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APPLICATION OF TOXICOKINETIC MODELS TO ESTABLISH BIOLOGICAL EXPOSURE INDICATORS*

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Abstract—This article is a critical review of the application of toxicokinetic models to the biological monitoring of occupational exposure to industrial chemicals. The experimentally based toxicokinetic models are used to determine the elimination half-lives, the metabolic clearance, the elimination rate constants and the volume of distribution. The physiologically based multicompartmental simulation models, which describe the uptake, distribution and elimination of inhaled or percutaneously absorbed organic solvents, contributed to the understanding of the transport of the xenobiotics in the body. They are used for describing and predicting the dependence of concentrations of indicators of exposure in biological specimens on the extent of exposure and time (duration of exposure and sampling time), and for depicting the contribution of various biological and exposure factors to differences in biological response to the exposure. In biological monitoring, toxicokinetic models are used for matching biological concentrations and body burden of indicators of exposure with extent of inhalation or dermal exposure, and for predicting half-lives. They lay the grounds for the strategy used in collecting biological specimens and controlling external and internal factors which alter the biological concentrations and possibly increase the health risk from the exposure. Elimination half-lives are used as guidelines in selecting the appropriate indicators of exposure, in designing the procedure for the collection of biological specimens, and in interpreting the measured data. Predictive models are needed for heavy metals, particulates and compounds undergoing binding to constituents of tissues.

INTRODUCTION

EXPOSURES to toxic compounds in the workplace have traditionally been monitored by measurements of airborne concentrations. Area sampling is used to detect and evaluate the source of exposure, and personal sampling is used to determine the exposure of individual workers. Air monitoring, however, helps to control only inhalation exposure, neglecting uptake resulting from dermal exposure, from exposure to non-occupational sources, or from unexpected excessive exposure resulting from peculiarities of certain jobs or from poor working practices (FISEROVA-BERGEROVA, 1987a, 1990a). Since there are no external means of measuring the extent of these exposures, monitoring of parent compounds, their metabolites or biochemical changes induced by exposure in blood and excreta ('indicators of exposure') is recommended for the evaluation of the integrated exposure of the worker (ACGIH, 1989; COMMISSION FOR THE INVESTIGATION OF HEALTH HAZARDS, 1989). Moreover, the measurement of these indicators in biological specimens is the only means of measuring the effectiveness of respirators and protective clothing, and of monitoring exposure in the workplace outdoors, or exposure of workers with non-stationary workplaces.

Toxicokinetics, which study and describe uptake, distribution, metabolism and

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elimination of toxic compounds from the body, provide information on the relationship between external (environmental) and internal (body burden) exposures which contributes to our understanding of the link between external exposure and the development of adverse effects. The purpose of this article is to review the application of toxicokinetic models to biological monitoring of occupational exposure.

In the past, the application of biological monitoring was hindered by the lack of suitable analytical methods, by the variability of biological concentrations of indicators of exposure which resulted from the same extent of exposure, and by the complexity of the kinetics of uptake, distribution and elimination of compounds from the body. This has changed in the last two decades: modern technology has provided instruments for suitable analytical methods. The development of physiologically based multicompartmental simulation models for organic solvents has provided a tool for understanding the fate of these compounds in the body, and for depicting the contribution of various exposure and biological factors to the variability of biological response to the exposure. Simulation models have also provided the foundation for strategies used in biological monitoring, for collecting biological specimens, for matching biological concentrations and body burden with extent of inhalation or dermal exposure, and for controlling factors which alter the biological concentrations and possibly increase the health risk from the exposure.

TOXICOKINETIC MODELS

There are three types of toxicokinetic models used in the biological monitoring of exposure to industrial chemicals: (1) empirical equations; (2) experimentally based toxicokinetic models; and (3) physiologically based simulation models.

Empirical equations, such as correlation equations frequently used to compare, under specified conditions, the extent of exposure with biological concentrations of indicators of exposure, are based on field or laboratory observations. Empirical equations are also used to describe kinetic processes by simple mathematical expressions. For example, the pulmonary uptake of vapours is a function of the blood/gas partition coefficient and the square root of time (LOWE, 1972), or the elimination of the parent compound or metabolites from the body is an exponential function fitting the experimental data. Empirical equations provide no insight into the movements of the compound in the body, and their use is very restricted.

