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MODELLING OF RESPIRATORY EXCHANGE OF POLAR SOLVENTS*

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Abstract—Physiologically based pharmacokinetic (pbpk) models are frequently used to describe the kinetics of inhaled gases and vapours. In these models the conducting airways of the respiratory tract are generally assumed to act as inert tubes. The function of the inert tubes is merely to conduct the vapour to the alveolar regions where the actual exchange between ambient air and body takes place. Such an 'inert tube' model may be adequate to describe the inhalation and exhalation kinetics of inert vapours, for example non-polar solvents which have a low water solubility. Experimental data suggest, however, that the 'inert tube' model may be erroneous for polar solvents which have a high water solubility. To explore this possibility further a tentative pbpk model was developed. Model structure and parameters were obtained from the literature on lung anatomy and physiology and by visual fitting to experimental acetone, carbon dioxide, diethyl ether and ethanol data. The model was written and solved by spreadsheet programming on a personal computer. Simulations were carried out to illustrate the difference between end-exhaled and alveolar air and how water solubility and workload influence the uptake and excretion kinetics of polar solvents. It is concluded that the model is valuable for predicting the lung kinetics of polar vapours under various circumstances. It may therefore be useful in the development of biological monitoring methods based on breath sampling and help us to understand and to explain experimental data.

NOMENCLATURE

pbpk	physiologically based pharmacokinetic (model)
Symbols	
C	concentration
D	diffusion constant
F	transfer or clearance term
λ	partition coefficient
L	length (of tube)
M	molecular weight
P	pressure or partial pressure
Q	flow
T	absolute temperature
V	volume
Subscripts	
alv	alveolar air
b/a	blood/air
c	central compartment
end	end-exhaled air
i	index of region
in	air entering tube
out	air leaving tube
p	peripheral compartment
pulm	pulmonary air
sys	systemic circulation
w/a	water/air

*Paper based on a presentation made at the International Workshop on Pharmacokinetic Modelling in Occupational Health, Leysin, Switzerland, in March 1990.

INTRODUCTION

THE respiratory exchange of gases and vapours only slightly soluble in water has been extensively described (see for example FISEROVA-BERGEROVA, 1983a), and is comparatively well known. Commonly used physiologically based pharmacokinetic (pbpk) models consider the conducting regions of the respiratory tract as inert tubes used for the transport of the substance while the actual exchange with the body takes place in the alveolar region (respiratory bronchioles, alveolar ducts and alveoli). While such models can accurately describe the lung kinetics of substances only slightly soluble in water (i.e. those with low water:air partition coefficients, $\lambda_{w/a}$), such as anaesthetic gases and many non-polar solvents, they may not be applicable to highly water-soluble substances such as alcohols and ketones.

Published data on the relative respiratory uptake of some polar organic solvents were collected and plotted against reported blood:air partition coefficients ($\lambda_{b/a}$) in Fig. 1 (generally there is a strong correlation between $\lambda_{w/a}$ and $\lambda_{b/a}$ of polar solvents, owing to the high water content of blood, and either can be used). There appears to be no clearcut relationship between the relative respiratory uptake of the solvent vapours and their blood solubility. On the other hand, especially for acetone, there are marked differences in observed relative uptake values between investigators. These differences may be due to methodological factors but may also be due, at least in part, to physiological factors such as differences in pulmonary ventilation, nose or mouth breathing, breathing frequency and breathing pattern.

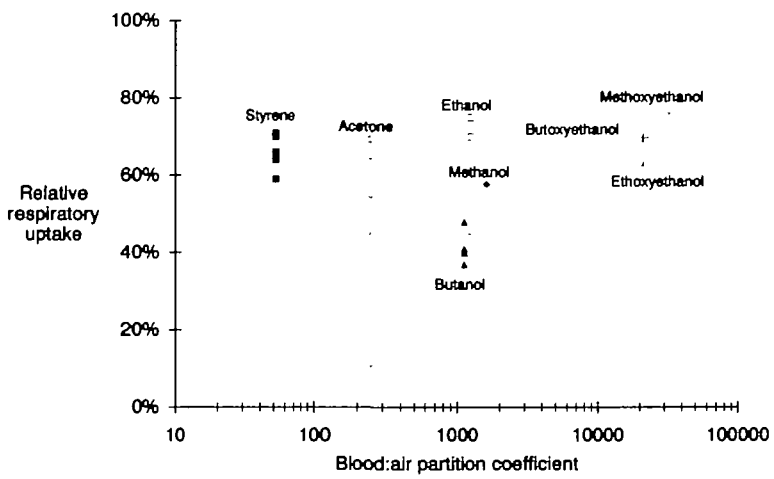

FIG. 1. Experimentally observed relative respiratory uptake of some polar solvents in relation to their blood solubility. Uptake data and $\lambda_{b/a}$ values were collected from the following sources. *Acetone:* IMBRIANI *et al.* (1985); LANDAHL and HERRMANN (1950); NOMIYAMA and NOMIYAMA (1974); SATO and NAKAJIMA (1979); TERAMOTO *et al.* (1987); WIGAEUS *et al.* (1981). *Butanol:* LINDQVIST (1977); ÅSTRAND *et al.* (1976). *Butoxyethanol:* JOHANSON (1984); JOHANSON and DYNESIUS (1988); JOHANSON *et al.* (1986). *Ethanol:* FISEROVA-BERGEROVA and DIAZ (1986); LANDAHL and HERRMANN (1950). *Ethoxyethanol:* GROESENEKEN *et al.* (1986); JOHANSON and DYNESIUS (1988). *Methanol:* FISEROVA-BERGEROVA and DIAZ (1986); SEDIVEC *et al.* (1981). *Methoxyethanol:* GROESENEKEN *et al.* (1989); JOHANSON and DYNESIUS (1988). *Styrene:* ENGSTRÖM *et al.* (1978), SATO and NAKAJIMA (1979), WIGAEUS *et al.* (1983).

