

Toxicokinetics of organic solvents

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FISEROVA-BERGEROVA V. Toxicokinetics of organic solvents. *Scand J Work Environ Health* 11 (1985): suppl 1, 7-21. Organic solvents, because of their small molecules and large solubility in fat, water, or both, are expected to be readily absorbed through the skin or by inhalation. Toxicokinetic models (empirical, pharmacokinetic, and simulation) are used to describe the time course of their absorption and elimination. Special attention is given in this review to simulation models in which rate constants are derived from physiological parameters of the exposed subject (alveolar ventilation, tissue perfusion, body build) and from physicochemical properties of the inhaled chemical (partition coefficient, metabolic clearance). Such a simulation model is used to gain insight into the uptake, distribution, and elimination of inhaled vapors of organic solvents. Large differences between kinetic patterns of hydrophobic and hydrophilic solvents are indicated by the effects of biosolubility, metabolic clearance, changes in physiological parameters, exposure duration, and concentration fluctuation on the uptake, distribution, and elimination of solvents. Because kinetics is the basis for interindividual and intraindividual differences in pulmonary uptake and bioavailability and in the development of toxic effects, simulation models have practical application in the biological exposure monitoring and medical surveillance of exposed workers.

Key terms: biological monitoring, elimination, hydrophilic, hydrophobic, inhalation, pulmonary uptake, simulation model.

Toxicokinetics is the study of the time course of the absorption, distribution, and elimination of toxic chemicals in man and animals. Modern toxicokinetics is a powerful tool for the design of experiments, the interpretation of data, extrapolation from animals to man, extrapolation from one exposure regimen to another, and the evaluation of the effect of a variety of physiological and pathological changes on the dwelling of toxic chemicals in the body. Since computer technology has made the practical application of toxicokinetic models accessible to professionals lacking expertise in mathematics, toxicokinetics can provide health personnel with valuable information on the dwelling of industrial chemicals in the body. For example, biological monitoring of environmental and occupational exposure to toxic vapors and gases and the health surveillance of exposed subjects can be improved if toxicokinetic techniques are employed in setting exposure standards compatible with particular exposure conditions (13, 14, 23, 29, 34, 36, 40, 41, 45, 63, 65, 72, 76, 80).

Kinetic data are commonly described by mathematical functions in which time and concentration are the variables. The functions are usually exponentials (describing first-order processes) or rectangular hyperbolas (describing saturable processes). The

constants used in the functions are derived by statistical, pharmacokinetic, or physiological means. The following three types of mathematical models describe kinetic data: (i) empirical models, (ii) pharmacokinetic models, and (iii) simulation models.

Empirical models describe experimental data but lack flexibility for application to altered conditions. The function and the values of the constants are found by optimum fit to the experimental data. The most common application is in determining the amount of chemicals eliminated in urine or in exhaled air. Some investigators (65, 70, 86, 87) have suggested applying empirical models to biological exposure monitoring. Such an application is restricted to precisely specified conditions however.

Lowe suggested an empirical model for maintaining safe clinical anesthesia (58). The anesthetic concentration of any inhalation anesthetic in the brain is rapidly reached and safely maintained if the inspired concentration (c_i) is proportional to the reciprocal square root of the time (t).

$$c_i = 1.3 \text{ MAC} (1 + \lambda_{bl/gas} t^{-1/2}), \quad (\text{eq } 1)$$

where **MAC** denotes the desired anesthetic concentration in alveolar air, $\lambda_{bl/gas}$ is the blood-gas partition coefficient of the anesthetic agents at body temperature, and t denotes minutes after the start of anesthesia administration.

Pharmacokinetic models utilize sophisticated mathematical techniques to describe the bioavailability of drugs (38, 57, 66). Such models were developed as a tool for designing the optimum therapeutic

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effect of drugs; they were applied to problems of industrial toxicology by Piotrowski (72). Compartments and their parameters — such as volume of distribution, elimination constants, area under curves, and systemic clearance — were introduced to facilitate the mathematical treatment of the model. Deep and shallow compartments were introduced to explain biphasic elimination. The compartments and their parameters are mathematical entities which, with few exceptions, have no immediate association with in vivo processes.

Up until the last decade, pharmacokineticists failed to recognize that experimental data are the result of the interaction of physiological and biochemical processes in organisms. In consequence, pharmacokinetic models lack the capability of interpreting data or extrapolating for changed physiological (or pathological) conditions of xenobiotic recipients. Recognition of the role of blood flow in drug distribution resulted in the introduction of the concept of flow-independent "intrinsic clearance of the organ" to deal with differences between blood-flow-limiting and organ-clearing processes (6, 89).

Simulation models utilize sophisticated mathematical techniques similar to those used in pharmacokinetic models. The mathematical expressions, however, utilize real physiological and physicochemical parameters to describe the biological processes which affect the dwelling of a xenobiotic in the body. The fitting of curves to experimental data is not used in the preparation of the simulation model, but is used to verify the model (30, 40). This procedure contrasts with the procedure used for the preparation of empirical and pharmacokinetic models. Simulation models have the capability to interpret the data, to extrapolate for altered physiological conditions of exposed subjects and altered exposure regimens, and to predict behavior of new chemicals in the body. The most significant contributions to the development of a simulation model were made in studies of the uptake, distribution, and elimination of gases and vapors of industrial solvents and inhalation anesthetics.

Organic solvents are small-molecule compounds which are liquid at room temperature. The vapor pressure of organic solvents at room temperature is usually high enough to produce intoxication by inhalation. Organic solvents are soluble in water or in lipids or in both. Water and lipids being the main constituents of the body, organic solvents are soluble in blood and soft tissues. Their small molecules and good biosolubility allow them to cross biomembranes readily and be absorbed if ingested, inhaled, or placed in contact with the skin. Kinetic studies of inhalation exposure have provided a sufficient data base for the development of a simulation model. But skin exposure and skin absorption are so complex, and the kinetic data so scattered, that no simulation model has yet been proposed.

Skin penetration is related to the structural features of the skin at the site of exposure and to the physical properties of the chemical (82, 83). Studies of percutaneous absorption are subject to divergencies caused by regional variation of skin permeability and by the varying effects of the form in which the chemical is applied to the skin (60). Because the stratum corneum has affinity for both water-soluble and lipid-soluble compounds, organic solvents appear as likely candidates for skin absorption (92). Also, the small molecules of organic solvents facilitate rapid penetration through the stratum corneum.

Skin absorption of organic solvents was studied in man through exposing the skin of volunteers to vapors (15) or liquids of solvents while the volunteers breathed clean air (5, 16, 17, 18, 77, 85). The rapid skin penetration of liquid solvents seems to be related to the weakened barrier function of the skin caused by impairment of the horny layer by the solvent (77, 83). Riihimäki (74) showed that skin absorption of a solvent can be different if the solvent is applied in a mixture with another solvent. Dutkiewicz and co-workers were the first to collect kinetic data on the skin absorption of solvents. They showed that penetration through the skin is a temperature-dependent process (5) which can be explained on the principle of Fick's law (16). They also determined the rate of skin penetration of several solvents (17, 18), showed that skin uptake of methanol is a biphasic process (16), and reported differences in metabolic clearance following cutaneous and inhalation exposure to ethylbenzene (17). Sato & Nakajima (77) suggested that the difference in metabolic clearance can be explained by migration of the chemical in the body. Blood concentration of a volatile chemical absorbed through the skin is reduced prior to entering the hepatoportal vein by the first pass through the lung. Thus, after skin absorption, the availability of volatile solvents to biotransformation is diminished by pulmonary clearance.