Experimentally based toxicokinetic models are based on experimental data, which show the concentration of indicators of exposure during and following exposure. These models determine kinetic parameters—such as elimination rate constants and the area under the curve (AUC)—which are used to calculate elimination half-life, volume of distribution and metabolic clearance. Metabolic clearance is defined by a single constant or by two constants when a saturable process occurs. These models provide, however, very little insight into the effect of biological and circumstantial factors on biological concentrations of the parent compound or its metabolite.

Physiologically based multicompartmental simulation models are based on physiological parameters of the exposed subject (pulmonary ventilation, and volume and perfusion of tissues), and on solubility of the compound in blood and tissues (described by the appropriate partition coefficients). These parameters needed for

describing uptake, distribution and elimination of non-metabolized organic solvents can be found in the literature or can be easily measured or predicted (FISEROVA-BERGEROVA, 1983; FISEROVA-BERGEROVA *et al.*, 1984; FISEROVA-BERGEROVA and DIAZ, 1986). In order to include metabolism and excretion of metabolite(s), the model employs parameters provided by experimentally based toxicokinetic models (metabolic clearance, elimination constants and volume of distribution of metabolites). As in pharmacokinetic models used for describing the elimination of drugs, each metabolic pathway in a toxicokinetic model is described either by a single constant, clearance (DROZ, 1978; FISEROVA-BERGEROVA *et al.*, 1974, 1980; PERBELLINI *et al.*, 1986) or by two constants (ANDERSEN *et al.*, 1984; FISEROVA-BERGEROVA, 1981, 1983; RAMSEY and ANDERSEN, 1984), and elimination of metabolites is described by elimination constants (DROZ, 1978; DROZ and GUILLEMIN, 1983; PERBELLINI *et al.*, 1986; RAMSEY and ANDERSEN, 1984; SATO *et al.*, 1990a, b). In order to simulate dermal absorption, the percutaneous penetration rate (flux) of the compound and the area of the exposed body surface must be given (FISEROVA-BERGEROVA, in preparation).

Simulation models provide insight into the movements of the compound in the body, and are a powerful tool for predicting the effects of a variety of factors on the biological concentrations and thus on the results of biological monitoring of occupational exposure to organic solvents. There is an urgent need for similar simulation models for metals and particulates, and for compounds which undergo binding to constituents of tissue.

Solutions of simulation models

Simulation models are described by simultaneous differential equations, the number of which is dictated by the number of compartments needed for describing the kinetic processes (DROZ, 1978; FISEROVA-BERGEROVA *et al.*, 1974, 1980; RAMSEY and ANDERSEN, 1984). At low exposures, the processes approximate to first-order kinetics. At high exposures, however, as the biological system approaches saturation, the kinetics deviate from first-order. Most susceptible to saturation are metabolizing enzyme systems and availability of binding sites, but limited solubility of some compounds can also result in non-linearity. The equations can be solved by numerical integration (DROZ, 1978; JOHANSON, 1986; PATERSON and MACKAY, 1986; PERBELLINI *et al.*, 1986; RAMSEY and ANDERSEN, 1984). The spread sheet template developed for Microsoft Excel software makes the solution of the model accessible to those not mathematically sophisticated (JOHANSON and NASLUND, 1988).

At the low exposures permissible in the workplaces, almost all processes are governed by first-order kinetics. Under such conditions, the uptake, distribution and elimination of the inhaled vapours can be described by a linear model in which biotransformation is described by a single constant—metabolic clearance (FISEROVA-BERGEROVA *et al.*, 1974). For extensively metabolized compounds, the product of hepatic blood flow and blood/gas partition coefficient can be substituted for clearance. Solution of such linear models can be found by a mathematical operation—the Laplace transform—which replaces differentiation by algebraic operations, with the resulting functions expressed as a sum of exponential functions (VLACH, 1983). In these functions, exponential constants are reciprocal to half-lives ($k = \ln(2)/t_{\frac{1}{2}}$) (WAGNER, 1976). Even the application of the Laplace transform is very limited (it cannot be used to describe high exposures, the excretion of metabolites or dermal absorption), its

usefulness in solving linear models is nevertheless quite high, since many decisions in biological monitoring are based on biological half-lives (DROZ, 1989).