Polar solvents are highly soluble in water and in blood, i.e. the coefficients $\lambda_{w/a}$ and $\lambda_{b/a}$ are high. In addition, they are in general fairly rapidly metabolized. Thus, during exposure the respiratory uptake of highly blood-soluble vapours is limited by ventilation and not by cardiac output. In other words, the blood is far from saturated with respect to solvent and practically all solvent vapour that reaches the alveolar region is removed by the blood. Hence, assuming that the conducting airways behave as inert tubes, the relative respiratory uptake should be equal to the ratio of alveolar to pulmonary ventilation. This ratio changes with the level of physical exercise, as alveolar ventilation increases faster than pulmonary ventilation with increased work loads. Some of the uptake data displayed in Fig. 1 are plotted according to the level of physical exercise in Fig. 2. Three of the eight solvents (butoxyethanol, ethoxyethanol and styrene) for

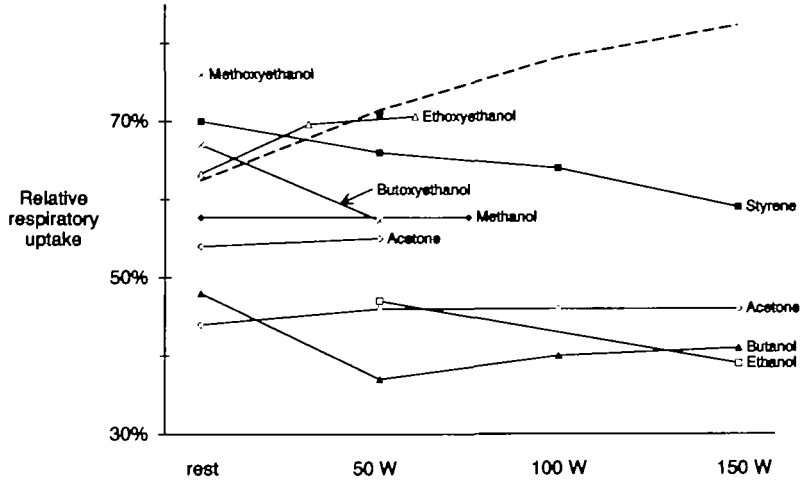

FIG. 2. The relation between physical exercise and relative respiratory uptake of some polar solvents. The uptake data for acetone were taken from IMBRIANI *et al.* (1985) and WIGAEUS *et al.* (1981). The sources for the other solvents are given in Fig. 1. The broken line represents the ratio of alveolar to pulmonary ventilation ('inert tube' model). Ventilation values are from MALMBERG *et al.* (1987).

which data were found have relative uptake values corresponding approximately to that expected from the 'inert tube' model. Methoxyethanol (data for rest only) has a higher uptake value while the remaining four solvents have lower values. Only the relative uptake of ethoxyethanol increases according to what is expected from the 'inert tube' model, while that of the other solvents remains unchanged or decreases with increased workload. The relative uptake of styrene was measured during four consecutive 30-min intervals with increased workload. Styrene has a relatively low $\lambda_{b/a}$ of 51.9 (SATO and NAKAJIMA, 1979). Hence, with time the build-up of styrene in blood will reduce the relative respiratory uptake. However, this is not a likely explanation for the more polar solvents. The lower than expected relative respiratory uptake of polar solvents has been explained [see for example FISEROVA-BERGEROVA (1983b); JOHANSON *et al.* (1986); SCHRICKER *et al.* (1985); WIGAEUS *et al.* (1981, 1983); and ÅSTRAND *et al.* (1976)] as follows: during inhalation the polar solvent vapour is partly adsorbed by, or dissolves in, the surface of the respiratory epithelium and during exhalation it is desorbed back into the air. In consequence, the amount of solvent vapour that reaches

the alveoli is reduced and the relative respiratory uptake decreased. Although this so-called washin–washout effect has been proposed by several authors it has been experimentally studied only to a limited extent (e.g. by LANDAHL and HERRMANN, 1950; MORRIS and CAVANAGH, 1986; SCHRICKER *et al.*, 1985) and there appears to be no model which describes the phenomenon quantitatively.

The aim of this study was to develop a tentative pbpk model which describes the lung kinetics of inhaled organic solvents in man. The suggested model describes the adsorption of solvent in the respiratory epithelium of the airways during inhalation and the desorption during exhalation taking into account the anatomy and physiology of the lung, breathing frequency, pulmonary ventilation, cardiac output, and the $\lambda_{w/a}$ and $\lambda_{b/a}$ values of the solvent in question.

PHYSICAL AND ANATOMICAL CONSIDERATIONS

The conducting airways may be considered as a set of tubes of cylindrical shape. If air containing a foreign gas, for example solvent vapour, is inhaled (or exhaled) some of the molecules will hit the walls in each of these tubes as a result of radial diffusion. The penetration, i.e. the amount or concentration of foreign gas molecules that will pass a tube without hitting the wall divided by the amount that entered the tube (C_{out}/C_{in}), is a function of the diffusion constant (D), the length of the tube (L) and the air flow (Q) through the tube. The relationship, as given by DAVIES (1985), is:

$$C_{out}/C_{in} = f[\pi \cdot D \cdot L/(4 \cdot Q)]. \quad (1)$$

The diffusion constant (D) of the gas may either be determined experimentally or calculated by the formula given by DAVIES (1985):

$$D = 0.0043 \cdot T^{3/2} \cdot (1/M_{gas} + 1/M_{air})^{1/2}/[(V_{gas}^{1/3} + V_{air}^{1/3})^{1/2} \cdot P], \quad (2)$$

where T is the absolute temperature, M_{gas} the molecular weight in grammes of the gas, M_{air} that of air (28.8), V_{gas} the molar volume in ml of gas, V_{air} that of air (29.9) and P the pressure in atmospheres. According to Equation (2) the value of D for a typical solvent vapour is about 0.1 $cm^2\ s^{-1}$.

Experimentally determined values of C_{out}/C_{in} are tabulated in the work by DAVIES (1985) for plug flow and for viscous flow, both of which probably occur to various extents in different parts of the lung. Depending on the type of flow the penetration of the gas will differ somewhat. For convenience, viscous flow was assumed in all regions of the lung model.

Moving downwards from the trachea (nose and mouth are excluded in this tentative model) the airways are characterized by increased branching, increased cross-sectional area, lower air velocity and increased surface area to volume ratio. Dimensions and cross-sectional areas relevant to the anatomy of the human lung derived from the literature, are given in Table 1. Interpolation of the tabulated values of the function given in Equation (1) on the different anatomical levels indicates that several per cent of inhaled solvent vapour will hit the wall surface, and thus be able to partition between air and mucus, even in the uppermost regions of the respiratory tree (Fig. 3). The percentage increases as the vapour moves further down in the respiratory tree and practically 100% of the solvent molecules will have wall contact in the bronchioles and lower regions. Hence, a large fraction of inhaled, and exhaled, vapours

TABLE 1. ANATOMICAL FEATURES OF THE RESPIRATORY TRACT USED IN THE MODEL. THE DATA ARE ADAPTED FROM BOUHUYS (1974). AREAS AND VOLUMES WERE COMPUTED ASSUMING CYLINDRICAL SHAPES, EXCEPT FOR THE ALVEOLI, WHERE SPHERICAL SHAPE WAS ASSUMED. THE NUMBERS IN THE TABLE ARE ROUNDED OFF

