

APPLICATION OF TOXICOKINETIC MODELS TO ESTABLISH BIOLOGICAL EXPOSURE INDICATORS*

VERA FISEROVA-BERGEROVA

Department of Anesthesiology, University of Miami School of Medicine, Miami, FL 33101, U.S.A.

(Received 3 April 1990 and in final form 18 September 1990)

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

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

describing uptake, dis
can be found in the
BERGEROVA, 1983; FIS
1986). In order to it
employs parameters
bolic clearance, elimir
pharmacokinetic mo
pathway in a toxicok
(DROZ, 1978; FISERO
two constants (ANDE
ANDERSEN, 1984), and
(DROZ, 1978; DROZ
ANDERSEN, 1984; SA
percutaneous penetr.
surface must be give

Simulation models of the human body, and are a powerful tool for biological concentration of occupational exposure simulation models binding to constituents

Solutions of simulat

Simulation models are a number of which is used for kinetic processes (I ANDERSEN, 1984). At high exposures, kinetic processes deviate from enzyme systems and compounds can also be integrated (DROZ *et al.*, 1986; RAMS). Microsoft Excel is a mathematically sound

At the low ex-
governed by first-
elimination of th
biotransformation
BERGEROVA *et al*
hepatic blood flow
Solution of such a
transform—which
functions expres
functions, expon
1976). Even the
used to describe

used to describe

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 ($k = \ln(2)/t_{1/2}$) (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 decision 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 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 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 appearing in urine provides no information on the workplace. Monitoring system may alter the metabolism of DMAC, the DMAC metabolite limit which is the current limit (FISEROVA-BERGEROVA, 1987a). renal cortex prolonged or long-late excreted in urine cadmium concentration

Evaluation of time effect

Since the urinary excretion of metabolites are timing and duration of the biological monitoring, life, which depends on the activity of the indicator of exposure.

FISEROVA-BERGEROVA, 1987a. Sampling time phase (with half-life) sample for measurement of polluted area, the sample was (a single breath

measurements or a couple of shorter than 5 time and period. Since it is the elimination half-life

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	2 min	$t_{1/2}$ 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' 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; FISEROVA-BERGEROVA *et al.*, 1974, 1980; FISEROVA-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

$t_{1/2}$	Exposure	Sampling time
$t_{1/2} < 2$ h	Recent	Very critical
$2 < t_{1/2} < 5$ h	Daily	Critical
$5 < t_{1/2} < 48$ h	Weekly	End of work week
$t_{1/2} > 48$ 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) pro respectively. Both airborne and biological concentrations likely result from chronic exposure and are obtained (170 cm tall, 70 kg). On the other hand, after exposure to MAK higher than BEIs, exposure derived concentrations will be toxicokinetic basis: they are re-examined.

To simplify the comparison for samples collected 'end of the shift' (after the end of the working week), the sampling specimens collected in 1986; COMMISSION

Factors affecting

Information on factors affecting exposure evaluation by comparing measured indicators of exposure with reference values or unrepresentative values depicted by an additional or further exposure (GUILLEMIN, 1985, 1987b; FISEROVA-BERGEROVA, 1974; SATO *et al.*, 1990b). The distribution of exposure is affected by the distribution of exposure (BERGEROVA, 1987; JOHANSON and FISEROVA, 1984; FISEROVA-BERGEROVA, 1987). The functions induced by coexposure to chemical agents or ethnically different populations (BERGEROVA *et al.*, 1987; GUBERAN and FISEROVA, 1987). The activities (FISEROVA-BERGEROVA, 1987) of airborne and dermal exposure to excessive work

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 $15-20 \text{ l min}^{-1}$). 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 biodegraded 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 (depicted by the exposed area); NVRG (well-perfused given in the upper right corner of the diagram); 'c_{air}' denotes in

half-lives of elimination differences between concentrations provide data; concluded that concentration determination; Simulation

