Predictable "individual differences" in uptake and excretion of gases and lipid soluble vapours simulation study

VERA FISEROVA-BERGEROVA,[1] JIRI VLACH,[2] AND JANET C CASSADY[3]

From the Department of Anesthesiology,[1] *and Department of Epidemiology and Public Health,*[3] *University of Miami School of Medicine, Miami, Florida, USA, and Department of Electrical Engineering,*[2] *University of Waterloo, Waterloo, Ontario, Canada*

ABSTRACT   A five-compartment pharmacokinetic model with two excretory pathways, exhalation and metabolism, based on first order kinetics is used to outline the effect of body build, pulmonary ventilation, and lipid content in blood on uptake, distribution, and clearance of low solubility gases and lipid soluble vapours during and after exposure. The model shows the extent that individual differences have on altering uptake and distribution, with consequent changes in blood concentration, rate of excretion, and toxicity, even when variations in these parameters are within physiological ranges. The model is also used to describe the concentration variation of inhaled substances in tissues of subjects exposed to concentrations with permitted excursions. During the same course of exposure, the tissue concentrations of low solubility gases fluctuate much more than tissue concentrations of lipid soluble vapours. The fluctuation is reduced by metabolism of inhaled substance. These conclusions are recommended for consideration whenever evaluating the effect of excursions above the threshold limit values used in the control of industrial exposures (by excursion factors).

The main problem in establishing threshold limit values of airborne contaminants (TLV) and biological threshold limits (BTL) is the number of factors that affect their concentrations in the body,[1][2] the most important being:

Type of exposure—duration of exposure, concentration variations in the air, repetition of exposure, duration of resting period, work load, etc.

Time—time intervals between the onset and termination of exposure and sampling.

Individual differences among exposed subjects.

In our previous papers we presented a mathematical model verified by experimental data,[3] and used the model to outline the effect of metabolism and solubility on uptake, distribution, and exhalation of organic solvents in man;[3-7] to define the role of sampling time for data interpretation;[3] and to show the effect of metabolism and vapour solubility in blood and tissues on the accumulation of vapours in the body during chronic (continuous and interrupted)

exposure.[5] The model is a flow-limited system in which the rate constants are determined predominantly by tissue perfusion and by maximum volume of distribution of inhaled substance.[3-7] Therefore, factors such as body build, changes in ventilation caused by work load, or changes in lipid content in blood caused by food uptake, affect the fate of inhaled substances. In this study the model was used to investigate the effect of variation in body build, pulmonary ventilation, solubility in blood, duration of exposure, and excursion factor on uptake, distribution, and clearance (exhalation and metabolism) of lipid soluble vapours and low solubility gases.

Methods

MATHEMATICAL MODEL

The model used in this study has five pharmacokinetic compartments, described by a set of five first-order differential equations (A-19 to A-23 in the appendix) linear to the first approximation.

Tissues are assigned to the pharmacokinetic compartments according to perfusion, ability to metabolise the inhaled substance, and solubility of

the substance in the tissue. 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 vapour equilibrates with four peripheral compartments. Vessel-rich tissues form two peripheral compartments: BR-compartment includes brain, which lacks capability to metabolise most xenobiotics, and is treated as a separate compartment because of its biological importance and the toxic effect of many vapours and gases on the central nervous system. VRG-compartment includes tissues with sites of vapour metabolism such as liver, kidney, glands, heart, and tissues of the gastro-intestinal tract. Muscles and skin form compartment "MG", and adipose tissue and white marrow form compartment "FG". The FG-compartment is treated separately, since the dumping of lipid soluble vapours in this compartment has a smoothing effect on concentration variation in other tissues, caused by changes in exposure concentrations, minute ventilation, and exposure duration. The one-compartment model used for evaluating body burden did not describe this smoothing effect.[8-10]

Body build
Body build affects the volume of distribution. To study the effect of body build on uptake, distribution, and clearance of inhaled vapours and gases, the volumes of pharmacokinetic compartments and their perfusion were estimated for three somatotypes of body weight 70 kg: slim person (body height 185 cm), person with normal build (170 cm), and slightly obese person (150 cm). The volumes of pharmaco-kinetic compartments were related to the ratio of body fat and lean body mass, estimated from specific density (appendix, equations A-1 to A-8). The percentages of body fat (adipose tissue) calculated for the three somatotypes were 1·9%, 8·6%, and 18·8%, respectively. Minute ventilation of 10 l/min and alveolar ventilation of 6·7 l/min were assumed for a person with normal build unless otherwise specified. Alveolar ventilations and cardiac outputs for other somatotypes were adjusted in proportion to body surface area (appendix, equations A-11 to A-17).