The **basis for the theory of pulmonary uptake and elimination** of volatile chemicals was established at the end of the last century by studies of pulmonary uptake and the elimination of inert gases during and following hyperbaric conditions (96, 104) and by studies of the elimination of ethanol and acetone (100, 101, 102) from man. The transfer of vapors and gases from air to blood and from blood to tissues was explained on the principle of **Henry's law**. Blood-gas and tissue-blood partition coefficients were used to describe the equilibrium. The equilibration of vapor pressures in the body and in the environment was recognized as a driving force in the pulmonary uptake and elimination of vapors and gases. It was concluded that pulmonary uptake is predetermined by tissue uptake. It was explained that the equilibration rate is dictated by pulmonary ventilation, or by cardiac output, or by a combination of both, depending on the solubility of the inhaled chemical in the blood. The

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interaction of pulmonary functions, hemodynamics, and solubility was further elucidated in connection with the search for a safe technique to administer clinical inhalation anesthesia (19, 31, 42, 43, 53, 58, 67). Hydraulic (19, 47, 61) and electric (59, 62) analogues were suggested as teaching models for anesthesiologists. Such a teaching model was recently marketed for the Apple computer (71).

Kety (53) considered *diffusion* across the cellular membranes as another rate-limiting step in vapor exchange between air, blood, and tissue. The diffusion of nonionized chemicals is so fast, however, that it does not affect kinetic data of anesthetic agents or of organic solvents.

The effect of *metabolism* on pulmonary uptake and the elimination of toxic vapors was first recognized by Haggard et al (44) and by Teisinger & Souček (88). Haggard et al determined the maximal metabolic rate of ingested ethanol and acetone from pulmonary elimination. Teisinger & Souček suggested that the metabolic rate in vivo can be determined from the pulmonary uptake rate at steady state and that metabolism is a first-order process with a rate constant defined by the "metabolic coefficient." Van Rees (93) published the first simulation model for the respiratory uptake of noninert gases. His model, utilizing physiological parameters of exposed volunteers and the solubility and metabolic clearance of styrene, was too complex to be solved by conventional mathematics. Van Rees performed a series of experiments with volunteers engaged in *physical exercises* during exposure in order to document the important role of pulmonary ventilation and cardiac output in pulmonary uptake and elimination. Åstrand and her co-workers systematically studied the effect of exercise on the uptake and distribution of 10 solvents in volunteers (1, 2). They documented the slow uptake and elimination of solvents from adipose tissue (2, 8, 20).

Two recent advances in technology have facilitated the acquisition and processing of kinetic data: (i) sensitive analytical methods utilizing gas chromatography, liquid chromatography, mass spectrophotometry, and ultraviolet and infrared spectrometry and (ii) computer technology. The new analytical methods, by providing a tool for determining small concentrations of chemicals in exhaled air, blood, and tissues, have made possible the observation of the triphasic pulmonary elimination of vapors. Computer programs for solving simultaneous differential equations describing nonlinear multicompartamental models have made simulation models and the compiling of kinetic data accessible to scientists who lack the mathematical expertise to perform the solution conventionally.

My colleagues and I first attempted to find the solution of a *multicompartamental simulation model* using an analogue computer (30). The precision of computation was improved when the solution was

programmed for a digital computer (35, 36, 94, 95). The solution of the model utilizes either the Laplace transform or numerical integration. Solution by Laplace transform has the advantage of substantially saving computer time and readily providing values of important kinetic parameters such as half-times and asymptotic values, but it is unsuitable if any process affecting uptake and elimination deviates from first-order kinetics. For example, during exposure to high concentrations, the capacity of the enzymatic system involved in the metabolism of the inhaled chemical can be exceeded (4, 24, 25, 28, 33, 37, 55, 73). Since metabolic clearance under such conditions is not constant, the solution of the model can be found only by numerical integration (94, 95). Computer programs for solving simulation models can be provided by electrical engineers, because the charging and discharging of an electrical network composed of capacitors and conductors are described by the same differential equations as the uptake and elimination of inhaled chemicals (27, 28, 36, 59, 62, 94, 95).

Droz (12) published the solution for two simulation models. In one of the models, respiration is presented as a continuous flow defined by alveolar ventilation; in the other model respiration is presented as a rhythmic process defined by alveolar ventilation and respiratory frequency. The results obtained from the use of both models are almost identical. In his models Droz incorporated the description of the elimination of metabolites of the inhaled chemical. Since the metabolites are distributed equally in the body water, their elimination kinetics are described by a single pharmacokinetic compartment for which the constants (volume of distribution and elimination constant) are determined from urinary excretion. Such a model was successfully applied to trichloroethylene (23, 40) and styrene (14).

The *simulation model for inhalation exposure* used in our laboratory can accommodate up to seven compartments. Tissues are assigned to compartments according to the degree of perfusion and solubility and the capability to remove the inhaled chemical from systemic circulation. With these assignment criteria, five compartments usually accommodate all tissues. Additional compartments can be added if special consideration is given to target organs. For example, it might be convenient to treat the brain as a separate compartment if the development of the analgesic effect of organic solvents is being investigated or to treat the kidney separately if renal elimination of hydrophilic solvents is being investigated. The differential equations describing the model have been given in reference 35. The solution of the model has been programmed in Basic for an Apple II Plus computer; it is available upon request.

For the application of the model the following information is needed: the alveolar ventilation (l/min), tissue perfusion (l/min), and tissue volume (l) of the exposed subject and the biosolubility and

intrinsic clearance of the inhaled chemical. Physiological parameters for the model can be determined by measurement, or they can be found in biological tables or in references 2, 35, or 23. A review of interspecies extrapolation can be found in references 10 and 32. Biosolubility is defined by blood-gas and tissue-gas partition coefficients at body temperature. The partition coefficients of some solvents have been determined and can be found in reference 26. The methods used for determining partition coefficients have been reviewed in the same reference. Partition

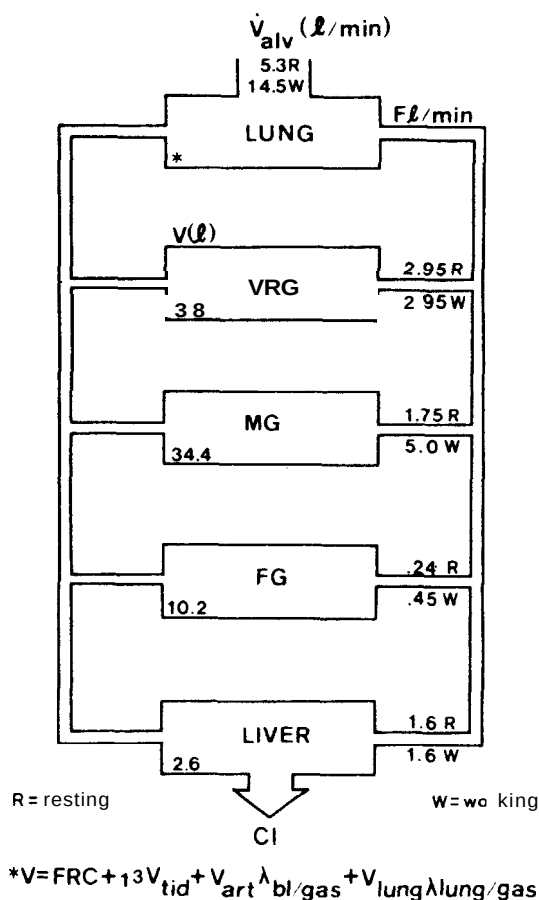


Figure 1 Simulation model: Tissues are assigned to the lung compartment, which includes functional residual capacity (FRC), one-third of the tidal volume (V_{tid}), lung tissue, and arterial blood; the VRG (vessel-rich group) compartment, which includes brain, gastrointestinal tract, glands, heart, kidneys, and spleen; the MG (muscle group) compartment, which includes muscles and skin; the FG (fat group) compartment, which includes adipose tissue and white marrow; and the liver compartment. The volume (V) of each compartment (in liters) is indicated in the lower left-hand corner of the compartments. Perfusion (F) rates (in liters per minute) are indicated at the right of the compartments, the top numbers indicating the rates for a resting (R) man and the lower numbers indicating the rates for a working (W) man (50 W). $\dot{V}_{alv}$ is alveolar ventilation (in liters per minute). The parameters given for a standard man (70 kg, 170 cm) are taken from reference 2. The arrow at the bottom of the liver compartment indicates intrinsic metabolic clearance (Cl) (in liters per minute).