APPLICATION OF SIMULATION MODELS IN BIOLOGICAL MONITORING

Selection of indicators of exposure

Selection of indicators of exposure is influenced by several factors: (1) by the sensitivity and specificity to exposure to the particular compound. This means that the monitored indicator of exposure must be measurable at the exposure permissible in the workplace (insufficient biological response or variability in background concentrations of the same compounds of endogenic or environmental origin can confound the result); and, preferably, the monitored indicator should not be observed after exposure to other compounds, though a non-specific indicator of exposure can be preferred over a specific indicator if its biological concentration correlates better with the extent of exposure; (2) by technical prerequisites such as availability of biological specimens, the stability of the sample and the availability of simple analytical methods with sufficient sensitivity and accuracy; and (3) by access to laboratories with a good quality control programme. The preconditions for the implementation of biological monitoring of occupational exposure to toxic compounds are: (1) information on kinetics of the indicator of exposure and information on uptake, distribution and elimination of the parent compound; (2) understanding of the relationship between biological concentrations of indicators of exposure and the extent of exposure and biological effect; (3) understanding of external (exposure duration and fluctuation, working conditions and workload, route of entry, coexposure to chemicals) and internal (ethnic, genetic, disease) factors affecting these relationships (DROZ and SAVOLAINEN, 1990; FISEROVA-BERGEROVA, 1987a, 1990a).

Toxicokinetic simulation models can provide the following information on which biological monitoring is designed and data are interpreted: (1) concentration effect; (2) time effect; (3) matching exposure in the workplace with worker's integrated exposure, which includes absorption through all entries (pulmonary, dermal and gastrointestinal), accumulated residues and possible non-occupational exposure; (4) depicting effects of external and internal factors which alter the relationship between intensity of exposure and biological concentration and body burden of the indicator of exposure; (5) extrapolation and prediction of biological concentrations resulting from exposure to new compounds or new exposure conditions; and (6) verification of data.

Evaluation of concentration effect

At low exposures, the relationship between extent of exposure and biological concentrations is usually linear. At high concentrations, saturable processes disturb the linear relationship and can induce undesirable biochemical and functional changes. Although saturability and its consequences are usually studied in laboratory animals, a limited amount of human data is available from field studies. The interference of saturable processes in biological monitoring of exposure and health effects is shown by the following two examples. (1) Saturated metabolism of dimethyl acetamide, DMAC, was observed in workers exposed to approximately 10 ppm of DMAC, which is the current limit for occupational inhalation exposure (KENNEDY, 1990). Since, at this exposure, the relationship between intensity of exposure and urinary excretion of

metabolites approaches the plateau, biological monitoring of DMAC metabolites in urine provides no quantitative information on the DMAC exposure permissible in the workplace. Moreover, the overloading of the microsomal mixed-function oxidase system may alter metabolism of other concurrently- present industrial chemicals and medications, the metabolism of which is mediated by the same enzyme system as DMAC metabolism. This raises the question of whether an occupational exposure limit which is outside the range of linear kinetics sufficiently protects the worker (FISEROVA-BERGEROVA, 1981). (2) The second example is the binding of cadmium to renal cortex proteins. When the capacity of the binding sites is exceeded as a result of large or long-lasting exposure, renal function is impaired and excessive cadmium is excreted in urine. Consequently, the relationship between the extent of exposure and cadmium concentration in urine is altered (KJELLSTROM *et al.*, 1984).

Evaluation of time effect

Since the uptake, distribution and elimination of industrial chemicals and their metabolites are kinetic processes, the outcome of the measurements depends on the timing and duration of the sampling. The concentration of the indicator of exposure in the biological matrix can change rapidly or slowly, depending on its elimination half-life, which depends on biosolubility of the compound, its susceptibility to metabolism, and the activity and body build of the worker (FISEROVA-BERGEROVA *et al.*, 1984; FISEROVA-BERGEROVA, 1985).