Blood flow
Cardiac output and its distribution were adjusted to body build and work load of the subjects. The following were assumed: basal cardiac output $\dot{Q}$ is related to surface areas of somatotypes according to cardiac index (3 l/m²/min).[11] Cardiac output under working conditions $\dot{Q}_n$ is related to given alveolar ventilation with the perfusion-ventilation ratio 1·25. The increase of cardiac output does not affect per-fusion of viscera (ml/min/g), but increases perfusion of MG and FG (appendix, equations A-16 to A-17).

Ventilation
The following were assumed: inhaled (exhaled) air flows in the direction of respiratory airways in which no mixing or uptake occurs. Tidal volume, perfusion-ventilation ratio, and ventilation ratio of dead space to alveoli remain constant, dead space taking one-third of tidal volume. Under these assumptions, only two-thirds of tidal volume of room air enter the alveoli with each breath: (one-third of tidal volume is alveolar air returning in the lung from respiratory airways). To account for dead space, the alveolar ventilation $\dot{V}_{alv}$, comprising two-thirds of minute ventilation $\dot{V}$, is used in our model.

Solubility
Lipid content in blood is higher postprandially than during fasting. The effect of a meal on blood-air partition coefficients of seven lipid-soluble vapours was investigated in 10 human volunteers. Blood-air partition coefficients were determined in blood samples collected 1-2 hours and 10-15 hours after a meal. The equilibration method was used for determination of blood-air partition coefficients at 37°C.[5] To show the effect of a meal on uptake, distribution, and clearance of vapour, the extreme values of blood-air partition coefficient ($\lambda_{bl/air}$ = 7·5 or 13) were used for modelling of hypothetical lipid soluble vapour (mean $\lambda_{bl/air}$ = 10).

Metabolic clearance
Clearance by metabolism is defined in the model by the constant G_X. To determine G_X, the rate of overall metabolism is measured at the apparent steady state, when retention of inhaled substance in tissues is negligible and the rate of metabolism u_m is almost equal to the uptake rate u.[3] The uptake rate is calculated from the difference of exposure con-centration (C_{exp}) and vapour concentration in mixed exhaled air (C_{exh}) and minute ventilation $\dot{V}$.

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

Constant G_X (expressed in the same units as pulmonary ventilation) can be calculated using equation 2.

$$\frac{1}{G_X} = \frac{C_{exp}}{(C_{exp} - C_{exh})\dot{V}} - \left(\frac{1}{F_{VRG} \lambda_{bl/air}} + \frac{1}{\dot{V}_{alv}}\right) \quad (2)$$

where $\dot{V}_{alv}$ is alveolar ventilation, $\lambda_{bl/air}$ is blood-air partition coefficient at 37°C, and F_{VRG} is blood flow to VRG-compartment.

Modelling was done for two hypothetical sub-stances of different solubility (low solubility gas and

Tissue-air partition coefficients (at 37°C) used for mathematical modeling

Compound	Blood	Brain	VRG	MG	FG	G_x
Low solubility gas	0·5	0·8	0·8	0·8	0·8	7·7
Lipid soluble vapour	10	40	20	20	500	9·2

lipid soluble vapour), each being modelled as non-metabolised (inert substances, $G_X = 0$) and as extensively metabolised ($G_X = 7·7$ for gas and 9·2 for vapour). Partition coefficients and metabolic clearance G_X used in the modelling (presented in the table) were selected arbitrarily as being representative for industrial gases and vapours of organic solvents.

To evaluate the significance of different factors on body exposure the following variables were compared: (1) total uptake, (2) saturation (partial pressures equilibration) of brain, MG, and FG at the end of exposure and 24 hours after the start of exposure, (3) amount metabolised during the exposure day, (4) fraction of uptake metabolised during exposure, and (5) fractions of uptake exhaled or metabolised on the exposure day.

Results

The effect of body build and exposure duration on uptake, distribution, and clearance of four hypothetical substances (inert low solubility gas,

metabolised low solubility gas, inert lipid soluble vapour, and metabolised lipid soluble vapour) during and after one-hour, five-hour, and eight-hour exposure are presented in figs 1-4. Body build affects most profoundly concentrations and pulmonary clearance of lipid soluble vapours—namely, those