Generation	Region	Name	Parallel paths	Average diameter (cm)	Average length (cm)	Total cross-section (cm^2)	Total wall area (cm^2)	Total volume (cm^3)
0	1	Trachea	1	1.8	12	2.5	68	31
1	2	Main bronchi	2	1.2	4.8	2.3	36	11
2	3	Lobar bronchi	4	0.82	1.9	2.1	20	4.1
3	4	Segmental bronchi	8	0.56	0.75	2.0	11	1.5
4	5	Subsegmental bronchi	24	0.54	1.2	5.6	66	6.5
5–10	6	Small bronchi	1500	0.17	0.41	33	470	14
11–13	7	Bronchioles	12000	0.11	0.24	114	1400	28
14–15	8	Terminal bronchioles	49000	0.087	0.18	290	3400	53
16–18	9	Respiratory bronchioles	390000	0.069	0.10	1500	12000	150
19–23	9	Alveolar ducts	8400000	0.042	0.047	12000	54000	550
24	9	Alveoli	300000000	0.028			740000	3400
				Total in region 9			810000	4200

will have the opportunity to partition between the air and the mucus layer covering the respiratory epithelium.

MODEL STRUCTURE

On the basis of the above considerations a well-stirred 18-compartment model of the lung was constructed (Fig. 4). The model consists of nine serially connected regions, each one corresponding to an anatomical level in the respiratory tree. Thus the first region corresponds to the trachea and the last to the alveolar region. Each region of the model has a central and a peripheral compartment.

The central compartment corresponds to the air and the outermost layer of the mucus lining the wall. The outer wall layer is assumed to be 1 μm thick in all regions of the lung. This is far less than the thickness of the mucus layer which is approximately 5–10 μm (SCHLESINGER, 1990). The effective volume of the central compartment [$V_{c,i}$ in Equations (3) and (4) below, and V_{alv} in Equations (7) and (9) below] is calculated as the sum of the air volume and the effective volume of the outer wall layer, which is calculated as the product of the wall surface area, the outer wall thickness, the probability of solvent molecules hitting the wall in the region, and the $\lambda_{w/a}$ value of the solvent. It is thus assumed that the solvent vapour is distributed instantaneously in the air within a region and also immediately equilibrates with a portion of the outermost layer of the respiratory lining (well-stirred model). As mucus is mainly made up of water the mucus:air partition coefficient is assumed to be equal to $\lambda_{w/a}$.

Radial diffusion of solvent between the outer layer and deeper portions of the wall is accounted for by introducing a peripheral compartment in the first eight regions. The effective volume of the peripheral compartment [$V_{p,i}$ in Equation (5) below] is calculated as the product of the surface area of the region, the thickness of the deeper layer (15 μm) and the $\lambda_{w/a}$ of the solvent. The net flux of solvent between the central and the peripheral compartment is calculated according to Fick's law by a transfer or clearance term [F in Equations (4) and (5) below] times the difference in partial pressure. The transfer term for a region is calculated as the product of a site-independent constant (150 l. min^{-1} cm^{-2}), the probability of wall hit and the area of the wall surface.

The central compartment of the ninth region corresponds to the respiratory bronchioles, alveolar ducts and alveoli. The volume of this alveolar compartment is not constant but increases during inhalation and decreases during exhalation. The peripheral compartment of the ninth region represents the rest of the body. An immediate equilibrium between alveolar air and arterial blood is assumed. The use of a single systemic compartment was thought appropriate when simulating the first few breaths of exposure. Neither the number of systemic compartments nor their volumes are critical for the polar solvents acetone and ethanol as recirculation makes practically no contribution during exposures of short duration. With solvents that are only slightly soluble, like diethyl ether, however, recirculation into the lungs plays an important role. An effective volume of the systemic compartment of 16 l. multiplied by the $\lambda_{b/a}$ of the solvent was obtained by fitting the simulated post-exposure partial pressure of diethyl ether in exhaled air to experimental observations (Fig. 6). This value corresponds approximately to three times the blood volume.

The lung model is thought to be homogenous, symmetrical and of ideal shape. This

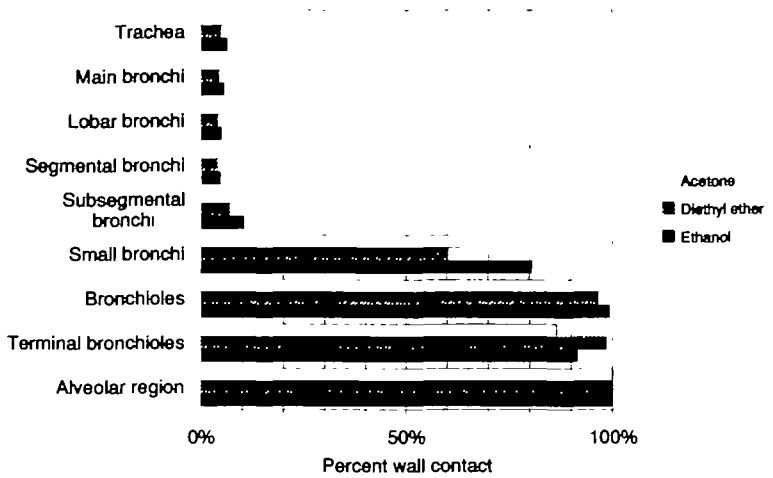

FIG. 3. The percentage of inhaled solvent vapour that will hit the wall in the various regions of the respiratory tree. The probabilities were calculated for light physical exercise (50 W), the conditions are given in Table 2.

means that no ventilation–perfusion inequalities exist, all tubes in a region are cylinders identical in size and all alveoli are spheres of the same diameter. In addition, it is assumed that there is immediate mixing within each compartment ('well-stirred' model) and that no cross-tissue diffusion of solvent vapour occurs except between the outer and inner wall layers and between the alveolar region and the systemic circulation.

Elimination of solvent from the peripheral and systemic compartments by metabolism or by diffusion into deeper wall layers was not considered in this first tentative model, but may easily be introduced in future model development, for example as a clearance factor proportional to the area of the wall surface.

The schematic structure of the model is presented in Fig. 4. The model is defined by the following set of differential mass balance equations.