Sampling time and the duration of the sampling period during the rapid elimination phase (with half-lives of a few minutes) are very critical. For example, if the exhaled air sample for measurement of a volatile compound is collected shortly after leaving the polluted area, the outcome of analysis very much depends not only on the exact time the sample was collected, but also on whether the sample was collected instantaneously (a single breath) or over a period of time (Table 1). Similar considerations apply to

TABLE 1. EFFECT OF DURATION OF SAMPLING ON CONCENTRATION OF INDICATORS OF EXPOSURE WITH A SHORT ELIMINATION HALF-LIFE*

Sampling period	$t_{\frac{1}{2}}$ 2 min	3 min	5 min
Instant	100	100	100
1 min	87	91	94
2 min	72	81	90
3 min	62	72	82
5 min	48	59	72

*The concentrations are related to the concentration in the instant sample, which for convenience equals 100.

measurements in random urine samples which may represent voidance of less than 1 h or a couple of hours. If the indicator of exposure is excreted rapidly (with a half-life shorter than 5 h), then the outcome of the measurements is significantly affected by the time and period between voiding.

Since it is difficult to control sampling for measurements of indicators with short elimination half-lives, the time factor (the time between leaving the polluted workplace

and sampling) may introduce an error in measurements. For this reason, measurements of volatile solvents in exhaled air or in blood, collected 'during exposure' or shortly after the end of exposure, are not suitable for routine quantitative testing.

Measurements of indicators with long elimination half-lives, or in samples collected during the slow elimination phase, are less likely to be affected by sampling time. However, if the half-life is longer than 10 h, the accumulation of the parent compound and/or its metabolite causes the biological concentrations to rise over the working week, month or lifetime. Consequently the concentrations in samples collected at the beginning of the working week are lower than those in samples collected at the end of the working week, or after months or years of exposure (DROZ, 1978, 1989; FIŠEROVA-BERGEROVA *et al.*, 1974, 1980; FIŠEROVA-BERGEROVA, 1987a, b).

The elimination half-life determines whether the measurement is an indicator of recent exposure or exposure over the day, week, month or lifetime (DROZ, 1989). Table 2 provides guidelines as to how the elimination half-life affects the sampling time and information on the type of exposure.

TABLE 2. DEPENDENCE OF EXPOSURE EVALUATION AND SAMPLING TIME ON ELIMINATION HALF-LIFE

$t_{\frac{1}{2}}$	Exposure	Sampling time
$t_{\frac{1}{2}} < 2$ h	Recent	Very critical
$2 < t_{\frac{1}{2}} < 5$ h	Daily	Critical
$5 < t_{\frac{1}{2}} < 48$ h	Weekly	End of work week
$t_{\frac{1}{2}} > 48$ h	Monthly or lifetime	Discretionary (after months of exposure)

Matching extent of exposure and biological concentrations

Evaluation of occupational exposure is usually based on comparing measured concentrations of the airborne compound with the reference values for occupational inhalation exposure. Simulation models, because of their ability to match the extent of exposures associated with the predetermined dose or biological concentrations of indicators of exposure, are a valuable tool in extrapolation of reference values for workers with unusual workshifts (ANDERSEN *et al.*, 1987b; SATO *et al.*, 1990b). If the health effect studied is associated with the biological concentration, then the concentration in the target organ should be of concern, as in acute effects such as carboxyhaemoglobinaemia, or depression of CNS function by organic solvents. If the health effect studied is associated with the capacity of the defence mechanism of the target organ, then the doses should be of concern, as in the development of renal injury resulting from exposure to some heavy metals.

The best known reference values are Threshold Limit Values (TLV) adopted by the American Conference of Governmental Industrial Hygienists (ACGIH, 1989) and the German Maximum Concentrations at the Workplace (MAK) recommended by the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (COMMISSION FOR THE INVESTIGATION OF HEALTH HAZARDS, 1989). It is the policy of both organizations that their reference values for biological concentrations of indicators of exposure (Biological Exposure Indices, BEI, and Biological Tolerance

Values, BAT) provide the same extent of health protection as TLV-TWA or MAK, respectively. Both organizations employ the toxicokinetic approach to compare airborne and biological concentrations. BEIs are usually derived as values which most likely result from occupational exposure to TLV-TWA (FISEROVA-BERGEROVA, 1990a), and are obtained by simulation of the occupational exposure of a reference worker (170 cm tall, 70 kg weight, light work—alveolar ventilation 15–20 l. min^{-1}). BATs, on the other hand, are derived as the highest values expected to result from occupational exposure to MAK (HENSCHLER, 1990). Therefore, BATs are usually two or three times higher than BEIs (FISEROVA-BERGEROVA, 1990b). If the reference value for indicators of exposure derived empirically from field studies (that is, by comparing biological concentrations with health effect) deviates from the reference value derived on a toxicokinetic basis (equivalent to the airborne reference value), both reference values are re-examined.