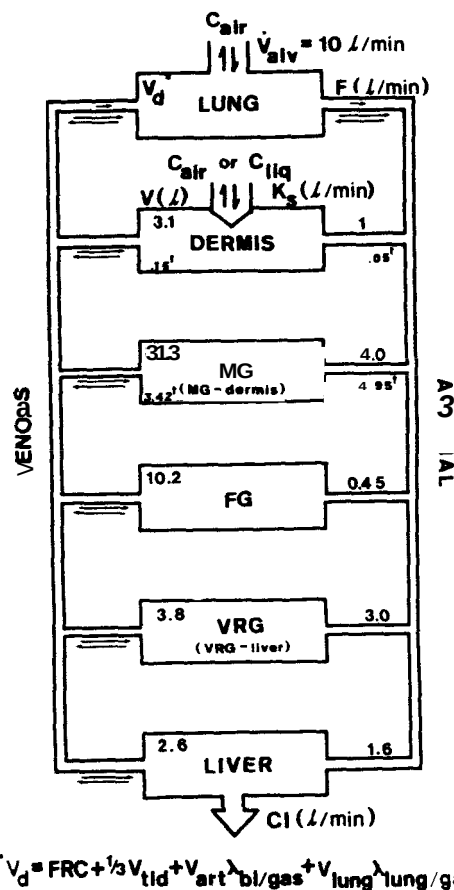


FIG. 1. Toxicokinetic model for simulation of dermal absorption of organic solvents. The compartments (depicted by the rectangles) are: **LUNG** (connective tissues and airspace); **DERMIS** (dermis under the exposed area); **MG** (dermis under unexposed area and muscles); **FG** (adipose tissue and 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

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 multicompartamental 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.

REFERENCES

- ACGIH (1986) Documentation of the threshold limit values and biological exposure indices (1986 with supplements to 1989). American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio, U.S.A.
- ACGIH (1989) Threshold limit values and biological exposure indices for 1989-1990. American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio, U.S.A.
- ANDERSEN, M. E., GARGAS, M. L., CLEWELL, H. J., III and SEVERYN, K. M. (1987a) Quantitative evaluation of the metabolic interactions between trichloroethylene and 1,1-dichloroethylene in vivo using gas uptake methods. *Toxicol. Appl. Pharmacol.* 89, 149-157.
- ANDERSEN, M. E., GARGAS, M. L. and RAMSEY, J. C. (1984) Inhalation pharmacokinetics: evaluating systemic extraction, total *in vivo* metabolism, and the time course of enzyme induction for inhaled styrene in rats based on arterial blood:inhaled air concentration ratios. *Toxicol. Appl. Pharmacol.* 73, 176-187.