Regions 1–8, *trachea-terminal bronchioles*
During inhalation

$$dP_{c,i}/dt = [2 \cdot Q_{pulm} \cdot (P_{c,i-1} - P_{c,i}) + F \cdot (P_{p,i} - P_{c,i})]/V_{c,i}. \quad (3)$$

During exhalation

$$dP_{c,i}/dt = [2 \cdot Q_{pulm} \cdot (P_{c,i+1} - P_{c,i}) + F \cdot (P_{p,i} - P_{c,i})]/V_{ci}. \quad (4)$$

Regions 1–8, *peripheral compartment*

$$dP_{p,i}/dt = F_i \cdot (P_{c,i} - P_{p,i})/V_{p,i}. \quad (5)$$

Region 9, *respiratory bronchioles, alveolar ducts and alveoli*
During inhalation

$$dV_{alv}/dt = Q_{pulm}/2 \quad (6)$$

$$dP_{alv}/dt = [2 \cdot Q_{pulm} \cdot P_{c,8} + Q_{sys} \cdot (P_{ven} - P_{alv})]/V_{alv}. \quad (7)$$

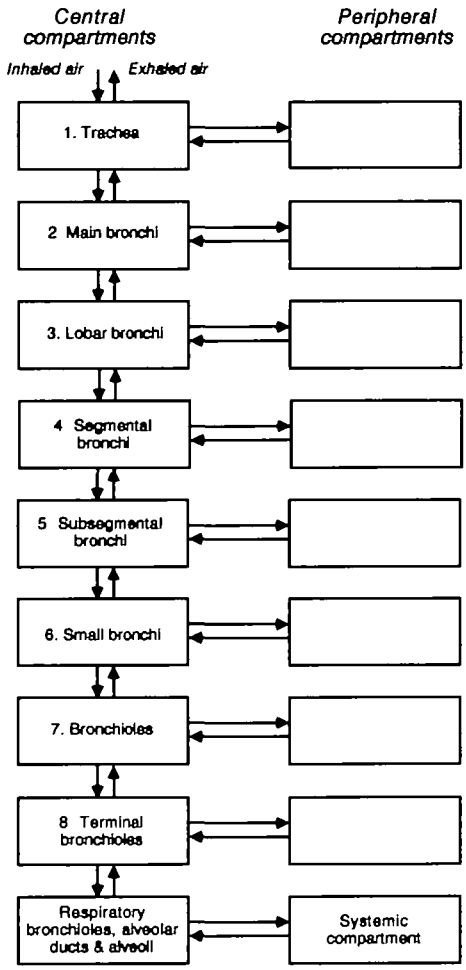

FIG. 4. Suggested physiologically based pharmacokinetic (pbpk) model for the retention and excretion of solvent vapours in the lung.

During exhalation

$$dV_{alv}/dt = -Q_{pulm}/2 \tag{8}$$

$$dP_{alv}/dt = Q_{sys} \cdot (P_{sys} - P_{alv})/V_{alv} \cdot \tag{9}$$

Region 9, systemic circulation

$$dP_{sys}/dt = Q_{sys} \cdot (P_{alv} - P_{sys})/V_{sys} \cdot \tag{10}$$

The terms P, V and F denote partial pressure (concentration), effective volumes and clearance, respectively, of the different regions. The subscripts c,i and p,i denote the central and peripheral compartments of region i, while alv and sys denote the alveolar and systemic compartments, respectively. The partial pressure in the alveoli, P_{alv},

equals that in arterial blood and the partial pressure in the systemic compartment, P_{sys}, equals that in mixed venous blood. Note that the pulmonary (Q_{pulm}) and not alveolar ventilation is used in the equations, since the dead-space is already included in the model structure. The systemic flow (Q_{sys}) is equal to cardiac output times $\lambda_{b/a}$.

The differential equations were written, numerically solved and graphically presented by spreadsheet programming (Microsoft Excel) on a personal computer (Apple Macintosh IIcx), an adaptation of the approach used by JOHANSON and NÄSLUND (1988). The Euler method of integration was used with a time step of 0.2–5 ms depending on the conditions of the simulation. The air flow caused by breathing was treated as a square-wave function. Inhalation was assumed to occupy 40% and exhalation 60% of the total time of a breath cycle. The relative respiratory uptake was calculated as one minus the quotient of exhaled to inhaled amount of solvent. The three solvent independent parameters—the outer wall thickness, the deep wall thickness and the transfer constant—were obtained by visual fitting of simulations to experimental observations on acetone, diethyl ether and ethanol made by SCHRICKER *et al.* (1985) and LANDAHL and HERRMANN (1950). Other parameters used are presented in Table 2.

RESULTS AND DISCUSSION

Experiments with acetone, diethyl ether and ethanol conducted by SCHRICKER *et al.* (1985) and by LANDAHL and HERRMANN (1950) were simulated to obtain the solvent independent parameters of the model. The results of these simulations are compared with experimental data in Figs 5 and 6. There is good agreement between simulated and experimentally observed curves with respect to the concentration in end-exhaled and mixed-exhaled air of acetone and diethyl ether as well as the shape of the entire concentration curve during and after exposure. Only data on relative uptake were found for ethanol. Also in this case there is a good correlation between simulated and observed data.

A closer look at the concentration curve of carbon dioxide during exhalation (Fig. 7) shows that the slope of the alveolar plateau is positive (there was no previous exposure to carbon dioxide but this gas is endogenously produced). In contrast, the slope of the alveolar plateau of acetone vapour is negative during the first exhalation after exposure. As seen in Fig. 7, the model correctly predicts these differences in behaviour. The differences between acetone and carbon dioxide can be explained as follows. Carbon dioxide has a low water solubility and there is practically no interaction with the walls of the conducting airways. Hence, the exhaled carbon dioxide emanates almost entirely from the alveolar region. On the other hand, acetone has a high water solubility and a fraction of the inhaled acetone deposits in the walls of the conducting airways during exposure (washin). The first deposition occurs in the uppermost part of the airways. With time, a concentration gradient is established in the wall and this gradient moves downwards during inhalation. During exhalation the gradient moves outwards and the deposited acetone is washed out. Because of the gradual washout from the walls the slope of the alveolar plateau is expected to flatten out and eventually reach positive values after a few breaths post-exposure (Fig. 8). Diethyl ether, which is much less water soluble, is expected to behave in a similar way, although less pronounced. As illustrated with acetone, carbon dioxide and diethyl ether

TABLE 2. MODEL PARAMETERS USED IN THE SIMULATIONS

	Acetone	Carbon dioxide	Diethyl ether	Ethanol	Hypothetical solvent
Diffusion constant ($cm^2\ s^{-1}$)	0.095*	0.180†	0.079*	0.109*	0.1
Partition coefficient					
Water/air	395‡	0.8§	13.1‖	1265¶	10–10000
Blood/air	245‡	4.0†	12.1‖	1265¶	10–10000
Pulmonary ventilation ($l.\ min^{-1}$)**					
rest	—	—	—	—	9.6
50 W	25.2	25.2	25.2	18††	25.2
100 W	—	—	—	—	38.4
150 W	—	—	—	—	57.6
Cardiac output ($l.\ min^{-1}$)‡‡					
rest	—	—	—	—	5.2
50 W	9.9	9.9	9.9	9.9	9.9
100 W	—	—	—	—	13.7
150 W	—	—	—	—	17.6
Breathing frequency (min^{-1})					
rest	—	—	—	—	15.4**
50 W	18.2§§	18.2§§	18.2§§	15.0††	17.1**
100 W	—	—	—	—	19.9**
150 W	—	—	—	—	24.0**