To simplify the evaluation of biological monitoring data, BEIs and BATs are given for samples collected at the specified time which, for convenience, is usually defined as 'end of the shift' (meaning end of exposure) or 'prior to the next shift' (meaning 16 h after the end of exposure). For chemicals with a long elimination half-life (days or weeks), the sampling time can be discretionary, but the BEI or BAT may apply only to specimens collected after a certain length of exposure (for example 6 months) (ACGIH, 1986; COMMISSION FOR THE INVESTIGATION OF HEALTH HAZARDS, 1989).

Factors affecting the relationship between exposure and biological concentrations

Information on possible additional sources of exposure, and on circumstantial factors affecting biological concentrations of indicators of exposure, can be generated by comparing the ratio of measured airborne and biological concentrations of indicators of exposure with the ratio of the reference values which were determined on a toxicokinetic basis. An unusual ratio, besides pointing to technical or analytical errors or unrepresentative samples, also points to other factors, the effect of which can be depicted by an appropriate simulation model. Examples of such factors are: (1) additional or fluctuating exposures, or unusual exposure duration (DROZ and GUILLEMIN, 1983; DROZ, 1978; FERNANDEZ *et al.*, 1977; FISEROVA-BERGEROVA, 1981, 1985, 1987b; FISEROVA-BERGEROVA *et al.*, 1974, 1980, 1984; GUBERAN and FERNANDEZ, 1974; SATO *et al.*, 1990b); (2) altered pulmonary ventilation or cardiac output distribution caused by workload or disease (DROZ and GUILLEMIN, 1983; FISEROVA-BERGEROVA, 1985, 1987a,b; FISEROVA-BERGEROVA *et al.*, 1980; JOHANSON, 1986, 1988; JOHANSON and NASLUND, 1988); (3) altered metabolism (FISEROVA-BERGEROVA *et al.*, 1984; FISEROVA-BERGEROVA, 1987b); (4) changes in metabolism or physiological functions induced genetically (DROZ and SAVOLAINEN, 1990), by medication or by coexposure to other chemicals (ANDERSEN *et al.*, 1987a; SATO *et al.*, 1990a); (5) dietary or ethnically based differences in body build and blood composition (FISEROVA-BERGEROVA *et al.*, 1980, 1984); and (6) accumulation over the week, month, etc. (DROZ and GUILLEMIN, 1983; FERNANDEZ *et al.*, 1977; FISEROVA-BERGEROVA *et al.*, 1974, 1980; GUBERAN and FERNANDEZ, 1974; PERBELLINI *et al.*, 1986), and effect of post-exposure activities (FISEROVA-BERGEROVA, 1987b). If the ratio of measured concentrations of the airborne and indicator of exposure is much smaller than the TLV-BEI ratio, then dermal exposure, additional non-occupational exposure, bad working practices, excessive workload or interference by other industrial chemicals or medication are

indicated. On the other hand, if the ratio of measured values is much larger than TLV-BEI ratio, then interference by another compound(s) is indicated.

There are four causes of interference by another compound: (1) the other compound is either the studied indicator of exposure or it is biodegradated to the studied indicator. Under such circumstances, the ratio of the measured concentrations is smaller than the TLV-BEI ratio; (2) the other compound inhibits the metabolism of the compound under study, the inhibition being manifested by the increased biological level of the parent compound (for which the measured values ratio $\ll$ TLV-BEI ratio) and by the decrease of biological concentrations of the metabolite (for which the measured values ratio $\gg$ TLV-BEI ratio); (3) the other compound acts as an enzyme stimulator (inducer) or releases the indicator of exposure from the bond to constituents of tissues. This interference has the opposite effect of inhibition; (4) the other compound alters the distribution of cardiac output or it alters the function of an organ (lung, kidney, liver, skin permeability) which plays a role in uptake and elimination of the compound.