- ANDERSEN, M. E., MACNAUGHTON, M. G., CLEWELL, H. J., III and PAUSTENBACH, D. J. (1987b) Adjusted exposure limits for long and short exposure periods using a physiological pharmacokinetic model. *Ind. Hyg. Ass. J.* **48**, 335-343.
- CLEWELL, H. J., III, ANDERSEN, M. E., MACNAUGHTON, M. G. and STUART, B. O. (1988) Toxicokinetic analytical tool for assessing chemical hazards to man. *Aviat. Space Environ. Med.* **59**, A125-A126 (November).
- COMMISSION FOR THE INVESTIGATION OF HEALTH HAZARDS OF CHEMICAL COMPOUNDS IN THE WORK AREA (1989) Maximum concentrations at the workplace and biological tolerance values for working materials. Report No. XXV. VCH Publishers, Weinheim, F.R.G.
- DROZ, P. O. (1978) Contribution to the research of biological exposure indices for solvents. Determination of their partition coefficients and a study of their compartments in the organism using simulation models. Institut de Chimie de l'Université de Neuchâtel, Switzerland (in French).
- DROZ, P. O. (1989) Biological monitoring I: Sources of variability in human response to chemical exposure. *App. ind. Hyg.* **4**, F-20-F-24.
- DROZ, P. O. and GUILLEMIN, M. P. (1983) Human styrene exposure V. Development of a model for biological monitoring. *Int. Archs occup. Environ. Hlth* **53**, 19-36.
- DROZ, P. O. and SAVOLAINEN, H. (1990) Effect of physiological and metabolic differences between Japanese and American populations on uptake, distribution and elimination of toxic chemicals. In *Biological Monitoring of Exposure to Industrial Chemicals* (Edited by FISEROVA-BERGEROVA, V. and OGATA, M.), pp. 185-188. *Proceedings of the United States-Japan Co-operative Seminar on Biological Monitoring*, Honolulu, 1989. American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio, U.S.A.
- DROZ, P. O., WU, M. M. and CUMBERLAND, W. G. (1989a) Variability in biological monitoring of organic solvent exposure. II. Application of a population physiological model. *Br. J. ind. Med.* **46**, 547-558.
- DROZ, P. O., WU, M. M., CUMBERLAND, W. G. and BERODE, M. (1989b) Variability in biological monitoring of solvent exposure. I. Development of a population physiological model. *Br. J. ind. Med.* **46**, 447-460.
- FERNANDEZ, J. G., DROZ, P. O., HUMBERT, B. E. and CAPEROS, J. R. (1977) Trichloroethylene exposure. Simulation of uptake, excretion, and metabolism using a mathematical model. *Br. J. ind. Med.* **34**, 43-55.
- FERNANDEZ, J. G., HUMBERT, B. E., DROZ, P. O. and CAPEROS, J. R. (1975) Exposure to trichloroethylene. Balance of absorption, excretion and metabolism in humans. *Arch. Mal. prof. Méd. trav.* **35**, 397-407 (in French).
- FISEROVA-BERGEROVA, V. (1981) Modeling of uptake and clearance of inhaled vapors and gases. In *Industrial and Environmental Xenobiotics* (Edited by GUT, I., CIKRT, M. and PLAA, G. L.), pp. 211-220. Springer, Berlin.
- FISEROVA-BERGEROVA, V. (Editor) (1983) *Modeling of Inhalation Exposure to Vapors: Uptake, Distribution, and Elimination*, Vols I and II. CRC Press, Boca Raton, Florida, U.S.A.
- FISEROVA-BERGEROVA, V. (1985) Toxicokinetics of organic solvents. *Scand. J. Work Environ. Hlth* **11**, suppl. 1, 7-21.
- FISEROVA-BERGEROVA, V. (1987a) Simulation model as a tool for adjustment of biological exposure indices to exposure conditions. In *Biological Monitoring of Exposure to Chemicals: Organic Compounds* (Edited by HO, M. H. and DILLON, H. K.), pp. 29-57. John Wiley & Sons, New York.