*Calculated from Equation (1).
†From DE VRIES and LUIJENDIJK (1982).
‡From SATO and NAKAJIMA (1979).
§Calculated from the solubility of carbon dioxide in water at 25°C. From DANIELS and ALBERTY (1967).
‖From EGER *et al.* (1963).
¶From FISEROVA-BERGEROVA and DIAZ (1986).
**From MALMBERG *et al.* (1987).
††From LANDAHL and HERRMANN (1950).
‡‡From ÅSTRAND (1983).
§§Calculated from SCHRICKER *et al.* (1985).

in Fig. 8, both simulations and experiments show these patterns with respect to the development of the post-exposure alveolar slopes.

The cyclic change during breathing of the concentration gradient in the respiratory tree is illustrated in Fig. 9. The gradient is flatter the more water soluble the substance. In fact, for polar sovents like acetone and ethanol, the gradient is so flat that the solvent concentration in exhaled air never reaches that in the alveoli during normal breathing. Thus, according to this model, the term 'alveolar air', which is frequently used to denote the last portion of the exhaled air, is inadequate and misleading for gases and vapours of high water solubility. From the curves in Fig. 9, it also follows that the results in biological monitoring based on alveolar sampling are highly dependent on sample timing and breathing pattern. The higher the $\lambda_{w/a}$ of the solvent, the more pronounced these dependencies become.

The model can be used to predict how altered conditions may affect the lung kinetics of a solvent. Conditions of major interest both in biological monitoring and in extrapolation from external to internal dose are: workload level (which in turn affects

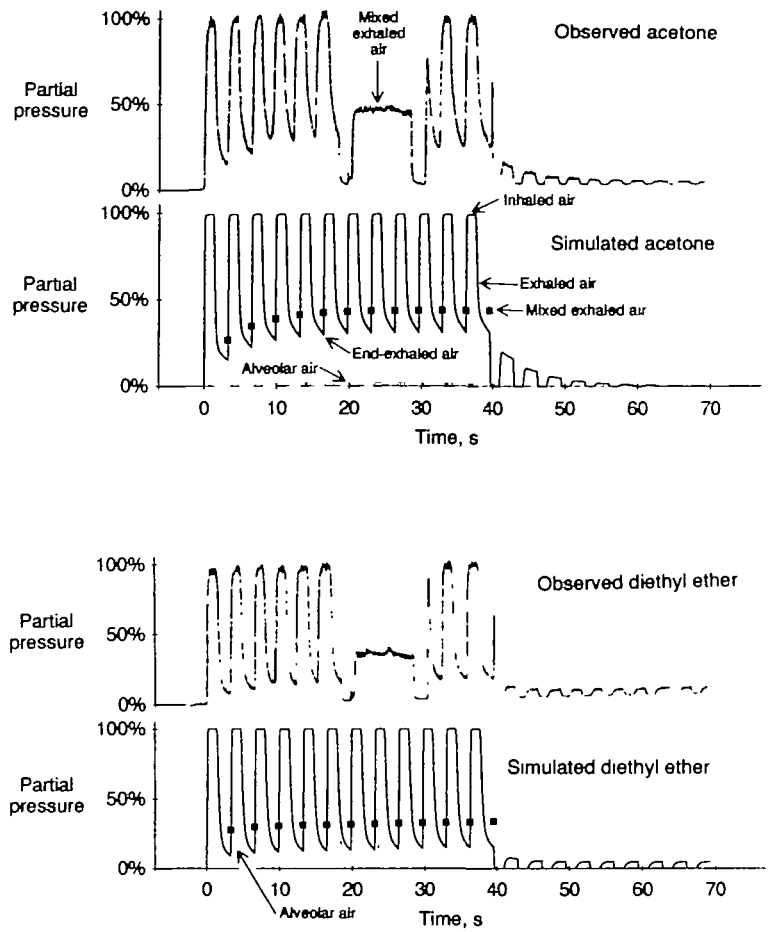

FIG. 5. Simulated and experimental partial pressure–time curves of acetone and diethyl ether in inhaled, exhaled and alveolar air during 12 breaths of exposure followed by nine breaths of washout. The partial pressure is expressed relative to that in ambient air during exposure. Experimental curves are redrawn from SCHRICKER *et al.* (1985), with permission.

pulmonary ventilation, breathing frequency and cardiac output); breathing pattern (e.g. breath holding, forced expiration); sample timing (time lapse between exposure and sampling as well as time of sampling within the breath cycle); and the $\lambda_{w/a}$ of the solvent in question. Interesting endpoints are the concentration in end-exhaled and in mixed-exhaled air (relative respiratory uptake).

At the beginning of an exposure the partial pressure in end-exhaled and in mixed-exhaled air increases and the relative respiratory uptake decreases as solvent builds up in the walls of the respiratory tree (Fig. 5). Figure 10 shows the simulated partial pressure in end-exhaled air (P_{end}) for hypothetical solvents with partition coefficients ranging from 10 to 10 000 during the first 15 breaths. These curves give an idea about how the solvent concentration in exhaled air may change when the exposure level is changed, an issue of major interest in biological monitoring strategy and evaluation. In

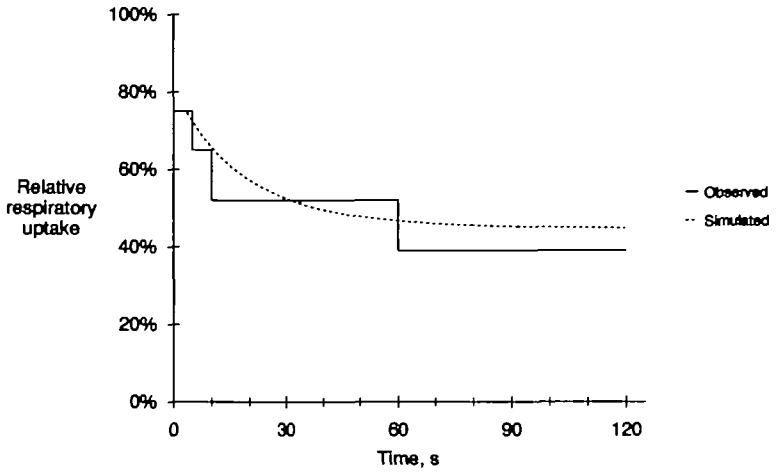

FIG. 6. Change in respiratory uptake of ethanol during the first 2 min of exposure. Simulated results are compared with experimental observations calculated from LANDAHL and HERRMANN (1950).