Dermal exposure

A simulation model for dermal exposure of volatile solvents is shown in Fig. 1. Dermis under the exposed area is treated as a separate compartment for which the inflow of the compound is defined by flux. Flux can be determined experimentally, or predicted from aqueous solubility, octanol–water distribution coefficient and molecular weight of the compound (FISEROVA-BERGEROVA *et al.*, 1990). Figure 2 shows the profound increase of alveolar concentration of methanol and toluene caused by short intermittent dermal exposures of 2.5% or 5% of body surface to the liquid solvent during inhalation exposure to TLV-TWA. The simulation study shows that the larger the exposed area, or the better the perfusion of dermis under the exposed area, the larger the increase in alveolar concentration and the smaller the pulmonary uptake. If the dermal exposure is extensive, the pulmonary uptake can be suppressed and the percutaneously absorbed solvent exhaled. Under such circumstances, the vapour concentration in exhaled air is larger than in the ambient air. Thus, concentrations of highly volatile solvents in exhaled air samples can be the most sensitive indicator of dermal exposures. Modelling of dermal penetration is used for identification of compounds with the potential to affect biological concentration of the compound or its metabolite and toxicity resulting from occupational exposure (FISEROVA-BERGEROVA *et al.*, 1990).

Prediction, extrapolation and verification

Simulation models can be used for description and verification of experimental data (CLEWELL *et al.*, 1988; DROZ and GUILLEMIN, 1983; DROZ, 1978; FERNANDEZ *et al.*, 1977; FISEROVA-BERGEROVA *et al.*, 1974; GUBERAN and FERNANDEZ, 1974; JOHANSON and NASLUND, 1988, JOHANSON, 1986; LIIRA *et al.*, 1990; PATERSON and MACKAY, 1986; PERBELLINI *et al.*, 1986; RAMSEY and ANDERSEN, 1984).

The following example shows how simulation models can be used to explain the inconsistency of information. FERNANDEZ *et al.* (1975) determined the elimination half-lives for triphasic pulmonary elimination of trichloroethylene to be 5–20 min, 1–3 h and 10–30 h. SATO *et al.* (1977), in similar experiments in volunteers, measured elimination half-lives of 2.7 min, 0.4 h and 4 h, respectively. The five-compartmental simulation model, solved by Laplace transform, showed the observable elimination