- FISEROVA-BERGEROVA (THOMAS), V. (1987b) Development of biological exposure indices (BEIs) and their implementation. *Appl. ind. Hyg.* **2**, 87-92.
- FISEROVA-BERGEROVA (THOMAS), V. (1990a) History and concept of BEIs. In *Biological Monitoring of Exposure to Industrial Chemicals* (Edited by FISEROVA-BERGEROVA, V. and OGATA, M.), pp. 19-23. *Proceedings of the United States-Japan Co-operative Seminar on Biological Monitoring*, Honolulu, 1989. American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio, U.S.A.
- FISEROVA-BERGEROVA (THOMAS), V. (1990b) Comparison of biological exposure indices (BEIs) and biological tolerance values (BATs). In *Biological Monitoring of Exposure to Industrial Chemicals* (Edited by FISEROVA-BERGEROVA, V. and OGATA, M.), pp. 31-33. *Proceedings of the United States-Japan Co-operative Seminar on Biological Monitoring*, Honolulu, 1989. American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio, 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.
- FISEROVA-BERGEROVA, V. and HUGHES, H. C. (1983) Species differences in bioavailability of inhaled vapors and gases. In *Modeling of Inhalation Exposure to Vapors: Uptake, Distribution and Elimination*, Vol. II (Edited by FISEROVA-BERGEROVA, V.), pp. 97-106. CRC Press, Boca Raton, Florida, U.S.A.
- FISEROVA-BERGEROVA, V., PIERCE, J. T. and DROZ, P. O. (1990) Dermal absorption potential of industrial chemicals: criteria for skin notation. *Am. J. ind. Med.* **17**, 617-635.
- FISEROVA-BERGEROVA, V., TICHY, M. and DI CARLO, F. J. (1984) Effects of biosolubility on pulmonary uptake and disposition of gases and vapors of lipophilic chemicals. *Drug Metab. Rev.* **15**, 1033-1070.
- FISEROVA-BERGEROVA, V. (1988) Uptake, distribution, and excretion of organic solvents. In *Biological Monitoring of Exposure to Industrial Chemicals* (Edited by FISEROVA-BERGEROVA, V. and OGATA, M.), pp. 15-18. *Proceedings of the United States-Japan Co-operative Seminar on Biological Monitoring*, Honolulu, 1989. American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio, U.S.A.
- GUERIN, E. and FISEROVA-BERGEROVA, V. (1989) Alveolar concentration of organic solvents. In *Biological Monitoring of Exposure to Industrial Chemicals* (Edited by FISEROVA-BERGEROVA, V. and OGATA, M.), pp. 19-23. *Proceedings of the United States-Japan Co-operative Seminar on Biological Monitoring*, Honolulu, 1989. American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio, U.S.A.
- HENSCHEL, D. (1990) Monitoring of exposure to organic solvents. In *Biological Monitoring of Exposure to Industrial Chemicals* (Edited by FISEROVA-BERGEROVA, V. and OGATA, M.), pp. 15-18. *Proceedings of the United States-Japan Co-operative Seminar on Biological Monitoring*, Honolulu, 1989. American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio, U.S.A.
- JOHANSON, G. (1986) Toxicokinetics of organic solvents. *Toxicol. Lett.* **34**, 1-10.
- JOHANSON, G. (1988) Toxicokinetics of organic solvents. In *Biological Monitoring of Exposure to Industrial Chemicals* (Edited by FISEROVA-BERGEROVA, V. and OGATA, M.), pp. 15-18. *Proceedings of the United States-Japan Co-operative Seminar on Biological Monitoring*, Honolulu, 1989. American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio, U.S.A.