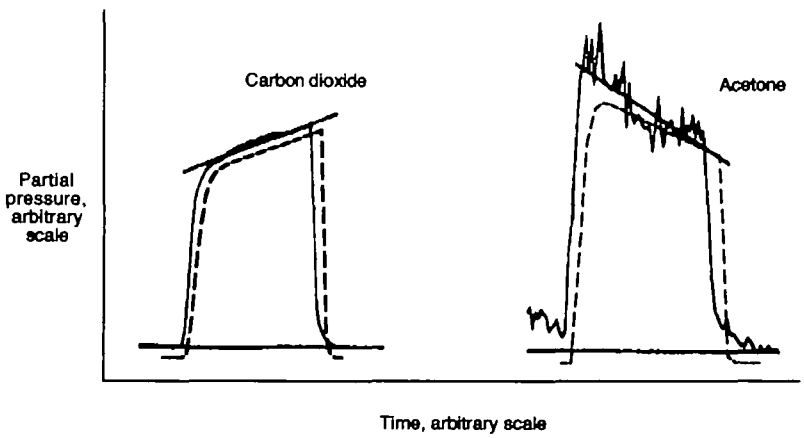

FIG. 7. Partial pressure–time curves of endogenously formed carbon dioxide and acetone in exhaled air during the first post-exposure breath cycle. The experimental curves are redrawn from SCHRICKER *et al.* (1985), with permission. To allow easier comparison the simulated curves (broken line) have been slightly shifted to the right and downwards.

the workplace, breath sampling is often preceded by a variable time of no, or lowered, solvent exposure.

According to the model (Fig. 10) P_{end} reaches an apparent steady-state after the second breath when the solvent has a λ value of 100 (as there is no metabolism, the 'true' steady-state is reached when the partial pressure in blood equals that in air). This apparent steady-state indicates that there is a rapid equilibrium between the inspired–expired air and the walls of the respiratory tree. At higher λ values the approach to the apparent steady-state is slower, and at 10 000 it is not reached during the first 15 breaths. The continuous increase in P_{end} at 10 000 is due to solvent buildup

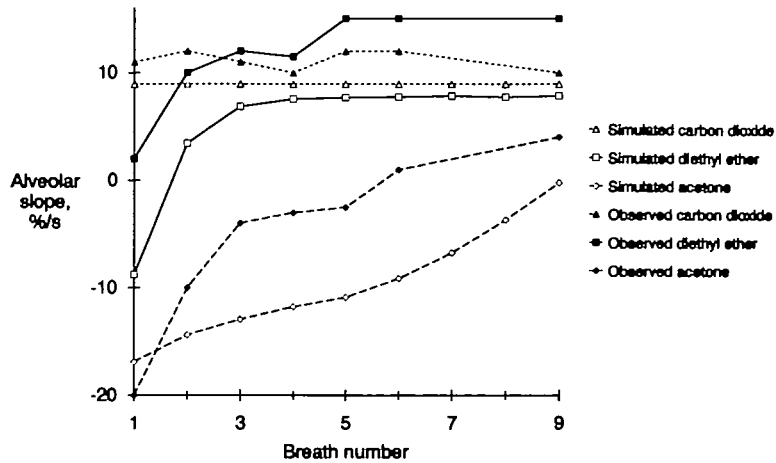

FIG. 8. Development of the slope of the alveolar plateau of acetone, carbon dioxide and diethyl ether during the first nine breaths after solvent exposure. The experimental curves are redrawn from SCHRICKER *et al.* (1985), with permission.

in the walls of the respiratory tree. The partitioning of solvent between air and blood is important only at the lowest λ of 10, in this case the increase in P_{end} with time seen is explained by solvent buildup in the systemic compartment. Thus, the curves $\lambda = 10$ and $\lambda = 10\,000$ have similar shape but the explanations are different.

Figure 11 shows how physical exercise influences the relative respiratory uptake of solvents with different solubilities. The relative uptake during the 15th breath decreases with increased workload at the lowest λ value of 10. The explanation is that at higher workloads increased pulmonary ventilation and cardiac output result in a faster solvent buildup in the systemic compartment. At the intermediate λ values of 100 and 1000 the relative uptake increases with increased workload, as in the 'inert tube' model, although at lower levels. However, at the highest λ value of 10 000 physical exercise has little influence on the uptake. These different patterns suggest that the relation between solvent uptake, solubility and workload is complicated and there may be physiological explanations for at least some of the scatter in relative respiratory uptake shown in Figs 1 and 2.

Several anatomical and physical considerations were not included in this first attempt to design a pbpk lung model. The nose and mouth were not included. According to BOUHUYS (1974) the air volume of the nose is about 20 cm^3 and the wall area is about 120 cm^2. These values are of the same orders of magnitude as those of the trachea, and the exclusion of nose and mouth from the model is not expected to affect greatly the tendencies in the results presented here. Complete symmetry was assumed in the model although the lung is known to be asymmetric with respect to branching of the respiratory tree, path lengths and the distribution of air and blood flows. The diffusion of the solvent molecules in the air and water phases was accounted for in a crude way by compartmentalization. The migration of solvent molecules between the air and water phases was assumed to be immediate. Lung metabolism and intertissue diffusion were not considered. For simplicity, only one systemic compartment was used. During long-term exposure, solvent buildup in the blood and in the rest of the