Fig 2 *Effect of body build on equilibration of partial pressures of inhaled low solubility gases in tissues with partial pressure of exposure concentration. Simulation for non-metabolised gas (upper graphs) and metabolised gas (lower graphs). Partial pressure ratios are calculated for brain, MG, and FG of a person with normal build (solid lines, $\dot{V}_{alv} = 6·7$ l/min), a slightly obese person (dashed lines), and a slim person (dotted lines). If lines coincide the broad line is used.*
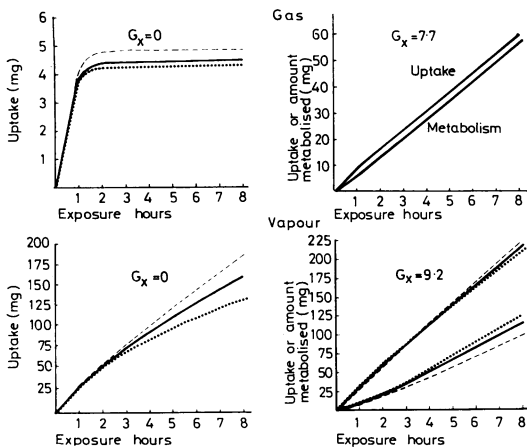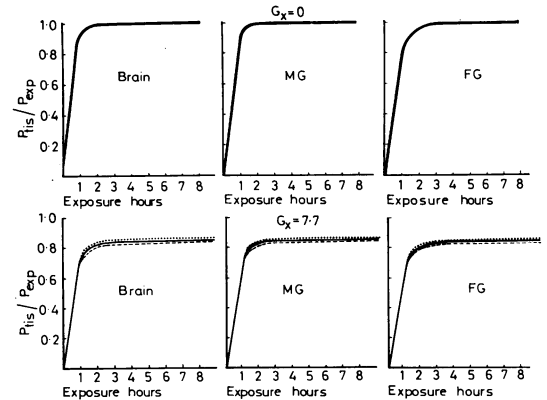
Fig 1 *Effect of body build on uptake and metabolism of low solubility gases (upper graphs) and lipid soluble vapours (lower graphs) during an eight-hour exposure to concentration 100 μg/l. Cumulative uptakes and amounts metabolised (mg) are calculated for a person with normal build (solid lines, $\dot{V}_{alv} = 6·7$ l/min), a slightly obese person (dashed lines), and a slim person (dotted lines). If lines coincide the broad solid line is used.*
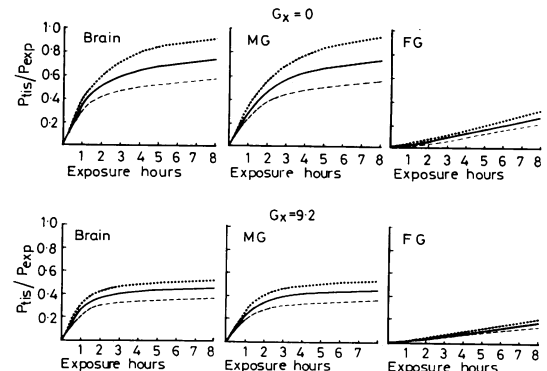
Fig 3 *Effect of body build on equilibration of partial pressures of inhaled lipid soluble vapours in tissues with partial pressure of exposure concentration. Simulation for non-metabolised vapour (upper graphs) and metabolised vapour (lower graphs). Partial pressure ratios are calculated for brain, MG, and FG of a person with normal build (solid lines, $\dot{V}_{alv} = 6·7$ l/min), a slightly obese person (dashed lines), and a slim person (dotted lines).*
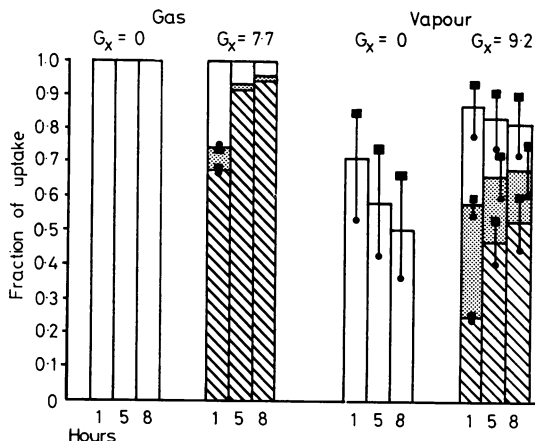
Fig 4 *Effect of body build on clearance of low solubility gases and lipid soluble vapours after one-hour, five-hour, and eight-hour exposures. Bars represent fractions of uptake exhaled on exposure day (open areas), metabolised during exposure (diagonally striped areas), and metabolised after exposure on exposure day (dotted areas). Bars are calculated for a person with normal build ($\dot{V}_{alv} = 6\cdot7$ l/min). Effect of body build is shown by lines drawn between values calculated for a slightly obese person (●) and a slim person (■). If effect is smaller than half per cent of value for a normal person, effect of body build is not shown.*

Fig 5 *Postprandial and fasting effects on blood-air coefficients of lipid soluble vapours. Intersections of crossed lines represent means of respective blood-air partition coefficients at 37°C (n = 5) for enflurane (E), halothane (H), methylene chloride (M), benzene (B), trichloroethylene (TRI), toluene (T), and methoxyfluorane (MOF). Crossed lines define standard deviations and diamonds the standard errors of means. Line (y = 0·61x + 0·246) is a regression defined by optimum fit to means, calculated by method of least squares.*

which are not metabolised. When exposed to the same concentration, obese people have smaller tissue concentrations of these vapours than thin persons (fig 3), and thin people have faster pulmonary clearance than obese people (fig 4).