coefficients can be predicted from chemical structure (34) or if tissue composition and the solubility of chemicals in water and oil are known (58). No standard method exists for determining intrinsic clearance. It has been suggested that metabolic clearance can be calculated from the metabolic rate determined from pulmonary uptake (4, 24, 25, 28, 31, 36, 88), from the distribution of chemicals or their metabolites in tissues at steady state (28, 33), from the elimination of metabolites at steady state (46), or from the slope of the elimination phase of the desaturation curve (44, 80). Metabolic clearance obtained by these indirect methods can embrace the effects of flow restriction and tissue redistribution and therefore can be unsuitable for use in the simulation model. Interspecies extrapolation of metabolic clearance by a scale-up power equation has also been suggested (4, 10). Such extrapolation must be done very cautiously because of unpredictable species differences in metabolic pathways (68).

The five basic compartments comprise a single central compartment connected to four tissue compartments (figure 1). The central compartment includes alveolar air, lung tissue, and arterial blood. The amount of chemical supplied to the central compartment during exposure consists of the amount inhaled and the amount returned by venous blood. The chemical is removed from the lung by arterial blood. Because the partial pressures of vapors and gases in alveolar air and arterial blood readily equilibrate, the amount removed is determined by cardiac output, alveolar concentration, and the blood-gas partition coefficient. When exposure terminates, the chemical continues to be brought into the lung by mixed venous blood and continues to be removed by arterial blood, but the role of breath reverses, as shown in the following scheme:

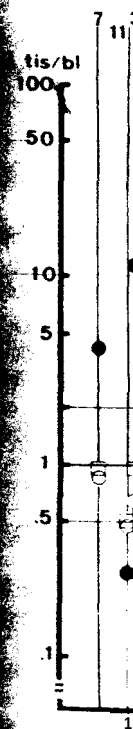
chemical flow into the lung	chemical flow out of the lung
During exposure: $\dot{V}_{alv} c_{exp} + Q c_{ven}$	$Q c_{al} \lambda_{bl/gas}$
After exposure: $c_{art} > c_{ven}$	$Q c_{al} \lambda_{bl/gas} + \dot{V}_{alv} c_{exp}$
After exposure: $c_{art} < c_{ven}$	$Q c_{al} \lambda_{bl/gas} + \dot{V}_{alv} c_{exp}$

where Q is cardiac output, $\dot{V}_{alv}$ is alveolar ventilation, and c is the concentration in blood or in air as indicated by the subscripts. The large concentration gradient across the lung is characteristic of volatile compounds and is the driving force behind pulmonary uptake and elimination.

Arterial blood carries the chemical to the tissues. The larger the perfusion, the faster the equilibration rate. Brain and viscera are the organs with the largest perfusion. These organs account for 9% of body mass and under resting conditions are perfused by 75% of the cardiac output. The perfusion rates of brain, spinal cord, glands, and the hepatoporta

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2. Comparison of tissue-blood concentrations (tis/bl) for various tissues (liver, brain, spinal cord, glands, and isobutan) over time.

predicted from chemical structure, composition and the solubility and oil are known (58). No exists for determining intr been suggested that metab alculated from the metabolic pulmonary uptake (4, 24, 25). the distribution of chemical n tissues at steady state (28). on of metabolites at steady ope of the elimination phase o e (44, 80). Metabolic clear indirect methods can embrace striction and tissue redistrib be unsuitable for use in the sim species extrapolation of metal e-up power equation has also. Such extrapolation must be cause of unpredictable species bolic pathways (68).

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output, $\dot{V}_{\text{alv}}$ is alveolar ven concentration in blood or in a bscripits. The large concentra lung is characteristic of vol the driving force behind pul imination. carries the chemical to the tiss usion, the faster the equilibra era are the organs with the lar rgans account for 9 % of b stng conditions are perfused c output. The perfusion rates, glands, and the hepatop

system are similar, average $0.75 \text{ ml } \text{g}^{-1} \cdot \text{min}^{-1}$, are little affected by exercise or exposure to the chemical. These organs can thus be treated as a single compartment, which will be referred to as the vessel (VRG). If the inhaled chemical undergoes metabolism, it is convenient to treat the liver as a separate compartment. The perfusion of muscle, skin, and adipose tissue is significantly less than the perfusion of the vessel rich group and depends on the physical activity of the exposed subjects. The perfusion varies from $0.027 \text{ ml } \cdot \text{g}^{-1} \cdot \text{min}^{-1}$ in a resting man to $0.8 \text{ ml } \cdot \text{g}^{-1} \cdot \text{min}^{-1}$ in a man performing strenuous exercise. Muscle, skin, and adipose tissue, because of the similarity of their perfusion, can be treated as a single compartment, unless special stress is imposed on particular muscles. Adipose tissue should, nevertheless, be treated as a separate compartment because of the large differences in the solubility of most chemicals in lean and fatty tissue.

Before steady state or equilibrium is reached in an exposure, the partial pressure of an inhaled chemical in arterial blood is larger than the partial pressure in tissue. Partial pressures in tissues equilibrate with partial pressures in regional venous blood how-

ever. At steady state, the partial pressures in arterial blood, venous blood, and tissues are equilibrated, except for those in the excretory organ, in the blood perfusing the excretory organ, and in mixed venous blood (in which the partial pressure is always smaller). This concentration gradient across the excretory organ is the driving force behind pulmonary uptake at steady state. At steady state, the pulmonary uptake rate equals the elimination rate. When exposure is interrupted, the chemical is removed from tissues by venous blood, part being eliminated from the body and part being redistributed in the body and tending toward equilibration.

Metabolism, the main excretory pathway of solvents, is described in the model by the intrinsic clearance of liver. At a small exposure concentration, the hepatic metabolism of many solvents is restricted by hepatic flow so that the metabolic rate is $\mu = F_{\text{hep}} C_{\text{art}}$. Intrinsic metabolic clearance can, however, be larger than the flow of the inhaled chemical into the liver.