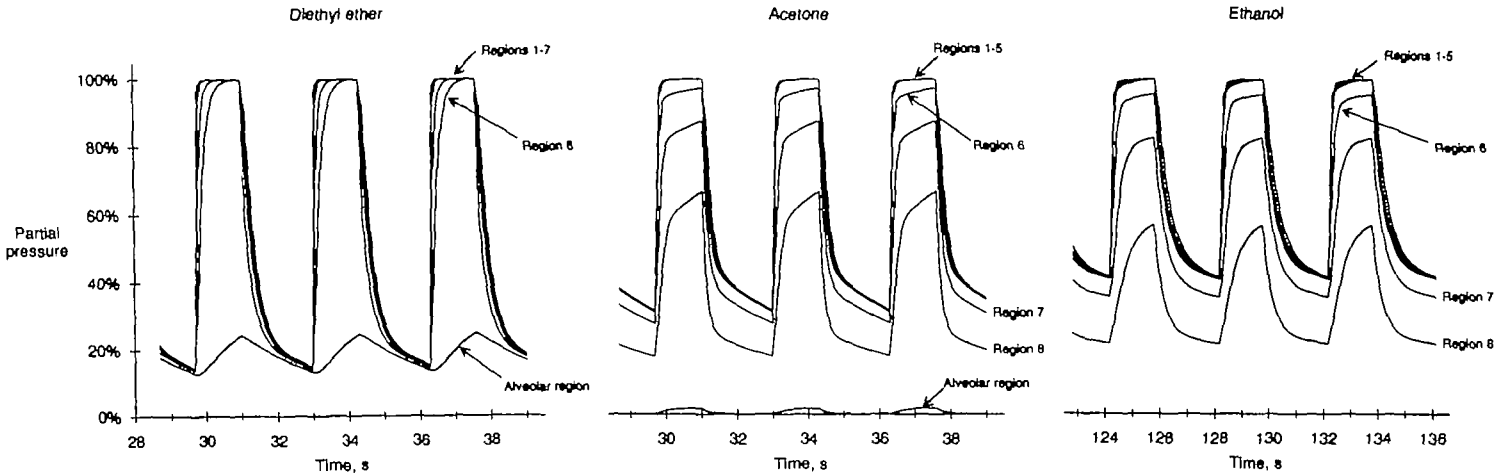

FIG. 9. Simulated partial pressure–time curves at apparent steady-state in different regions of the lung during exposure to three solvents with widely different $\lambda_{w/a}$ values; diethyl ether, acetone and ethanol. The partial pressures are expressed relative to that in ambient air.

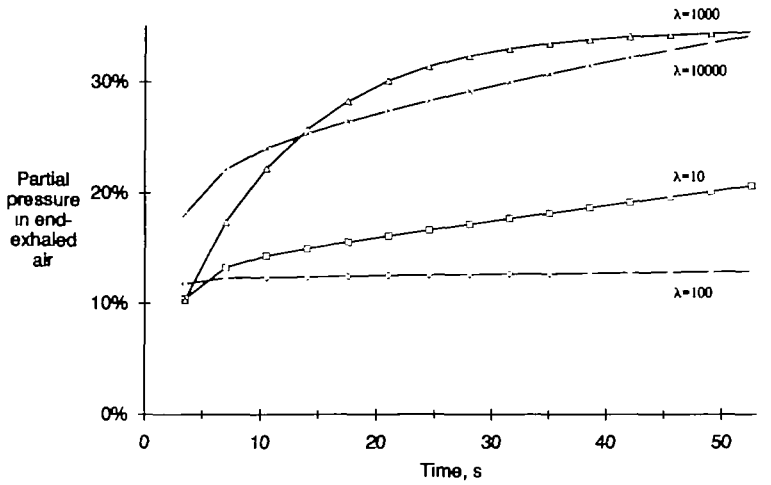

FIG. 10. Partial pressure of solvent in end-exhaled air during the first 15 breaths of exposure to hypothetical solvents with $\lambda_{b/a} = \lambda_{w/a}$ values between 10 and 10 000. The curves were simulated at a physical workload of 50 W. The partial pressures are expressed relative to that in ambient air.

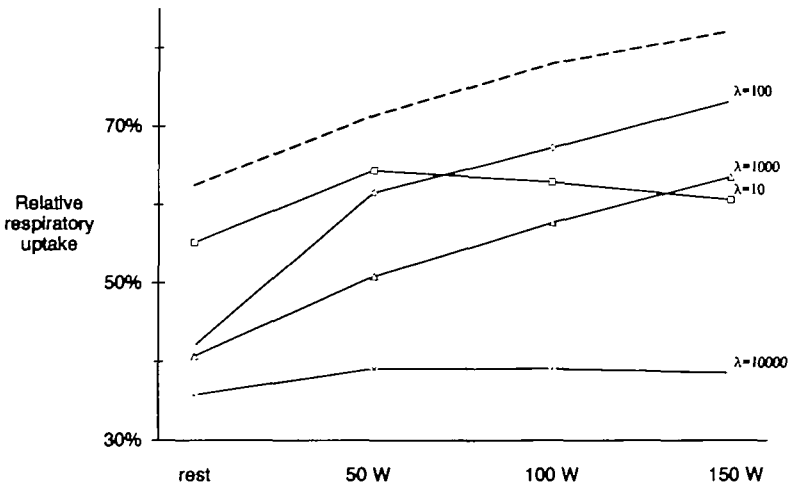

FIG. 11. Influence of physical exercise on the relative respiratory uptake of solvent during the 15th breath of an exposure. The curves were simulated for hypothetical solvents with $\lambda_{b/a} = \lambda_{w/a}$ values between 10 and 10000. The broken line represents the ratio of alveolar to pulmonary ventilation ('inert tube' model). Ventilation values are from MALMBERG *et al.* (1987).

body as well as metabolism have to be considered. This is easily done by attaching a conventional multicompartment pbpk model to the lung model.

The errors introduced by the simplifications listed above are not known at present. On the other hand, it may also be possible further to simplify the model by lumping together the compartments representing the upper regions, thus reducing the number of compartments.

Thus more thorough physical and anatomical considerations are needed to refine the model. Additional experimental data will be needed for further development and validation. Useful objectives include relative respiratory uptake and concentration in end-exhaled air under well-defined conditions. Fast recordings of the concentration changes during the breathing cycle, such as in the excellent work by SCHRICKER *et al.* (1985), allow several comparisons including post-exposure changes in the slope of the alveolar plateau and the volume of exhalation phase 1, as well as the shape of the entire concentration curve during and after exposure. In addition, the air flow changes during breathing should be recorded.

SUMMARY AND CONCLUSION

A tentative pbpk model has been developed which describes the lung kinetics of polar solvent vapours. The model successfully predicts the observed kinetics of acetone, carbon dioxide, diethyl ether and ethanol with respect to concentration in end-exhaled air, relative respiratory uptake and the slope of the alveolar plateau. With a model of this kind it is possible to predict the uptake and excretion kinetics of polar vapours under various cirumstances, such as increased workload, breath holding, forced expiration, etc. Such predictions would help in the development of biological monitoring methods based on breath sampling. It should further be possible to understand and explain experimental observations on the lung kinetics of polar solvents.

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REFERENCES

ÅSTRAND, I. (1983) Effect of physical exercise on uptake, distribution, and elimination of vapors in man. In *Modeling of Inhalation Exposure to Vapors: Uptake, Distribution and Elimination* (Edited by FISEROVA-BERGEROVA, V.), Vol. II, pp. 107–130. CRC Press, Boca Raton, Florida, U.S.A.

