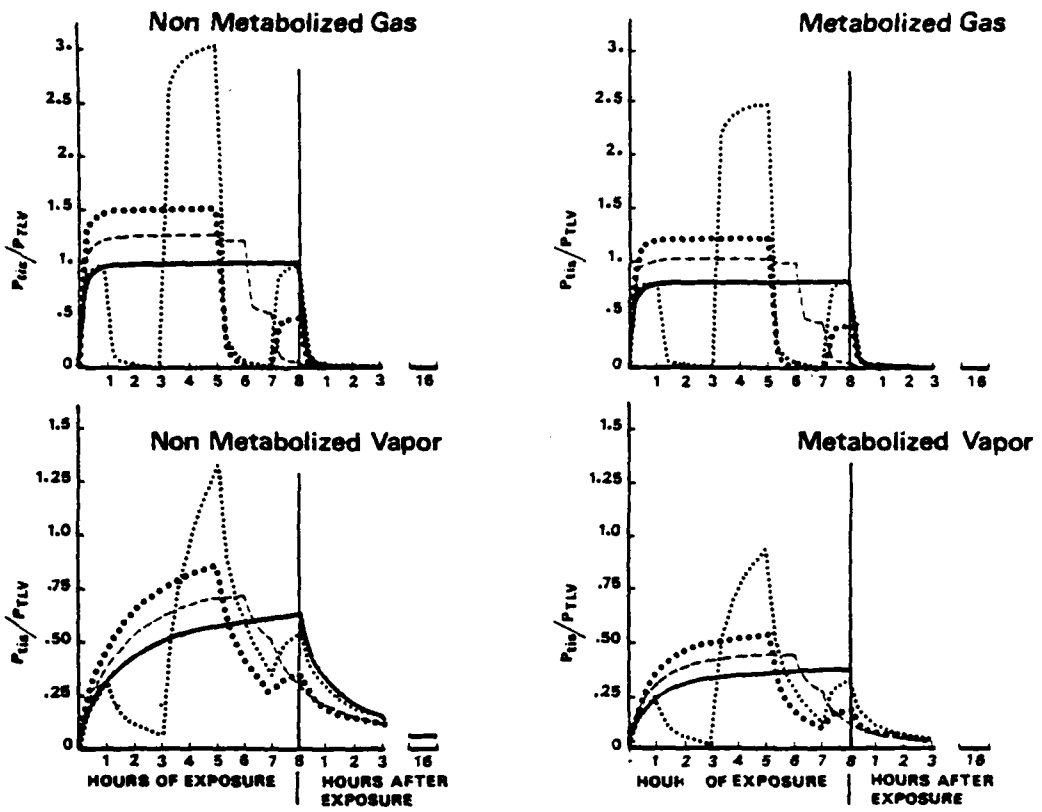
The partial pressure ratios are calculated for brain of a normal build person (solid lines), a slightly obese person (dashed lines) and a slim person (dotted lines). If the lines coincide, the broad solid line is used.

Conclusion: Partial pressure equilibration of low soluble gas in brain is rapid, and body build has no significant effect on brain concentration. Equilibration of lipid soluble vapors is slow, and concentration reached in brain of slim person is much higher than concentration in brain of obese person. If the inhaled vapor is metabolized, the brain concentrations are reduced.

(Reproduced from reference 5)

FIGURE 5

EFFECT OF FLUCTUATION OF EXPOSURE CONCENTRATION ON CONCENTRATION OF INHALED VAPORS IN BRAIN



The tissue concentrations are presented as partial pressure ratio of tissue to TVL. Solid lines represent 8-hour exposures to constant concentration (TLV). The interrupted lines represent examples of exposures with excursion factors approved by ACGIH (28): 1.25 (dashed lines), 1.5 (dark dotted lines) and 3 (light dotted lines). Excursions for each hour are as follows:

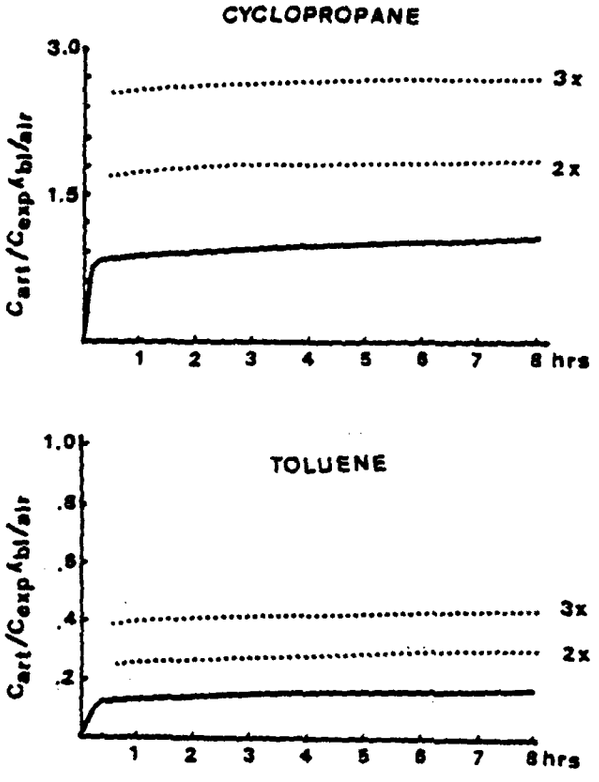
Excursion Factor	Exposure Hour							
	1st	2nd	3rd	4th	5th	6th	7th	8th
1.25	1.25	1.25	1.25	1.25	1.25	1.20	0.5	0.005
1.5	1.5	1.5	1.5	1.5	1.5	0	0	0.5
3.0	1.0	0	0	3.0	3.0	0	0	1.0

Conclusion: Brain concentrations of low soluble gas (upper graphs) fluctuate with exposure concentration. The smoothing effect of FG-compartment on brain concentrations of lipid soluble vapor is apparent in lower graphs. Metabolism diminishes concentrations reached in brain.