The effect of changes of blood-air partition coefficient on uptake was studied by modelling eight-hour exposures to hypothetical lipid soluble vapours. The blood-air partition coefficients measured in samples collected after a meal are greater than in those collected after fasting (fig 5). As shown in fig 5, the blood air partition coefficient of hypothetical lipid soluble vapour can vary from 7·5 to 13 (mean $\lambda_{bl/air}$ = 10). Variation of blood-air partition coefficient in this range affects uptake of such vapour by less than 10% and slightly affects vapour distribution in tissues (fig 6).

The effect of alveolar ventilation and cardiac output on uptake, distribution, and clearance of gases and vapours was studied for alveolar ventilations 5·2, 6·7, and 10 l/min (for a person with normal build). A positive relation exists between alveolar ventilation and equilibration rate. Apparent steady state (defined as 95% of the steady-state partial pressure in the FG-compartment) is reached
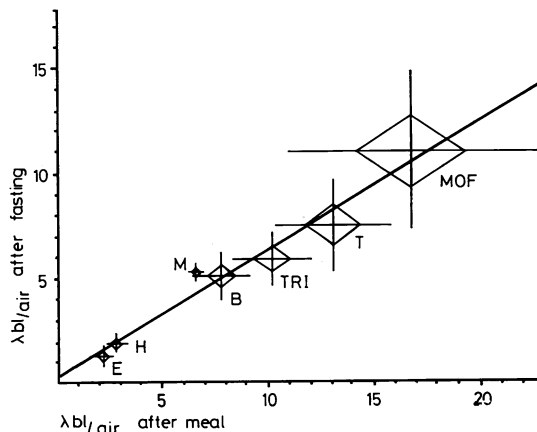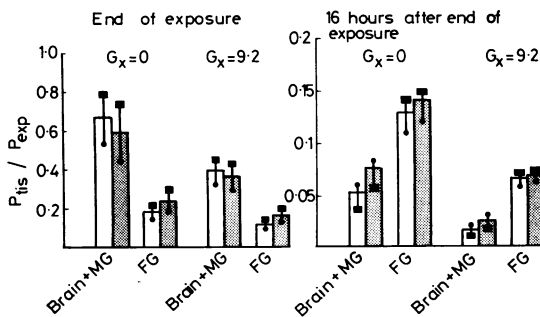

Fig 6 *Effect of blood-gas partition coefficient on equilibration of partial pressures of inhaled lipid soluble vapour in tissues with partial pressure of exposure concentration. Bars represent partial pressures ratios calculated for a person with normal build ($\dot{V}_{alv} = 6\cdot7$ l/min) at end of an eight-hour exposure and at end of exposure day for vapour with blood-air partition coefficients 7·5 (open bars) and 13 (dotted bars). Tissues-air partition coefficients are in table. Effect of body build is shown by lines drawn between values calculated for a slightly obese person (●) and a slim person (■).*
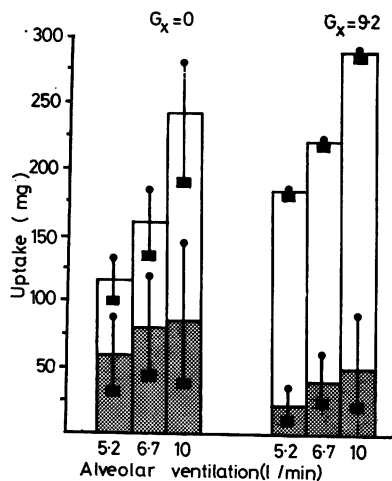
Fig 7 *Effect of alveolar ventilation on uptake of lipid soluble vapour. Bars represent uptakes (mg) by a person with normal build during an eight-hour exposure to concentration 100 µg/l. Dotted areas represent amounts (mg) of unchanged vapour remaining in body at end of exposure day. Effect of body build is shown by lines, drawn between values calculated for a slightly obese person (●) and a slim person (■).*
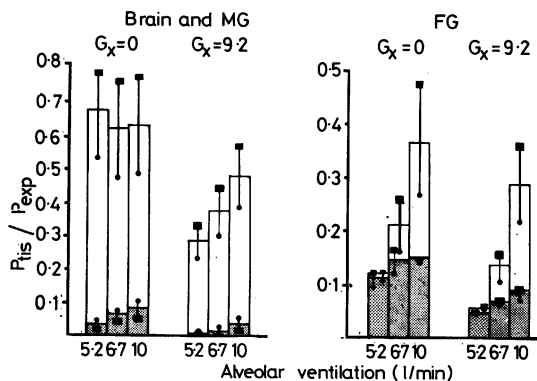