Metabolic intrinsic clearance is a constant unless exposure is so large that the capacity of the microsomal enzyme system is exceeded. If the metabolic capacity is exceeded or if metabolism is inhibited or

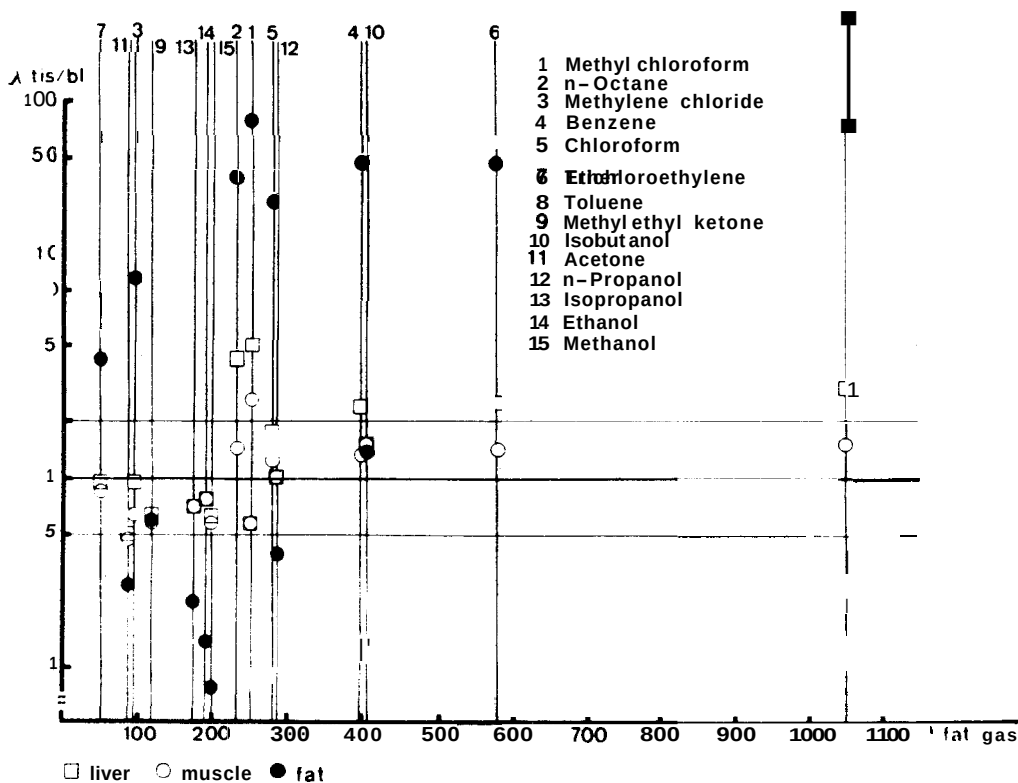


Figure 2. Comparison of partition coefficients of 15 selected solvents. The points correspond to values of fat-gas (abscissa) and tissue-blood (ordinate) partition coefficients at body temperature, as obtained from an earlier report (26) or as recently determined in our laboratory. Lean tissues are represented by human liver (□) and muscles (○); fat is represented by human subcutaneous adipose tissue (●). The numbers at the top of each vertical line identify the solvents, which are shown ordered and numbered in sequence according to increasing blood-gas partition coefficients. With the exceptions of methyl ethyl ketone and isobutanol, the solubility of solvents in fat is significantly different from their solubility in lean tissues.

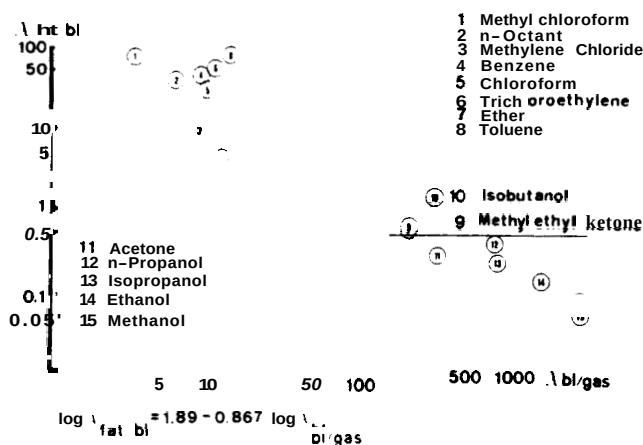


Figure 3. Correlation between fat-blood and blood-gas partition coefficients. The numbered circles identify the solvents and indicate the values of the blood-gas (abscissa) and fat-blood (ordinate) partition coefficients. The correlation between the logarithms of the fat-blood and blood-gas partition coefficients is described by the regression equation shown below the graph. Additional information on partition coefficients can be found in figure 2.

Rising of alv conc of selected solvents

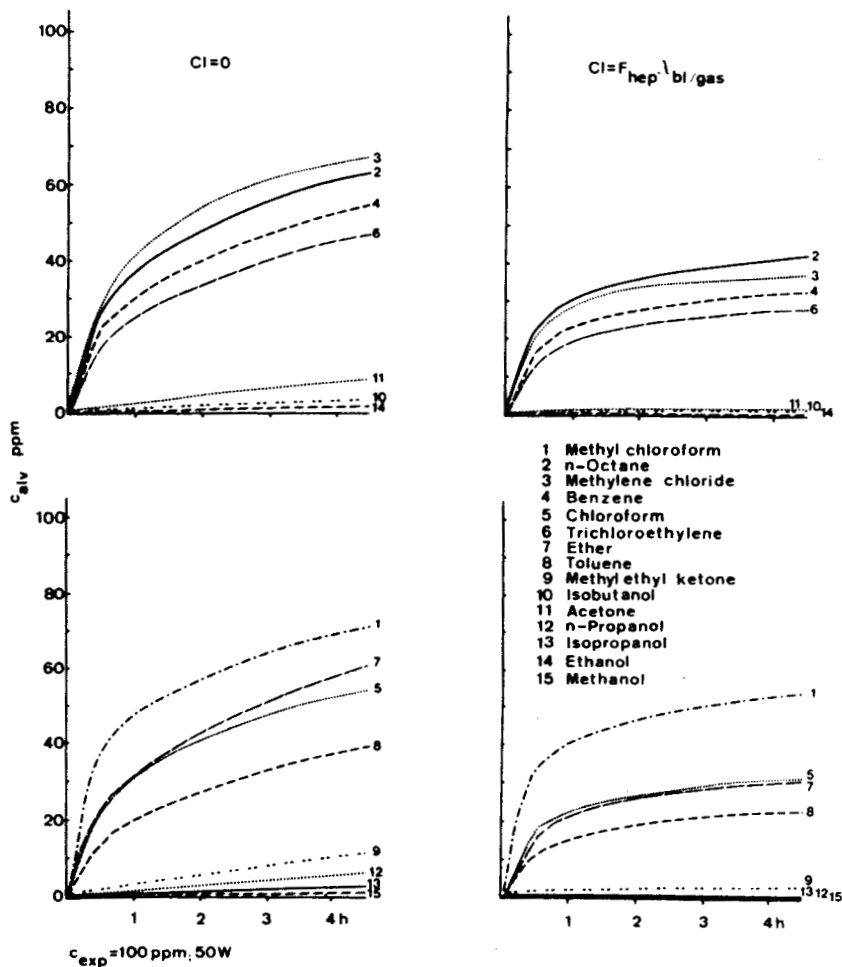


Figure 4. Effect of solubility and metabolism on the rise of alveolar (alv) concentration (conc). Simulation conditions: The simulation model shown in figure 1 was used to simulate exposures of a standard working man (70 kg, 170 cm) to 100 ppm of 15 selected solvents. (The solvents were split into two groups — upper and lower graphs — in order to avoid the lines overlapping as much as possible.) The simulations were done under the following two hypothetical conditions: (i) the solvents not metabolized (clearance = 0, left-hand side); (ii) the fraction of inhaled solvent reaching the liver completely metabolized (clearance = $F_{hep} \lambda_{bi/gas}$, right-hand side). The striking difference between the rise of the alveolar concentration of hydrophobic (1–8) and hydrophilic (9–15) solvents is apparent. The effect of metabolism can be seen from a comparison of the graphs on the right- and left-hand sides.

relation between fat-blood partition coefficients. The numbers indicate the solvents and indicate blood-gas (abscissa) and fat-blood partition coefficients. The correlation of the fat-blood partition coefficients is described by the equation shown below the graph on partition coefficient in figure 2.