ÅSTRAND, I., ÖVRUM, P., LINDQVIST, T. and HULTENGREN, M. (1976) Exposure to butyl alcohol: uptake and distribution in man. *Scand. J. Wk Environ. Hlth.* **3**, 165–175.

BOUHUYS, A. (1974) *Breathing. Physiology, Environment and Lung Disease.* Grune & Stratton, New York, U.S.A.

DANIELS, F. and ALBERTY, R. A. (1967) *Physical Chemistry.* John Wiley & Sons, New York, U.S.A.

DAVIES, C. N. (1985) Absorption of gases in the respiratory tract. *Ann. occup. Hyg.* **29**, 13–25.

DE VRIES, W. R. and LUIJENDIJK, S. C. M. (1982) Shape of single-breath washout curves of gases with different diffusion coefficients and blood solubilities. *Bull. Eur. physiopath. Resp.* **18**, 215–227.

EGER, E. I., SCHARGEL, R. and MERKEL, G. (1963) Solubility of diethyl ether in water, blood and oil. *Anesthesiology* **24**, 676–678.

ENGSTRÖM, J., BJURSTRÖM, R., ÅSTRAND, I. and ÖVRUM, P. (1978). Uptake, distribution and elimination of styrene in man. Concentration in subcutaneous adipose tissue. *Scand. J. Wk Environ. Hlth* **4**, 315–323.

FISEROVA-BERGEROVA, V. (Editor) (1983a) *Modeling of Inhalation Exposure to Vapors: Uptake, Distribution, and Elimination*, Vols I–II. CRC Press, Boca Raton, Florida, U.S.A.

FISEROVA-BERGEROVA, V. (1983b) Physiological models for pulmonary administration and elimination of inert vapors and gases. In *Modeling of Inhalation Exposure to Vapors: Uptake, Distribution, and Elimination* (Edited by Fiserova-Bergerova, V.), Vol. I, pp. 73–100. CRC Press, Boca Raton, Florida, U.S.A.

FISEROVA-BERGEROVA, V. and DIAZ, M. L. (1986) Determination and prediction of tissue–gas partition coefficients. *Int. Archs occup. Environ. Hlth* **58**, 75–87.

GROESENEKEN, D., VEULEMANS, H. and MASSCHELEIN, R. (1986) Respiratory uptake and elimination of ethylene glycol monoethyl ether after experimental human exposure. *Br. J. ind. Med.* **43**, 544–549.

GROESENEKEN, D., VEULEMANS, H., MASSCHELEIN, R. and VAN VLEM, E. (1989) Experimental human exposure to ethylene glycol monomethyl ether. *Int. Archs occup. Environ. Hlth* **61,** 243–247.

IMBRIANI, M., ROMAGNOLI, F., PUGLIESE, F. and GHITTORI, S. (1985) Esposizione ad Acetone. Studio sperimentale dell'assorbimento e della eliminazione polmonare in soggeti normali. *G. Ital. Med. Lav.* **7,** 223–229.

JOHANSON, G. (1984) Toxicokinetic studies of 2-butoxyethanol. Undersökningsrapport 1984:39. (English abstract.) Arbetarskyddsstyrelsen, Stockholm, Sweden.

JOHANSON, G. and DYNESIUS, B. (1988) Liquid/air partition coefficients of six commonly used glycol ethers. *Br. J. ind. Med.* **45,** 561–564.

JOHANSON, G., KRONBORG, H., NÄSLUND, P. H. and NORDQVIST, M. B. (1986) Toxicokinetics of inhaled 2-butoxyethanol (ethylene glycol monobutyl ether) in man. *Scand. J. Wk Environ. Hlth* **12,** 594–602.

JOHANSON, G. and NÄSLUND, P. H. (1988) Spreadsheet programming—a new approach in physiologically based modeling of solvent toxicokinetics. *Toxicol. Lett.* **41,** 115–127.

LANDAHL, H. D. and HERRMANN, R. G. (1950) Retention of vapors and gases in the human nose and lung. *Archs ind. Hyg. occup. Med.* **1,** 36–45.

LINDQVIST, T. (1977) The partition coefficients blood/air and water/air for some common solvents. [Fördelningskvoterna bold/luft och vatten/luft för några vanliga lösningsmedel.] *Arbete och Hälsa* **8,** 1–15.

MALMBERG, P., HEDENSTRÖM, H. and FRIDRIKSSON, H. V. (1987) Reference values for gas exchange during exercise in healthy nonsmoking and smoking men. *Bull. Eur. physiopath. Resp.* **23,** 131–138.

MORRIS, J. B. and CAVANAGH, D. G. (1986) Deposition of ethanol and acetone vapors in the upper respiratory tract of the rat. *Fundam. Appl. Toxicol.* **6,** 78–88.

NOMIYAMA, K. and NOMIYAMA, H. (1974) Respiratory retention, uptake and excretion of organic solvents in man. Benzene, toluene, *n*-hexane, trichloroethylene, acetone, ethyl acetate and ethyl alcohol. *Int. Arch. Arbeitsmed.* **32,** 75–83.

SATO, A. and NAKAJIMA, T. (1979) Partition coefficients of some aromatic hydrocarbons and ketones in water, blood and oil. *Br. J. ind. Med.* **36,** 231–234.

SCHLESINGER, R. B. (1990) The interaction of inhaled toxicants with respiratory tract clearance mechanisms. *Crit. Rev. Toxicol.* **20,** 257–286.

SCHRICKER, A. C. M., DE VRIES, W. R., ZWART, A. and LUIJENDIJK, S. C. M. (1985) Uptake of highly soluble gases in the epithelium of the conducting airways. *Pflügers Arch* **405,** 389–394.

SEDIVEC, V., MRÁZ, M. and FLEK, J. (1981) Biological monitoring of persons exposed to methanol vapours. *Int. Archs. occup. Environ. Hlth* **48,** 257–271.

TERAMOTO, K., HORIGUCHI, S., NAKASEKO, H. and KAGEYAMA, M. (1987) Initial uptake of organic solvents in the human body by short-term exposure. *J. Sci. Labour* **63,** 13–19.

WIGAEUS, E., HOLM, S. and ÅSTRAND, I. (1981) Exposure to acetone. Uptake and elimination in man. *Scand. J. Wk Environ. Hlth.* **7,** 84–94.

WIGAEUS, E., LÖF, A., BJURSTRÖM, R. and NORDQVIST, M. B. (1983) Exposure to styrene. Uptake, distribution, metabolism and elimination in man. *Scand. J. Wk Envion. Hlth* **9,** 479–488.