- JOHANSON, G. and FISEROVA-BERGEROVA, V. (1989) Toxicokinetics of organic solvents. In *Biological Monitoring of Exposure to Industrial Chemicals* (Edited by FISEROVA-BERGEROVA, V. and OGATA, M.), pp. 15-18. *Proceedings of the United States-Japan Co-operative Seminar on Biological Monitoring*, Honolulu, 1989. American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio, U.S.A.
- KENNEDY, G. L., JR. (1989) Exposure to industrial chemicals. In *Proceedings of the American Conference of Governmental Industrial Hygienists*, Cincinnati, Ohio, U.S.A.
- KJELLSTROM, T. (1989) Exposure to industrial chemicals. In *Proceedings of the American Conference of Governmental Industrial Hygienists*, Cincinnati, Ohio, U.S.A.
- LIIRA, J., JOHANSON, G. and FISEROVA-BERGEROVA, V. (1989) Exposure to industrial chemicals. In *Proceedings of the American Conference of Governmental Industrial Hygienists*, Cincinnati, Ohio, U.S.A.
- LOWE, H. J. (1972) Dermal absorption of organic solvents. In *Proceedings of the American Conference of Governmental Industrial Hygienists*, Cincinnati, Ohio, U.S.A.
- PATERSON, S. and FISEROVA-BERGEROVA, V. (1989) Exposure to industrial chemicals. In *Proceedings of the American Conference of Governmental Industrial Hygienists*, Cincinnati, Ohio, U.S.A.
- PAUSTENBACH, D. J. (1989) Exposure to industrial chemicals. In *Proceedings of the American Conference of Governmental Industrial Hygienists*, Cincinnati, Ohio, U.S.A.
- PERBELLINI, L. (1989) Exposure to industrial chemicals. In *Proceedings of the American Conference of Governmental Industrial Hygienists*, Cincinnati, Ohio, U.S.A.
- PERBELLINI, L., MOSE, J. and FISEROVA-BERGEROVA, V. (1989) Exposure to industrial chemicals. In *Proceedings of the American Conference of Governmental Industrial Hygienists*, Cincinnati, Ohio, U.S.A.
- RAMSEY, J. C. and FISEROVA-BERGEROVA, V. (1989) Exposure to industrial chemicals. In *Proceedings of the American Conference of Governmental Industrial Hygienists*, Cincinnati, Ohio, U.S.A.
- REITZ, R. H. (1989) Exposure to industrial chemicals. In *Proceedings of the American Conference of Governmental Industrial Hygienists*, Cincinnati, Ohio, U.S.A.
- SATO, A., ENDOH, K. and FISEROVA-BERGEROVA, V. (1989) Exposure to industrial chemicals. In *Proceedings of the American Conference of Governmental Industrial Hygienists*, Cincinnati, Ohio, U.S.A.
- SATO, A., KANEKO, T. and FISEROVA-BERGEROVA, V. (1989) Exposure to industrial chemicals. In *Proceedings of the American Conference of Governmental Industrial Hygienists*, Cincinnati, Ohio, U.S.A.
- SATO, A., NAKAJIMA, T. and FISEROVA-BERGEROVA, V. (1989) Exposure to industrial chemicals. In *Proceedings of the American Conference of Governmental Industrial Hygienists*, Cincinnati, Ohio, U.S.A.
- SHELLEY, M. L., AN, S. and FISEROVA-BERGEROVA, V. (1989) Exposure to industrial chemicals. In *Proceedings of the American Conference of Governmental Industrial Hygienists*, Cincinnati, Ohio, U.S.A.
- VLACH, J. (1983) Exposure to industrial chemicals. In *Proceedings of the American Conference of Governmental Industrial Hygienists*, Cincinnati, Ohio, U.S.A.
- WAGNER, J. G. (1989) Exposure to industrial chemicals. In *Proceedings of the American Conference of Governmental Industrial Hygienists*, Cincinnati, Ohio, U.S.A.