Fig 8 *Effect of alveolar ventilation on equilibration of partial pressures of inhaled lipid soluble vapour in tissues with partial pressure of exposure concentration. Bars represent the partial pressure ratios calculated for a person with normal build at end of an eight-hour exposure and at end of exposure day (dotted areas). Effect of body build is shown by lines drawn between values calculated for a slightly obese person (●) and a slim person (■).*
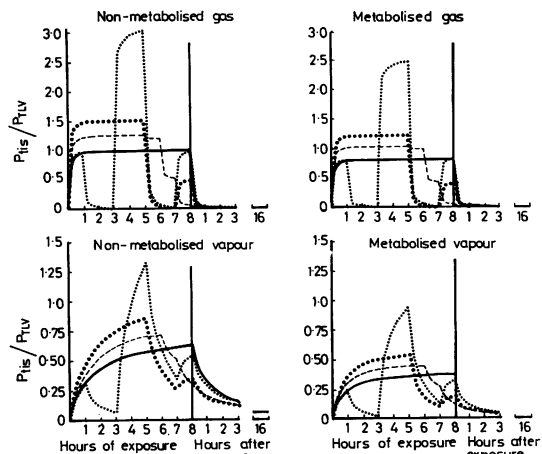

Fig 9 *Effect of fluctuation of exposure concentration on concentrations of inhaled low solubility gases and lipid soluble vapours in brain. Partial pressure ratios of gas or vapour concentrations in tissue to partial pressure of the time-weighted average exposure concentration (TLV) for a normal person ($\dot{V}_{alv} = 6.7$ l/min). Solid lines represent eight-hour exposures to constant concentration (TLV). Interrupted lines represent examples of exposures when concentrations vary around TLV, using excursion factors 1·25 (dashed lines), 1·5 (dark dotted lines), and 3 (light dotted lines). Exposure concentrations are expressed as multiple of TLV ($C_{exp} = f$ TLV). fs for each hour are:*

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

for the studied low solubility gas within four hours, two hours, and one hour, respectively, for each alveolar ventilation. In steady state the partial pressure ratios of inert gas in tissues and air equal one. For the studied metabolised gas, the partial pressure ratios at steady state are 0·75, 0·82, and 0·88 respectively, for each alveolar ventilation, and uptake and amount metabolised increase about 3·8% by increasing alveolar ventilation by 1 l/min. Uptake of lipid soluble vapour is greatly enhanced by increasing alveolar ventilation (fig 7). Vapour concentrations in all tissues during exposure, as well as during the desaturation period, are positively related to alveolar ventilation (fig 8).

The effect of concentration variations during industrial exposure on uptake, distribution, and clearance was studied for hypothetical substances using
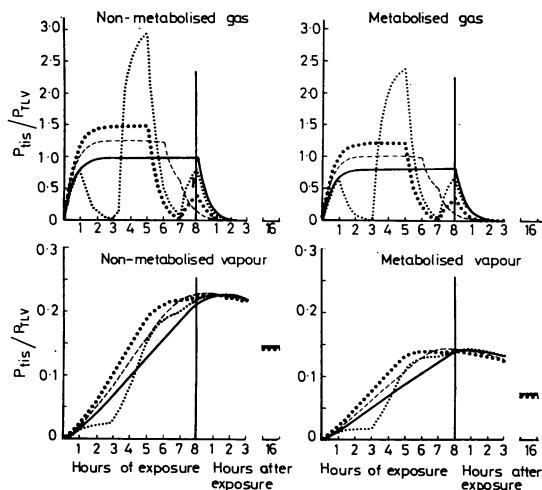
Fig 10 *Effect of fluctuation of exposure concentrations on concentration of inhaled low solubility gases and lipid soluble vapours in adipose tissue.*
For legend, see fig 9.

the excursion factors 3, 1·5, and 1·25 respectively.[12] All variables change proportionally to the mean concentration, but the concentration fluctuation, excursion factor, significantly affects only vapour concentrations in tissues. In figs 9 and 10 the partial pressures in brain and FG-compartments during the eight-hour exposure to constant concentration are compared with partial pressures during exposure to variable concentrations having the same time-weight concentration. Concentrations in tissues reflect the concentration variations in room air. The concentration variation in brain is greater than in FG. The variation in all tissues is greater during exposure to low solubility gas than to lipid soluble vapour, and greater during exposure to inert substances than to substances undergoing metabolism. The concentration fluctuation did not affect the substance concentration in blood and in alveolar air at the end of exposure day.