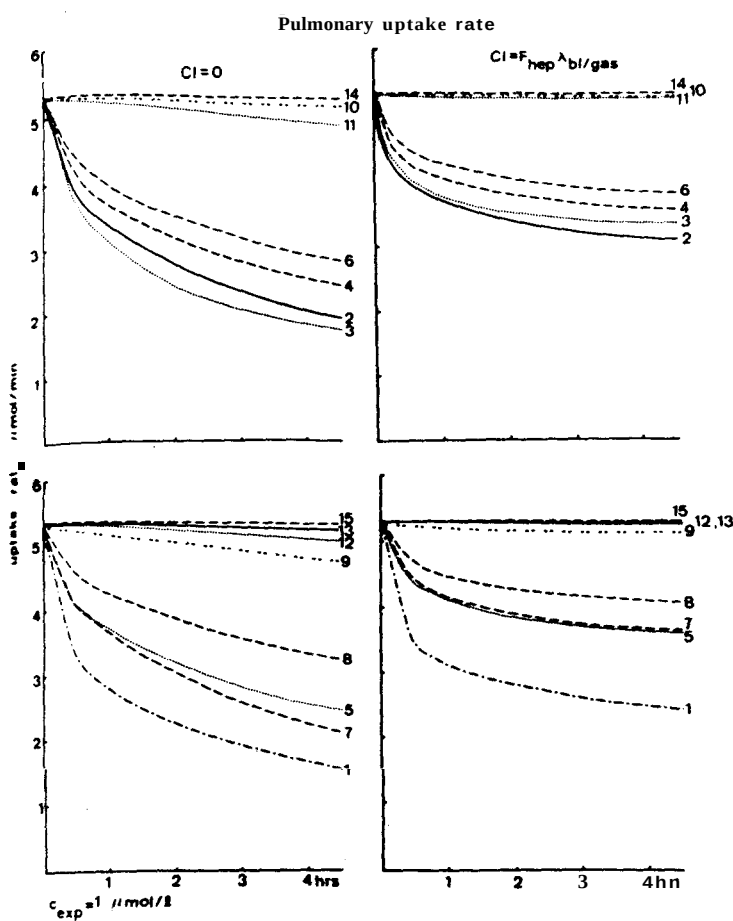
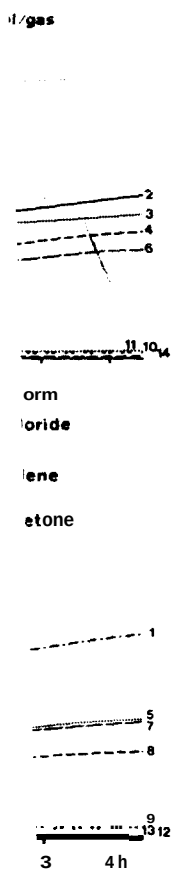


Figure 5. Effect of solubility and metabolism on rate of pulmonary uptake. The simulation conditions are the same as in figure 4, but the exposure concentration is 1 $\mu\text{mol/l}$. The striking difference between the uptake of hydrophobic and hydrophilic solvents and the increase in pulmonary uptake by metabolism is clearly noticeable.

induced during or following exposure, then the metabolic clearance is no longer a constant but changes with the concentration of the chemical in the liver. Capacity-limited metabolism can be accommodated in the model if metabolic clearance is made dependent on the rise or decline of the concentration in liver as follows:

$$Cl_t = \frac{u_t}{c_t} = \frac{V_{\max}}{K_m + c_t} \quad (\text{eq } 2)$$

where Cl_t is the metabolic clearance at time t when the metabolic rate u_t depends on the actual concentration in hepatic venous blood, c_t ; $V_{\max}$ and K_m are constants ($V_{\max}$ is defined as the maximal rate by which the chemical can be metabolized if no flow restrictions are imposed, and K_m denotes hepatic venous blood concentration at which $u_t = \frac{1}{2} V_{\max}$) (25, 28, 37).

If a chemical has more than one metabolic pathway, each pathway is described by a pair of constants ($V_{\max}$ and K_m). If the constants for the pathways are different, then the ratio of produced metabolites depends on the exposure concentration (33). Such a concentration-dependent ratio of meta-

bolites was observed, for example, in experimental studies of styrene (39) and trichloroethylene (52). My colleague J Vlach and I recently prepared a program for the solution of such a nonlinear model.

Toxicokinetics of organic solvents in view of the simulation model

Organic solvents are not similar to one another in chemical structure or in hydrophobic characteristics. To obtain insight into the effects of the solubility and metabolism of organic solvents on their uptake, distribution, and elimination, we simulated exposures to 15 organic solvents for which the blood-gas and tissue-gas partition coefficients are known. These 15 solvents are listed in the sequence of increasing blood-gas partition coefficients in figure 2. Statistical analysis shows no correlation between fat-gas and blood-gas partition coefficients or between fat-gas and fat-blood partition coefficients. Figure 2 shows that, with few exceptions, tissue-blood partition coefficients for lean tissues are between 0.5 and 2. This range indicates that the solubility of organic solvents in blood and in lean tissues is similar. Fat-

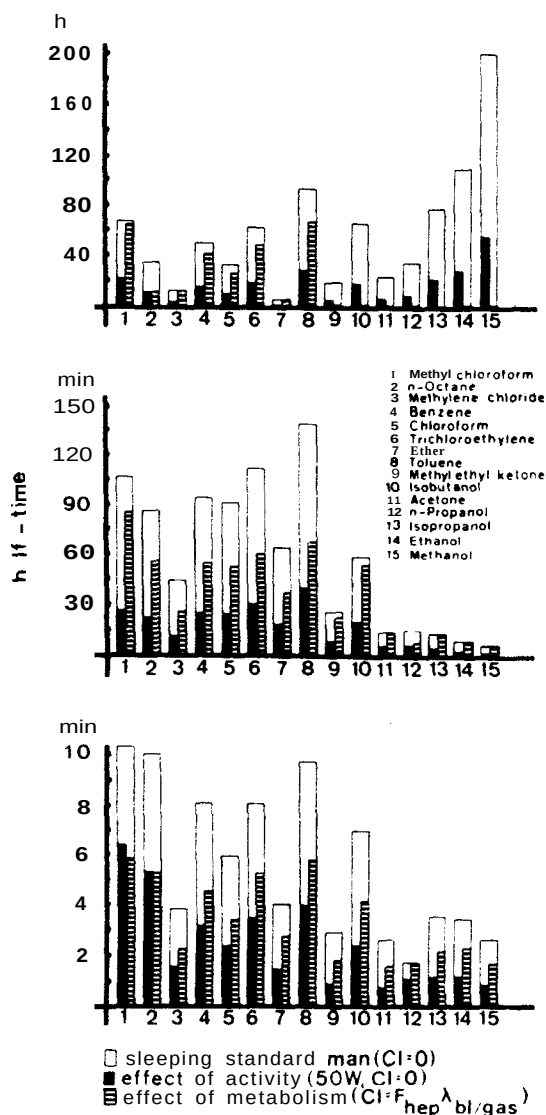


Figure 6. Effect of activity and metabolism on the half-times of the three decays apparent on desaturation curves. The half-times were obtained for the 15 selected solvents with the use of the simulation model in figure 1. The solvents are identified by the numbers on the abscissa. To show the most common range of diurnal fluctuation, the half-times were calculated for a standard man (70 kg, 170 cm) either sleeping (plain bars, parameters taken from reference 2) or working (solid bars, parameters shown in figure 1). Activity largely reduced all the half-times of all the solvents. To show the effect of metabolism, the simulations for a sleeping man were repeated, this time on the assumption that solvents are extensively metabolized in liver (clearance = $F_{hep} \lambda_{bl/gas}$). It is clearly noticeable that metabolism reduced all the half-times of all the solvents, that for hydrophilic solvents the half-time of the elimination phase (upper graph) was reduced the most, and that the half-time of the other two decays was reduced the least (middle and lower graphs).