- D. J. (1987b) Adjustment of a pharmacokinetic model. *Br. J. ind. Med.* **34**, 42-49.
- FISEROVA-BERGEROVA, V., VLACH, J. and CASSADY, J. C. (1980) Predictable 'individual differences' in uptake and excretion of gases and lipid soluble vapours simulation study. *Br. J. ind. Med.* **37**, 42-49.
- FISEROVA-BERGEROVA, V., VLACH, J. and SINGHAL, K. (1974) Simulation and prediction of uptake, distribution, and exhalation of organic solvents. *Br. J. ind. Med.* **31**, 45-52.
- GUBERAN, E. and FERNANDEZ, J. (1974) Control of industrial exposure to tetrachloroethylene by measuring alveolar concentrations: theoretical approach using a mathematical model. *Br. J. ind. Med.* **31**, 159-167.
- HENSCHLER, D. (1990) Biological monitoring and exposure limits as perceived in Germany. In *Biological Monitoring of Exposure to Industrial Chemicals* (Edited by FISEROVA-BERGEROVA, V. and OGATA, M.), pp. 25-30. *Proceedings of the United States-Japan Co-operative Seminar on Biological Monitoring*, Honolulu, 1989. American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio, U.S.A.
- JOHANSON, G. (1986) Physiologically based pharmacokinetic modeling of inhaled 2-butoxyethanol in man. *Toxicol. Lett.* **34**, 23-31.
- JOHANSON, G. (1988) Aspects of biological monitoring of exposure to glycol ethers. *Toxicol. Lett.* **43**, 5-21.
- JOHANSON, G. and NASLUND, P. H. (1988) Spreadsheet programming—a new approach in physiologically based modeling of solvent toxicokinetics. *Toxicol. Lett.* **41**, 115-127.
- KENNEDY, G. L., JR (1990) Biological monitoring in American chemical industry. In *Biological Monitoring of Exposure to Industrial Chemicals* (Edited by FISEROVA-BERGEROVA, V. and OGATA, M.), pp. 63-67. *Proceedings of the United States-Japan Co-operative Seminar on Biological Monitoring*, Honolulu, 1989. American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio, U.S.A.
- KJELLSTROM, T., ELINDER, C. G. and FRIBERG, L. (1984) Conceptual problems in establishing the critical concentration of cadmium in human kidney cortex. *Environ. Res.* **33**, 284-295.
- LIIRA, J., JOHANSON, G. and RIIHIMAKI, V. (1990) Dose dependent kinetics of inhaled methyl ethyl ketone in man. *Toxicol. Lett.* **50**, 195-201.
- LOWE, H. J. (1972) Dose-regulated Penthrane[®] methoxyflurane anesthesia. Abbott Laboratories, Chicago, Illinois, U.S.A.
- PATERSON, S. and MACKAY, D. (1986) A pharmacokinetic model of styrene inhalation with the fugacity approach. *Toxicol. Appl. Pharmacol.* **82**, 444-453.
- PAUSTENBACH, D. J., CLEWELL, H. J., III, GARGAS, M. L. and ANDERSEN, M. E. (1988) A physiologically based pharmacokinetic model for inhaled carbon tetrachloride. *Toxicol. Appl. Pharmacol.* **96**, 191-211.
- PERBELLINI, L., MOZZO, P., BRUGNONE, F. and ZEDDE, A. (1986) Physiologicomathematical model for studying human exposure to organic solvents: kinetics of blood/tissue n-hexane concentrations and of 2,5-hexanedione in urine. *Br. J. ind. Med.* **43**, 760-768.
- RAMSEY, J. C. and ANDERSEN, M. E. (1984) A physiologically based description of the inhalation pharmacokinetics of styrene in rats and humans. *Toxicol. Appl. Pharmacol.* **73**, 159-175.
- REITZ, R. H., MENDRALA, A. L., PARK, C. N., ANDERSEN, M. E. and GUENGERICH, F. P. (1988) Incorporation of *in vitro* enzyme data into the physiologically-based pharmacokinetic (PB-PK) model for methylene chloride: implications for risk assessment. *Toxicol. Lett.* **43**, 97-116.
- SATO, A., ENDOH, K. and KANEKO, T. (1990a) Effects of ethanol on uptake, distribution, and elimination of inhaled vapors of organic solvents. In *Biological Monitoring of Exposure to Industrial Chemicals* (Edited by FISEROVA-BERGEROVA, V. and OGATA, M.), pp. 155-158. *Proceedings of the United States-Japan Co-operative Seminar on Biological Monitoring*, Honolulu, 1989. American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio, U.S.A.
- SATO, A., KANEKO, T., ENDOH, K. and JOHANSON, G. (1990b) Relationship between external and internal doses of organic solvent vapors. In *Biological Monitoring of Exposure to Industrial Chemicals* (Edited by FISEROVA-BERGEROVA, V. and OGATA, M.), pp. 137-143. *Proceedings of the United States-Japan Co-operative Seminar on Biological Monitoring*, Honolulu, 1989. American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio, U.S.A.
- SATO, A., NAKAJIMA, T., FUJIWARA, Y. and MURAYAMA, N. (1977) A pharmacokinetic model to study the excretion of trichloroethylene and its metabolites after an inhalation exposure. *Br. J. ind. Med.* **34**, 56-63.
- SHELLEY, M. L., ANDERSEN, M. E. and FISHER, J. W. (1988) An inhalation distribution model for the lactating mother and nursing child. *Toxicol. Lett.* **43**, 23-29.
- VLACH, J. (1983) Simulation. In *Modeling of Inhalation Exposure to Vapors: Uptake, Distribution, and Elimination*, Vol. I (Edited by FISEROVA-BERGEROVA, V.), pp. 133-153. CRC Press, Boca Raton, Florida, U.S.A.
- WAGNER, J. G. (1976) Linear pharmacokinetic equations allowing direct calculation of many needed pharmacokinetic parameters from the coefficients and exponents of polyexponential equations which have been fitted to the data. *J. Pharmacokinet. Biopharm.* **4**, 443-467.