Discussion

A compartmentalised model based on first-order kinetics has been developed to program the uptake, distribution, and clearance of inhaled vapours.[3 13–16] It is assumed that the inhaled substance does not react with blood components or affect blood flow, and that pulmonary washout and metabolism are the only excretory pathways. Conclusions do not reflect alterations in blood flow distribution and ventilation due to such factors as pathological

changes, physical load on specific muscles, posture, heat, and effect of inhaled substance. Although simplifying the actual situation, the model makes possible predictions that are consistent with experimental data.[3–7 17] Constants for the model may be derived from easily estimated variables, making the model suitable for predicting the role of various factors in uptake, distribution, clearance, and related toxicity of inhaled substances. Previous models for occupational exposure determined rate constants of metabolic clearance from slopes of excretion of metabolites or exhalation of the parent substance.[17–20] The slopes are affected by various factors such as exposure duration, concentration variation, redistribution, binding, and renal clearance of metabolites. The proposed determination of metabolic clearance from pulmonary uptake has an advantage over the previous method in that the effects of distribution, binding, and renal clearance are by-passed.

Although the model used in this study has five pharmacokinetic compartments, partial pressures or concentrations are reported for only three compartments—brain, muscle, and fat. The central compartment values are not reported because, after about 30 minutes of exposure, they are almost identical to brain values. VRG-compartment partial pressures are not reported because, for inert substances, VRG-values are identical to brain values, and if the substance is metabolised the partial pressure in tissue is negatively related to tissue capability to metabolise the substance. Since only the rate of overall metabolism may be determined by the non-invasive method,[21] G_X was calculated on the assumption that all tissues of VRG-compartment participate equally in metabolism. Although this assumption made the prediction possible, information on substance distribution in tissues of VRG is irrelevant.

In this study the effect of three physiological variables on the pharmacokinetic data of both inert and metabolised substances was investigated. Differences in somatotype and changes in alveolar ventilation and cardiac output affected pharmacokinetic data to the extent of observed individual differences in vapour concentrations in blood, rate of clearance, and toxic reaction to vapour exposure. Body build greatly affects the maximum volume of distribution (defined by equation A-9 in appendix). Pulmonary ventilation, tissue perfusion, and blood-air partition coefficients affect the transportation rate of substance from the environment to tissues and vice versa (defined by equation A-18 in appendix). The increased uptake observed in individuals subjected to the work load during short-term exposure[22 23] is explained by such

increased transportation rate and retention rate of avpours in MG and FG compartments (fig 8). The work load has no effect on uptake or body burden, once the steady state is reached.

The changes of blood-air partition coefficients in the range caused by food uptake had no significant effect on the fate of inhaled substance. According to the simulation, uptake during postprandial exposure is greater than during fasting, deposition in fat being enhanced but deposition in lean tissues (and with it related availability for biotrans-formation) being lowered, due to changes in tissue-blood partition coefficients (fig 6).

Simulation by our model shows that the exposure duration has a striking effect on the ratio of fractions of uptake exhaled and metabolised (fig 4). This agrees with experimental data. For example, Teisinger *et al*[24] recovered one-third of uptake in exhaled air after a two-hour benzene exposure, while Teisinger *et al*[25] recovered only 16% of uptake in exhaled air after a five-hour benzene exposure. Our simulation showed exhaled fractions of 30% and 16% respectively.

Equilibration of partial pressures of low solubility gases is much faster than of lipid soluble vapours, and is prevented by metabolism. Accordingly, the concentration variation in room air during exposure to gases causes a greater concentration variation in tissues than does exposure to lipid soluble vapours. (Note that when excursion factor 3 is used for two hours (figs 9 and 10) the partial pressures of inert lipid soluble vapour in tissues did not equilibrate with mean exposure concentration, but the partial pressures of inert gas in tissues temporarily exceeded three times the partial pressure of corresponding mean exposure concentration-TLV.) The variation is always diminished if the substance is metabolised. Since toxic effect is related to concentration in tissue, the feasibility of considering solubility (or other storage mechanisms) in establishing excursion factors should be explored.