blood partition coefficients are, with two exceptions, much smaller or much larger than 1. Therefore some solvents are significantly more soluble and some significantly less soluble in fat than in blood and in

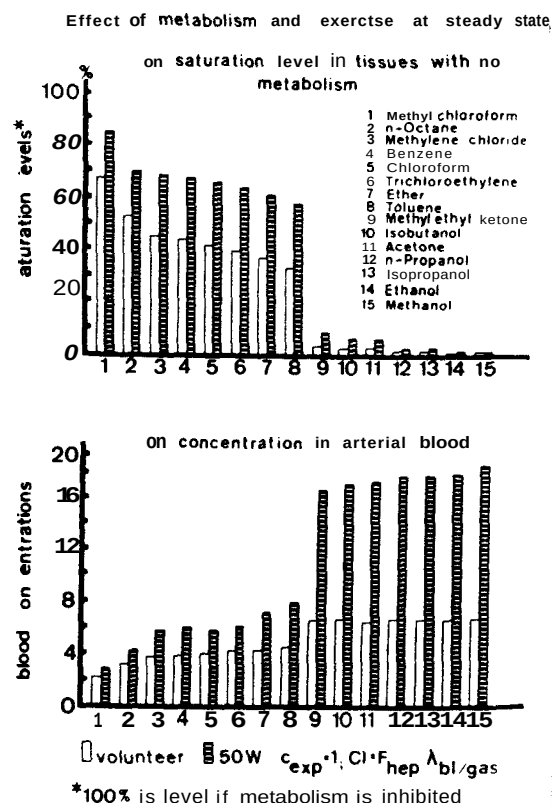
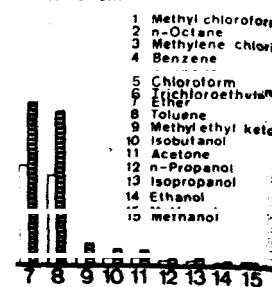


Figure 7. Effect of activity and metabolism on saturation levels and blood concentrations at steady state. The simulation conditions are as in figure 4. The bars represent the asymptotic values for a resting (plain bars) and working (striped bars) man. The solvents are identified by the numbers on the abscissa. Metabolism reduces the saturation levels of all the solvents (upper graph), the reduction being larger in a resting man than in a working man. Although hydrophilic solvents reach the lowest saturation levels, their blood concentrations are larger than the blood concentrations of hydrophobic solvents (lower graph). This difference can be explained by the restriction of solvent supply by alveolar ventilation and by the large capacity of blood to retain hydrophilic solvents.

lean tissues. Figure 3 shows two distinct groups of solvents, the hydrophobic solvents (numbered 1-8) and the hydrophilic solvents (numbered 11-15). Hydrophobic solvents have relatively small blood-gas partition coefficients and have fat-blood partition coefficients much larger than 1. Hydrophilic solvents have blood-gas partition coefficients larger than 200 and have fat-blood partition coefficient, much smaller than 1. Figures 4 through 10 show that the kinetic patterns of hydrophobic and hydrophilic solvents are very different and show that the kinetics of two solvents with large solubility that is approximately equal in all tissues (methyl ethyl ketone, number 9 and isobutanol, number 10) resemble the kinetics of other hydrophilic solvents. Figure 4 shows the differences in the rise of alveolar concentrations, and figure 5 shows the differences in the pulmonary uptake rate of the selected solvents. Because the simulation is done on the assumption that the

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To obtain insight into the effect of metabolism on the kinetics of solvents, we repeated the simulation on the assumption that the metabolic rate of each solvent equals the flow of the solvent into the liver ($Cl = F_{hep} \lambda_{bl/gas}$; ie, extraction ratio equals 1). If the graphs on the right and left sides of figures 4 and 5 are compared, it is obvious that metabolism reduces the alveolar concentration and enhances the pulmonary uptake of all solvents. To obtain insight into the effects of alveolar ventilation and tissue perfusion on the kinetics of solvents, we simulated the same exposures twice by using the physiological parameters of a standard man. One exposure was under sleeping or resting conditions (volunteers in many laboratory studies), and one exposure was under working conditions (workers with energy expenditure of 50 W). Figure 6 shows that exercise, as well as metabolism, shortens the half-times of all compartments and that

half-times of the elimination phase of hydrophilic solvents by metabolism is shortened the most. (The half-times of two additional decays that were shorter than 4 min are not shown in figure 6.) Figure 7 shows that metabolism reduces the saturation levels of all solvents in all tissues, that the reduction is larger in a resting man than in a working man, and that,

despite the fact that saturation levels of hydrophilic solvents are smaller than saturation levels of hydrophobic solvents, the concentrations of hydrophilic solvents in blood are larger than the concentrations of hydrophobic solvents. Figure 8 shows that the pulmonary uptake of working individuals is much larger than the pulmonary uptake of resting individuals, that metabolism enhances the pulmonary uptake of all solvents, and that the pulmonary uptake of hydrophilic solvents is much larger than that of hydrophobic solvents. To obtain insight into the effect of body fat on pulmonary uptake, we simulated 8-h exposures to each solvent, using physiological parameters for men 150 cm or 185 cm tall and weighing 70 kg (35). The pulmonary uptake and the starting conditions of the elimination phase of the desaturation curves of hydrophobic solvents increased with body fat (35), but pulmonary uptake and the desaturation of hydrophilic solvents were little affected by body fat. Figure 9 shows the difference in the patterns of the desaturation curves of hydrophobic and hydrophilic solvents, trichloroethylene and acetone being the examples. Figure 9 also shows the differences in the effects of exposure duration on the pulmonary elimination of hydrophobic and hydrophilic solvents. Similar differences were documented by experimental data (11, 12). Figure 10 shows how the fluctuation of exposure concentration affects alveolar and blood concentrations of hydrophobic and hydrophilic solvents. Figure 10 shows

that the concentration variation of solvents in alveolar air and blood is small compared to the concentration variation of gases (represented in figure 10 by $CF_3 \cdot CH_2Cl$), that the larger the solubility of the solvent, the smaller the concentration variation in biological material, and that concentrations of hydrophilic solvents (represented by acetone) in alveolar air and blood maintain a rising trend during the entire exposure.