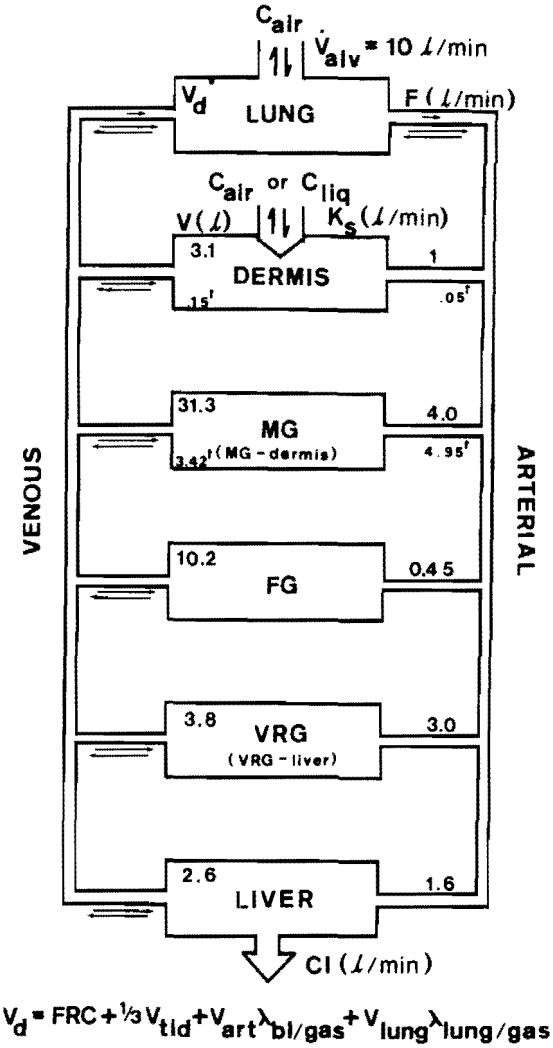

FIG. 1. Toxicokinetic model for simulation of dermal absorption of organic solvents. The compartments (depicted by the rectangles) are: LUNG (connective tissues and airspace); DERMIS (dermis under the exposed area); MG (dermis under unexposed area and muscles); FG (adipose tissue and white marrow); VRG (well-perfused organs, except the liver); and LIVER. Volumes of the compartments 'V' (in litres) are given in the upper left corner of each rectangle. The perfusion for each compartment, 'F' (in l. min^{-1}), is shown to the right, above the arterial flow. For the DERMIS and MG compartments, the perfusion and volume values for 5% of body surface exposure to liquid are given underneath the arterial flow and in the left lower corners of the rectangles, respectively (indicated by †). Alveolar ventilation, '$\dot{V}_{alv}$', equals 10 l. min^{-1}; 'c_{air}' denotes inspired concentration, FRC denotes functional residual capacity and 'λ' denotes the appropriate tissue–gas partition coefficient.

half-lives of 3 min, 0.8 h and 26 h. Further simulation revealed that the short elimination half-lives reported by SATO *et al.* (1977) cannot be attributed to ethnic differences but to the experimental design. These authors measured trichloroethylene concentrations in exhaled air for 10 post-exposure hours. This period is too short to provide data for the determination of the half-life of the slow elimination phase. We concluded that the study of FERNANDEZ *et al.* (1975), in which the trichloroethylene concentration in exhaled air was measured for 3 days, provides better data for the determination of elimination half-lives than the study by SATO *et al.* (1977).