Appendix

Volumes and perfusions of pharmacokinetic compartments were calculated by the following equations:[11] [13] [26]
Specific gravity SG is obtained from body weight BW in kilograms and body height BH in centimetres:

$$\log_{10} SG = 0.848 \ [0.242 \log_{10} BH - 0.1 \ (3 + \log_{10} BW) - 0.0172] \quad \text{(A-1)}$$

The percentage of body fat:

$$BF = \frac{420.1}{SG} - 381.3 \quad \text{(A-2)}$$

Total body volume:

$$TBV = \frac{BW}{SG} \quad \text{(A-3)}$$

Body volume after subtraction of adipose tissue:

$$BV = TBV \ (1 - 0.01 \ BF) \quad \text{(A-4)}$$

Volumes of peripheral compartments are given by

$$V_{VRG} = 0.081 \ BV \quad \text{(A-5)}$$
$$V_{BR} = 0.025 \ BV \quad \text{(A-6)}$$
$$V_{MG} = 0.58 \ BV \quad \text{(A-7)}$$

$$V_{FG} = BV \left(\frac{BF}{92} + 0.055 \right) \quad \text{(A-8)}$$

where the subscripts are related to pharmacokinetic compartments as described in the text.

The maximum volumes of distribution C of peripheral compartments are determined by volumes of compartments and tissue-air partition coefficients:

$$C_i = V_i \ \lambda_i \quad \text{(A-9)}$$

where "i" represents the various subscripts of V in (A-5)-(A-8) and the appropriate tissue-air partition coefficient λ at 37°C.

The maximum volume of distribution of the central compartment C_{LG} is determined by volumes of lung tissue V_{lung} and arterial blood V_{bl}, by function residual capacity of the lung and by appropriate partition coefficients:

$$C_{LG} = V_{lung} \ \lambda_{lung/air} + FRC + V_{bl} \ \lambda_{bl/air} \quad \text{(A-10)}$$

Surface area of body:

$$SA = 0.0072 \ BW^{0.425} \ BH^{0.725} \quad \text{(A-11)}$$

Basal cardiac output:

$$\dot{Q} = 3 \ SA \quad \text{(A-12)}$$

Cardiac output under normal conditions $\dot{Q}_n$ is related to alveolar ventilation $\dot{V}_{alv}$ in litres per minute:

$$\dot{Q}_n = 1.25 \ \dot{V}_{alv} \quad \text{(A-13)}$$

Blood flows in peripheral compartments are determined by

$$F_{VRG} = 0.75 \ V_{VRG} \quad \text{(A-14)}$$

$$F_{BR} = 0.53 \ V_{BR} \quad \text{(A-15)}$$

$$F_{MG} = \frac{0.033V_{MG} + (\dot{Q}_n - \dot{Q}) \ 0.033V_{MG}}{0.033V_{MG} + 0.022V_{FG}} \quad \text{(A-16)}$$

$$F_{FG} = \frac{0.022V_{FG} + (\dot{Q}_n - \dot{Q}) \ 0.022V_{FG}}{0.033V_{MG} + 0.022V_{FG}} \quad \text{(A-17)}$$

and the transportation rates of inhaled vapour from the lung to the compartments G_i are calculated by multiplying blood flows by blood-air partition coefficient at 37°C:

$$G_i = F_i \, \lambda_{bl/air} \qquad (A\text{-}18)$$

The uptake and clearance are described by the following system of differential equations:

$$\left(\dot{V}_{alv} + G_{VRG} + G_{BR} + G_{MG} + G_{FG} + C_{LG}\frac{d}{dt} \right) E_{LG}$$

$$- G_{VRG} \, E_{VRG} \; - G_{BR} \, E_{BR} \; - G_{MG} \, E_{MG}$$
$$- G_{FG} \, E_{FG} \; = \; C_{room} \, \dot{V}_{alv} \qquad (A\text{-}19)$$

$$- G_{VRG} \, E_{LG} + \left(G_{VRG} + G_X + C_{VRG}\frac{d}{dt} \right) E_{VRG}$$
$$= 0 \; (A\text{-}20)$$

$$- G_{BR} \, E_{LG} + \left(G_{BR} + C_{BR}\frac{d}{dt} \right) E_{BR} = 0 \; (A\text{-}21)$$

$$- G_{MG} \, E_{LG} + \left(G_{MG} + C_{MG}\frac{d}{dt} \right) E_{MG} = 0 \; (A\text{-}22)$$

$$- G_{FG} \, E_{LG} + \left(G_{FG} + C_{FG}\frac{d}{dt} \right) E_{FG} = 0 \; (A\text{-}23)$$

where Es are instantaneous partial pressures of inhaled vapour in compartments (or vapour concentration divided by appropriate tissue-air partition coefficients), G_X is determined by equations 1 and 2 in text, and C_{room} equals exposure concentration C_{exp} during exposure and equals zero after cessation of exposure.

The mathematical solution was described previously.[3] Calculation was done by Univac 1100/20 computer.

References

[1] Stokinger HE. Rationale for the use of biologic threshold limits in the control of worker exposure. *Proceedings of the 3rd Annual Conference on Environmental Toxicology.* Ohio: Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, 1972:5-26. (AMRL-TR-72-130.)