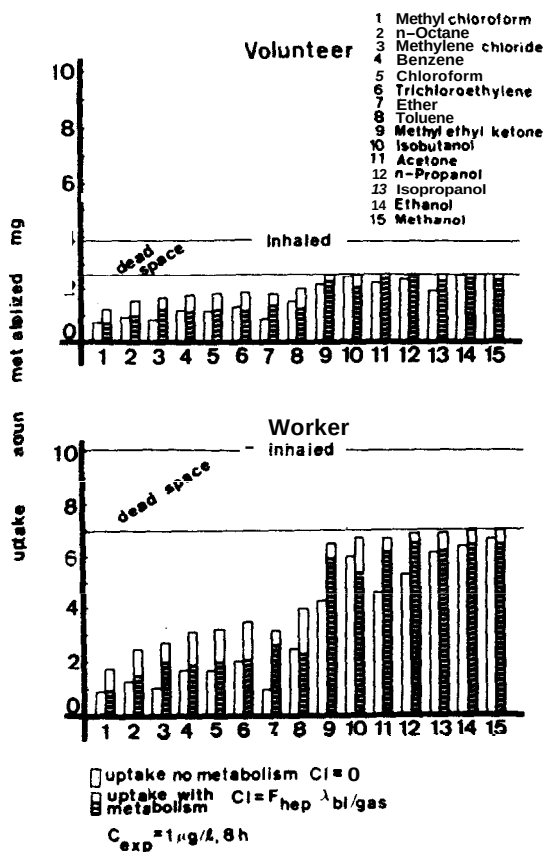
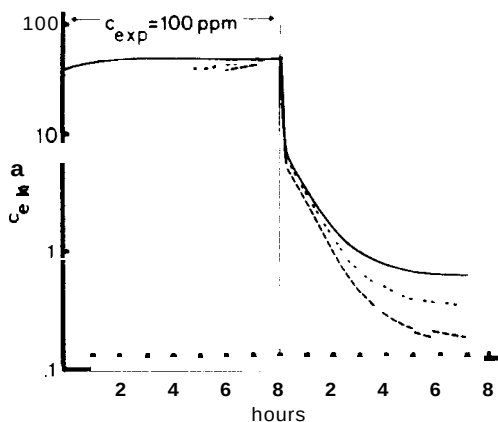


Figure 8. Effect of metabolism and activity on the pulmonary uptake of solvents during an 8-h exposure. The exposures to $1 \mu g/l$ were simulated for a resting (upper graph) and a working (lower graph) standard man with the simulation conditions in figure 4. The solvents are identified by the numbers on the abscissa. The distance between the two horizontal lines ("dead space") indicates the amounts of inhaled solvents which do not reach the alveoli. The plain bars represent body burden at the end of an 8-h exposure, on the assumption that the solvent is not metabolized (clearance = 0, plain bars to the left of the striped bars) or is extensively metabolized (clearance = $F_{hep} \lambda_{bl/gas}$, plain bars above striped bars). The striped bars represent the amount metabolized during the 8-h exposure. The sum of the body burden and the amount metabolized represents pulmonary uptake during an 8-h exposure. It is apparent that the hydrophilic solvents were extensively absorbed in alveoli and that metabolism increased their pulmonary uptake little but greatly reduced their body burden.

TRICHLOROETHYLENE



ACETONE

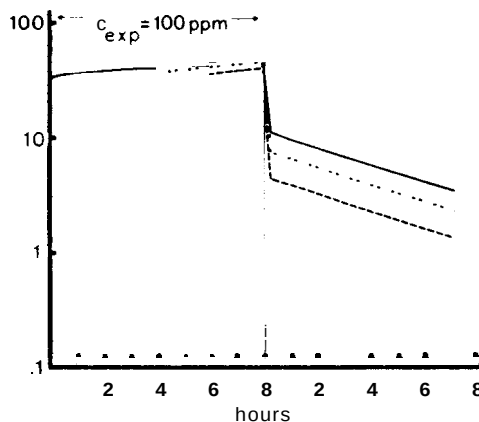


Figure 9. Effect of exposure duration and solubility on desaturation curves. Simulation was made of a 2-, 4-, and 8-h exposure (exp) of a working man to 100 ppm of trichloroethylene and acetone. The simulation conditions were as shown in figure 4, but real clearance (Cl) for trichloroethylene (Cl = 41 l/min) and acetone (Cl = 18 l/min) were used. The difference in the decline of the concentrations (c) of hydrophobic (trichloroethylene) and hydrophilic (acetone) solvents in mixed exhaled air (c_{exh}) is clearly noticeable.

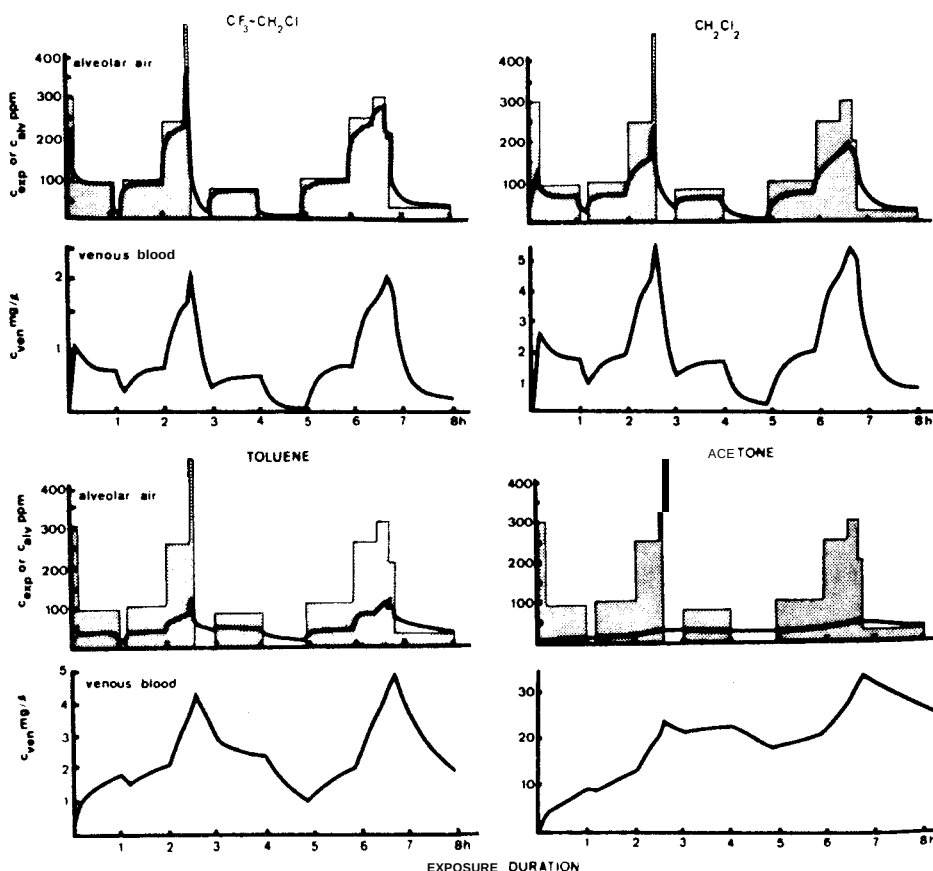
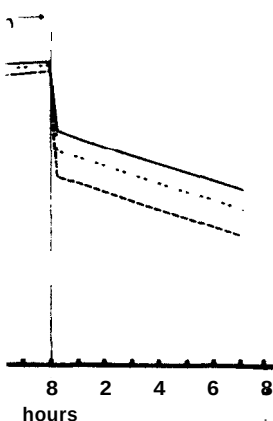


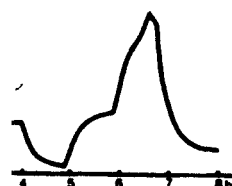
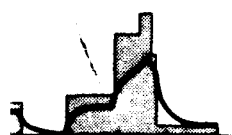
Figure 10. Effect of solubility on alveolar and venous blood concentrations during exposure to a fluctuating concentration. Eight-hour exposures to the gas 2,2,2-trifluoro-1-chloroethane (CF_3-CH_2Cl) and the solvents methylene chloride (CH_2Cl_2), toluene, and acetone were simulated for a standard working man exposed to a time-weighted average concentration of 100 ppm. The exposure (exp) concentration (c) fluctuated (the shaded areas) in the range restricted by the excursion factor. It is clearly noticeable that alveolar (alv) and blood (ven = venous) concentrations of solvents fluctuate less than concentrations of the gas and that the smaller the solubility the larger the fluctuation.