Simulation models can also be used for prediction of uptake, distribution and

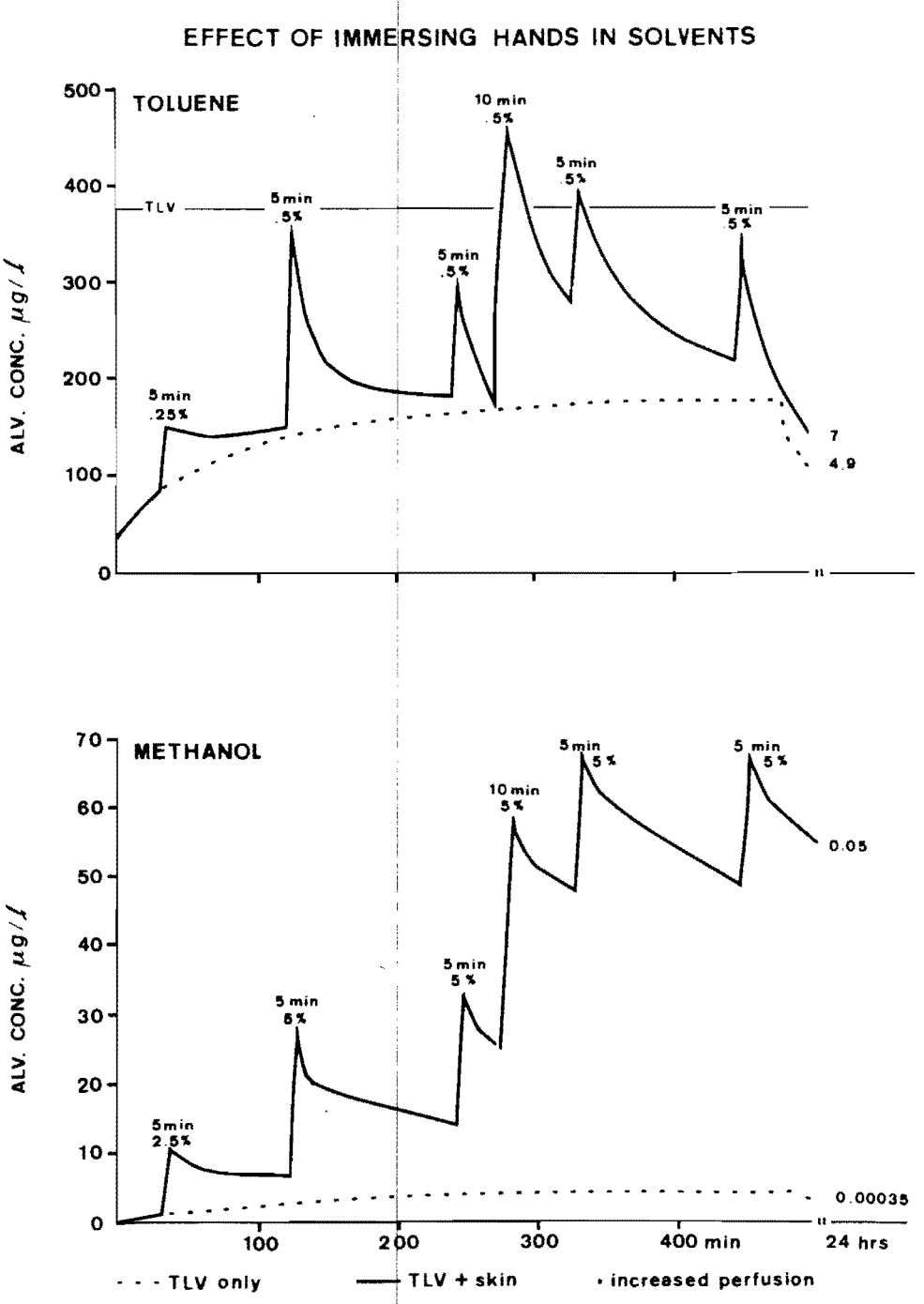

FIG. 2. Effect of short-term dermal exposure to liquid toluene and methanol on alveolar concentrations. The simulation is done using the model and values shown in Fig. 1. Broken lines depict alveolar concentrations during 8-h inhalation exposure to TLV-TWA. Solid lines depict alveolar concentration when dermal absorption is added. The peaks result from dermal exposures of given area (% of body surface) for a short period (min), both given at the top of the peaks. Flux values are taken from FISEROVA-BERGEROVA *et al.* (1990), and the partition coefficients are taken from FISEROVA-BERGEROVA and DIAZ (1986). Note, that after two dermal exposures the alveolar concentrations exceed the inspired concentration, thus reversing pulmonary uptake in pulmonary wash-out. The differences in the patterns of alveolar concentrations of toluene (relatively rapid decline to the concentration resulting from inhalation exposure only) and methanol (relatively slow decline resulting in a rising alveolar concentration to a level about 200 times higher than a concentration resulting from inhalation exposure only) reflect the differences in their solubility in blood.

elimination of new compounds if their solubility in water and lipids is known (FISEROVA-BERGEROVA *et al.*, 1984), and for prediction of biological concentration of indicators of exposure in organs and tissues (DROZ and GUILLEMIN, 1983; FERNANDEZ *et al.*, 1977; FISEROVA-BERGEROVA *et al.*, 1974, 1980, 1984; GUBERAN and FERNANDEZ, 1974; PERBELLINI *et al.*, 1986).

Simulation models are also used for extrapolation of data on pulmonary uptake and biological concentrations of the compound or its metabolites during and following occupational exposure (with workload) from data obtained in controlled studies in resting volunteers. Recently, the simulation model was employed to evaluate the effect of ethnic differences in physiological parameters (mainly body build, metabolizing enzyme activity and life style) on uptake and elimination of organic solvents (DROZ and SAVOLAINEN, 1990).

The simulation models are also used for extrapolation of uptake, distribution and elimination of vapours inhaled by different animal species and for extrapolation from animal to man (FISEROVA-BERGEROVA and HUGHES, 1983; PAUSTENBACH *et al.*, 1988; RAMSEY and ANDERSEN, 1984; REITZ *et al.*, 1988). However, unpredictable qualitative and quantitative species differences in metabolism make the extrapolation uncertain. The simulation model was also modified to study the uptake of industrial compounds by the suckling of a breast-feeding worker (SHELLEY *et al.*, 1988).

CONCLUSIONS

Toxicokinetic models are used for determining the relationships between the extent of inhalation and/or dermal exposure and the biological concentrations or dose of indicators of exposure. Physiologically based multicompartmental simulation models contribute to the understanding of the fate of inhaled or percutaneously absorbed compounds. They are used in biological monitoring for prediction, extrapolation and verification of data and principles on which the reference values for indicators of exposure are determined and the monitoring data are interpreted. They have been used for the evaluation of the effects of a variety of external and internal factors on the relationship between extent of exposure to organic solvents and dose or biological concentrations of indicators of exposure. The elimination half-life is considered in the selection of the appropriate exposure indicator, in the design of the sampling procedure, and in the interpretation of the measured data. There is a great need to develop similar predictive toxicokinetic models for exposure to metals, particulates and compounds undergoing binding to constituents of tissues.

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