[2] Astrand J, Gamberale F. Effects on humans of solvents in inspiratory air: method for estimation of uptake. *Environ Res* 1978;15:1-4.

[3] Fiserova-Bergerova V, Vlach J, Singhal K. Simulation and prediction of uptake, distribution, and exhalation of organic solvents. *Br J Ind Med* 1974;31:45-62.

[4] Fiserova-Bergerova V. Modeling of chronic toxicity. *Proceedings of the 6th Annual Conference on Environmental Toxicology.* Ohio: Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, 1975: 175-91. (AMRL-TR-75-125.)

[5] Fiserova-Bergerova V. *Biological-mathematical modeling of chronic toxicity.* Ohio: Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, 1975: 1-124. (Toxic Hazards Research Unit Annual Technical Report AMRL-TR-75-5.)

[6] Fiserova-Bergerova V. Simulation of uptake, distribution, metabolism, and excretion of lipid soluble solvents in man. *Proceedings of the 3rd Conference on Environmental Toxicology.* Ohio: Aerospace Medical Research Laboratory Wright-Patterson Air Force Base, 1972:53-69. (AMRL-TR-72-130.)

[7] Fiserova-Bergerova V. Mathematical modelling of inhalation exposure. *J Combustion Toxicol* 1976;3:201-10.

[8] Droz PO, Fernandez JG. Effect of physical workload on retention and metabolism of inhaled organic solvents. A comparative theoretical approach and its application with regards to exposure monitoring. *Int Arch Occup Environ Health* 1977;38:231-46.

[9] Roach SA. A most rational basis for air sampling programmes. *Ann Occup Hyg* 1977;20:65-84.

[10] Hickey JLS, Reist PC. Application of occupational exposure limits to unusual work schedules. *Am Ind Hyg Assoc J* 1977;38:613-21.

[11] Burton AC. *Physiology and Biophysics of the Circulation.* Chicago: Year Book Medical Publisher, 1965:164.

[12] *Threshold Limit Values of Airborne Contaminants.* American Conference of Governmental Industrial Hygienists, 1976.

[13] Eger EI. Mathematical model of uptake and distribution. In: Papper EM, Kitz RJ, eds. *Uptake and Distribution of Anesthetic Agents.* New York: McGraw-Hill, 1963: 72-103.

[14] Mapleson WW. Quantitative prediction of anesthetic concentrations. In: Papper EM, Kitz RJ, eds. *Uptake and Distribution of Anesthetic Agents.* New York: McGraw-Hill, 1963:104-19.

[15] Severinghaus JW. Role of lung factors. In: Papper EM, Kitz RJ, eds. *Uptake and Distribution of Anesthetic Agents.* New York: McGraw-Hill, 1963:9-71.

[16] Fiserova-Bergerova V, Cettl L. Electric model for the absorption, metabolism and excretion of benzene in man. *Pracovni Lekarstvi* 1972;24:56-61.

[17] Fernandez JG, Droz PO, Humbert BE, Caperos JR. Trichloroethylene exposure—simulation of uptake, excretion, and metabolism using a mathematical model. *Br J Ind Med* 1977;34:43-55.

[18] Piotrowski J. *The Application of Metabolic and Excretion Kinetics to Problems of Industrial Toxicology.* US Government Printing Office, 1971:276-382.

[19] Sato A, Nakajima T, Fujiwara Y, Hirosawa K. Pharmacokinetics of benzene and toluene. *Int Arch Arbeitsmed* 1974;33:169-82.

[20] Mason J, Dershin H. Limits to occupational exposure in chemical environments under novel work schedules. *J Occup Med* 1976;18:603-6.

[21] Teisinger J, Soucek B. Significance of metabolism of toxic gases for their absorption and elimination by man. *Cas Lek Cesk* 1952;91:1372-5.

[22] Zenz C, Berg BA. The influence of submaximal work on solvent uptake. *J Occup Med* 1970;12:367-9.

[23] DiVincenzo GD, Yanno FJ, Astill BD. Human and canine exposures to methylene chloride vapour. *Am Ind Hyg Assoc J* 1972:125-35.

[24] Teisinger J, Srbova J, Skramovsky S. Uptake and excretion of benzene in man. *Pracovni Lekarstvi* 1949;1:1-8.

[25] Teisinger J, Fiserova-Bergerova V, Kudrna J. Metabolism of benzene in man. *Pracovni Lekarstvi* 1952;4:175-88.

[26] Consolazio CF, Johnson RE, Pecosa LJ. *Physiological measurements of metabolic functions in man.* New York: McGraw-Hill, 1969:258-308.