CETONE

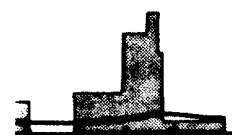


as made of a 2-, 4-, and 8-h exposure durations were as shown in figure 1. The difference in the concentrations of solvents in mixed exhaled air (c)

CH₂Cl₂



CETONE



to a fluctuating concentration of solvents, methylene chloride (CH₂Cl₂) weighted average concentration is restricted by the excursion factor. Solvents fluctuate less than concentrations

simulation model and experimental data

The objective of the simulations shown in figures 4 through 10 was to obtain general insight into the uptake, distribution, and elimination of organic solvents under different exposure conditions. If the simulation model is to be applied to a specific exposure situation such as biological exposure monitoring, thorough testing of the model by comparison of experimental and simulation data must precede its application. A good example of the testing of a simulation model was published by Guberan (40), who employed the model which was developed by Droz (12) for trichloroethylene to simulate experimental exposures by other investigators (21, 54, 86). Experimental data used in the testing were mean values obtained from a group of healthy volunteers exposed under well-controlled conditions. The experimental data and the simulation data matched well.

In actual fact, individual differences in physiology and life-style result in large differences in uptake and elimination among exposed persons. For example, our simulations have shown that the variability of physiological parameters of exposed subjects can cause the concentrations of lipophilic solvents in exhaled air collected 16 h after an 8-h exposure to differ up to 15 times, depending on the body build and activity of the subjects (29). As a more specific example, 16 h after exposure an overweight worker who performs moderate work (50 W) during a 8-h exposure to toluene and who rests and sleeps after his workshift will exhale a 12-times larger concentration of toluene than an underweight worker who performs sedentary work during the same exposure but who exercises after his workshift.

Furthermore, in actual fact, metabolic clearance varies among individuals and varies intermittently in the same individual as a result of circumstantial factors. For example, chronic alcohol intake enhances the metabolism of solvents (79), but acute alcohol intake (75, 81, 97, 99, 103) and coexposure to chemicals (24, 49, 50, 51, 69, 78, 91, 98) reduce the metabolic clearance of inhaled solvents. The reduction is explained by a competitive inhibition of microsomal mixed-function oxidase (56). It has been shown experimentally (24, 99), as well as by simulation (24, 25), that reduced metabolic clearance is manifested not only by smaller amounts of urinary metabolites, but also by reduced pulmonary uptake and increased concentrations of inhaled chemicals in blood, tissues, and exhaled air. Other factors, such as enzyme induction (9, 48, 51), polymorphism in metabolism (22), genetic factors (22), sex (54, 65), diet (64, 79), and altitude, change the uptake and elimination of chemicals by altering physiological parameters or metabolic clearance. The kinetics also change if inhalation exposure is accompanied by skin absorption.

Consistent differences between simulation and experimental data can, however, signal a particular

behavior of the inhaled chemical. An example is the simulation of inhalation exposure to hydrophilic solvents. Our simulation of experiments by Astrand and her co-workers (1) was successful for hydrophobic solvents, but was only partly successful for hydrophilic solvents. In simulation, the rising and declining of acetone in blood followed a pattern similar to the pattern of experimental data, but blood concentrations, pulmonary uptake, and the pattern of the concentrations in alveolar air were different from experimental data. These differences prompted us to investigate the retention of vapors of solvents in respiratory airways (27). Using a rabbit trachea, we showed that concentrations of vapors of hydrophilic solvents, such as acetone and alcohols, are reduced by 20 to 70 % during passage through the trachea and that the lost amount can be recovered if the trachea is washed with clean air. No significant retention of inert gases or vapors of hydrophobic solvents in the trachea was observed (table 1). Obviously, retention and desorption on the walls of the respiratory airways means that the concentration of hydrophilic solvents in end-exhaled air does not represent the concentration in alveolar air. These factors explain the differences between experimental and simulation data.

Before the simulation model is applied to specific hydrophilic solvents, the following two problems must be solved: (i) a method for evaluating retention in respiratory airways in man must be developed; (ii) the respiratory airways must be treated in the simulation model as a separate compartment.

Table 1. Retention of vapors in rabbit trachea in vitro:

Substance	Percentage of inflow concentration retained		
	N ^b	Mean	Standard error
2,2,2-Trifluoro-1-chloroethane	6	-0.1	0.9
1,1-Difluoro-2-chloroethylene	5	0.0	1.0
Methylene chloride	5	2.5	3.0
Halothane (CF ₃ - CHClBr)	5	6.7	0.5
Freon-12 (CCl ₂ F ₂)	5	6.9	0.3
Trichloroethylene	5	8.3	1.6
Toluene	10	10.6	1.2
Ethylene oxide	4	13.9	1.4
Styrene	6	17.6	1.7
Ethyl acetate	9	17.7	2.4
Acetone	9	21.9	1.8
n-Amyl alcohol	5	41.1	1.3
Acetyl acetone	6	45.8	1.4
1-Butanol	7	48.2	3.0
1-Propanol	5	54.0	1.5
Ethanol	11	58.2	2.4
1,4-Dioxane	3	59.5	1.7
Methanol	5	68.6	0.7

^a Retention was calculated from the difference between inflow and outflow concentrations as follows:

$$R = 100 \frac{C_{in} - C_{out}}{C_{in}} \%$$

^b N indicates the number of experiments performed

Toxicokinetics and toxic effect

Acute toxicity of organic solvents is frequently manifested by depression of the function of the central nervous system. Some lipophilic solvents, such as trichloroethylene, ethyl ether, and chloroform, have been used for clinical anesthesia. Berman et al (7), by exposing control rats and rats pretreated with phenobarbital to an anesthetic concentration of methoxyflurane, documented that the anesthetic effect is related to blood concentration rather than to exposure concentration. [Methoxyflurane ($\text{CH}_3\text{-O-CF}_2\text{-CHCl}_2$) is an anesthetic agent with solubility resembling that of toluene.] The untreated control rats were anesthetized within 10 min of exposure, but the pretreated rats, which had their blood concentration reduced by 25 %, showed no symptoms of anesthesia. The reduced blood concentration was the result of increased metabolic clearance caused by induction. The pretreated rats became anesthetized when their blood concentration was raised by 25 %. It is beyond the scope of this article to review the literature documenting that anesthetic effect is related to brain concentration of the agent, that the rates of submerging in and emerging from anesthesia are related to the blood solubility of the agent, that anesthetic concentration can be derived from the lipid solubility of the agent, and that anesthetic concentration can be predicted from physical constants and the chemical structure of the agent. The reviews can be found in references 19, 58, 67, and 90. Hydrophilic solvents also exhibit analgesic effects, yet they have not been used for clinical anesthesia or analgesia (with the exception of ethanol). In my opinion, their fat-blood partition coefficient, being smaller than 1, prevents the damping in cerebral lipids and lipoproteins. Thus hydrophilic solvents act upon other receptors, and cardiac or respiratory arrest precedes the development of the anesthetic effect.

The hepatotoxic effect of chemicals is usually related to their hepatic metabolism (84). In many instances, hepatotoxicity is related to the alteration of the metabolic pathway of the chemical after the capacity of one step in the metabolic pathway is saturated or when a particular enzyme is inhibited. Both capacity-limited metabolism and competitive inhibition during inhalation exposure to organic solvents have been documented. It remains to be seen whether hepatotoxic effect can be predicted from toxicokinetic parameters such as V_{max} and K_m in a similar manner as anesthetic effect can be predicted from solubility.

Acknowledgments

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