(Reproduced from reference 5)

FIGURE 6

EFFECT OF STEL ON CONCENTRATIONS OF CYCLOPROPANE AND TOLUENE IN ARTERIAL BLOOD

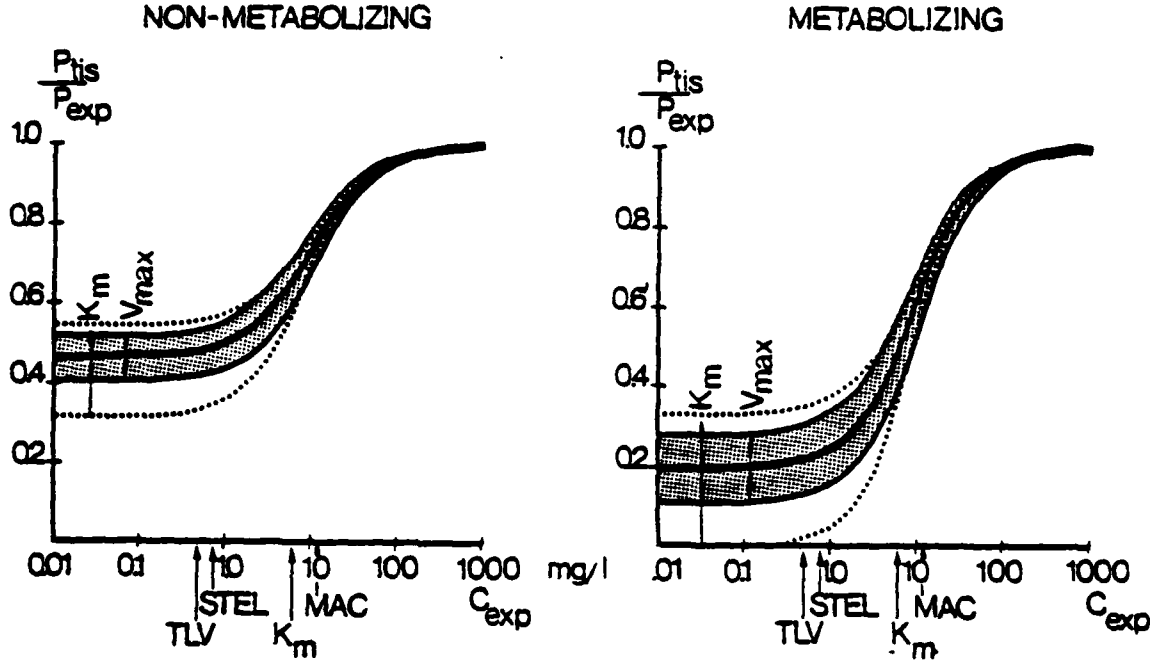


The unbroken lines represent blood concentrations during 8-hour exposure to constant concentrations of cyclopropane or toluene. The broken lines represent blood concentrations at the end of a single 15-minute excursion, with two-fold or three-fold increase of exposure concentration. The values are plotted for single excursions which happen any time during exposure.

Conclusion: The concentration increase in alveolar air (and in tissues) during short excursion is always smaller than the excursion factor (increase in exposure concentration). The increase depends on the excursion duration, excursion factor, duration of exposure prior to excursion, and physical and chemical properties of inhaled compound.

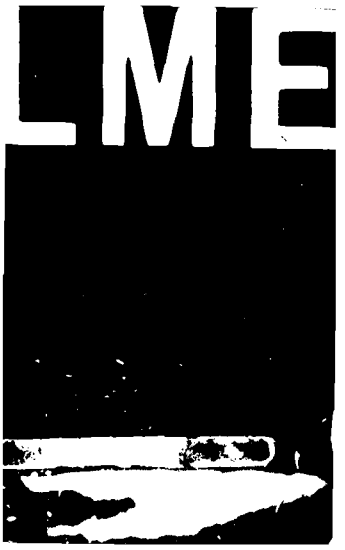
FIGURE 7

EFFECT OF CAPACITY LIMITED METABOLISM ON TRICHLOROETHYLENE CONCENTRATIONS IN NON-METABOLIZING AND METABOLIZING TISSUES DURING STEADY STATE



For Rhesus Monkey K_m = 3.17± 0.73 mg/l of alveolar air, and V_{max} = 1.1± 0.12 mg/min. (16). The trichloroethylene partial pressure ratios tissue/exposure concentrations are plotted against exposure concentrations. The curves on the left refer to alveolar air, arterial blood, and to tissues in which no metabolism of trichloroethylene occurs. The curves on the right refer to tissues and venous blood, leaving tissues in which trichloroethylene is metabolized. The middle line is calculated for K_m = 3.17 mg/l, and V_{max} = 1.1 mg/min. The shaded area demonstrates the changes caused by variation of V_{max} in range of 2 S.D. The dotted lines demonstrate the changes caused by variation of K_m in range of 2 S.D. The arrows indicate the direction of increasing V_{max} or K_m respectively. TLV and STEL refer to threshold limit concentrations (28), MAC to minimum anesthetic concentration.

Conclusion: The concentrations in non-metabolizing tissues are larger than in sites of metabolism. At low exposure concentrations, the partial pressures do not equilibrate, and $C_{tis} < C_{exp}\ \lambda_{tis/air}$. When exposure concentration approaches K_m tissue concentrations start to rise rapidly. At high exposure concentration, the ratio of tissue concentration to exposure concentration approaches the value of corresponding partition coefficient. The tissue concentrations increase with increasing K_m and decreasing V_{max}.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