The use of simulation models for setting BEIs for organic solvents

PIERRE O. DROZ, Ph.D.
Institute of Occupational Medicine and Industrial Hygiene, University of Lausanne, Switzerland

Biological exposure indices (BEI) for solvents exposure are traditionally set on the basis of experimental exposure data or after epidemiological or field studies. A third possibility consists in the use of either toxicokinetic or compartmental models to simulate industrial exposures.

Compartmental models are powerful tools for the prediction of organic solvents' behaviour in the human body. Their combination with the toxicokinetic description of the metabolic pathways allows a global understanding of the absorption, excretion and metabolism of the solvents. Such models can be used, after experimental confirmation, to establish BEIs (solvents in breath and blood, metabolites in blood and urine) from TLVs for a wide range of chemical compounds. Simulation models also allow critical evaluations of the effect of various factors on the BEIs, such as modification of the work schedule, physical workload, body fat, metabolic clearance. Simulation models can therefore play an important role in the establishment of the future BEIs.

Introduction

Biological monitoring of exposure to solvents can have two different goals depending on the indicator chosen: dose estimation (primary prevention) or early effect detection (secondary prevention).[1] The present work will deal with the first approach, that is the estimation of the dose absorbed.

Figure 1 shows the relationships between air monitoring and biological monitoring in the prevention of adverse effects.[2] Air monitoring and its related TLV is a measure of external dose, whereas biological monitoring and the associated BEI relates to the indirect monitoring of the internal dose.

The most logical way of setting BEIs would, of course, be by studying the relationships between internal dose (biological monitoring) and health effects. Nevertheless, it must be recognized that most of the available toxicological data relate to the virtual link external dose — health effects. In order to make use of this invaluable toxicological data base, it is very important to study the relationships between external and internal doses, that is, between TLVs and BEIs. This approach considers that the BEIs are bioequivalent to TLVs. Most of the biological limit values proposed up till now for organic compounds are drawn from this type of reasoning.[3] This is moreover true for the 1984 BEIs proposed by the ACGIH.[4]

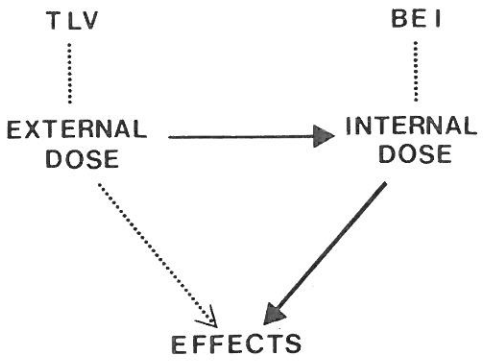

FIGURE 1 — Schematic relationships between Threshold Limit Values in air (TLV), Biological Exposure Indices (BEI) and effects.

The relationships between TLVs and BEIs basically can be established using three main approaches:

1. Field studies, on groups of workers occupationally exposed to the agent considered (simultaneous measurement of exposure and biological indicators).
2. Experimental studies, on volunteers exposed in controlled conditions (experimental chamber).
3. Simulation studies, using different kinds of mathematical models to allow the simulation of various exposure situations and individual characteristics.

These three approaches are complementary and have each their own advantages and disadvantages. As an example, Table I shows some of the important factors to consider while studying TLV-BEI relationships and the estimated qualities

TABLE I
Comparison of the Qualities of Field and Experimental Approach in the Study of TLV-BEI Relationships

Factor	Approach	
	Field	Experimental
Exposure (dose) measurement	++	+++
Physical workload characterization	+	+++
Timing of biological sampling	+	+++
Effect of exposure repetition	+++	++
Environmental variability	++	++
Representativity of the subjects	+++	+

+++ good; ++ medium; + bad

(good, medium, bad) of the two first approaches (field and experimental studies). The appreciations shown in Table I are of course indicative and depend largely on the experimental design chosen. They nevertheless give a general idea of the advantages and disadvantages of most of the past studies.

Simulation models can be considered as complementary to the approaches described above. Simulation models can be used mainly for two goals apart from the pure understanding of the processes:

1. Establishment of BEIs (level, timing) as equivalent to TLVs assuming standard exposure conditions and individual characteristics.[5–9]
2. Study of the influence of various factors (individual, environmental) on the BEIs.[6,7,9–12]

Both of these two goals will be considered here after some preliminary model description and validation.

Model fundamentals

Background

Mathematical models have now been used for many years for the description of the behavior of solvents in the body. They can be divided into three categories:[13]

1. Empirical models, in which the constants and functions are found by optimal fit to experimental data.
2. Pharmacokinetic models, which are sophisticated tools using the notions of compartment and rate constant, but without relationships to physiological or biochemical concepts.
3. Simulation models, in which the mathematical relationships and their variables have physiological and metabolic meanings.

All three types of models are very good tools for the description of the solvents' behavior. Nevertheless, simulation models alone allow a study of new situations, of the effect of physiological or metabolic factors because their variables are meaningful.

Only simulation models will thus be considered here. First developed by anesthesiologists,[14] they have then been applied to industrial toxicology to describe the behavior of organic volatiles in workers occupationally exposed.[7,8] About 20 industrial solvents have now been studied using simulation models,[13] but only a few of them have been compared thoroughly with human experimental data for validation.

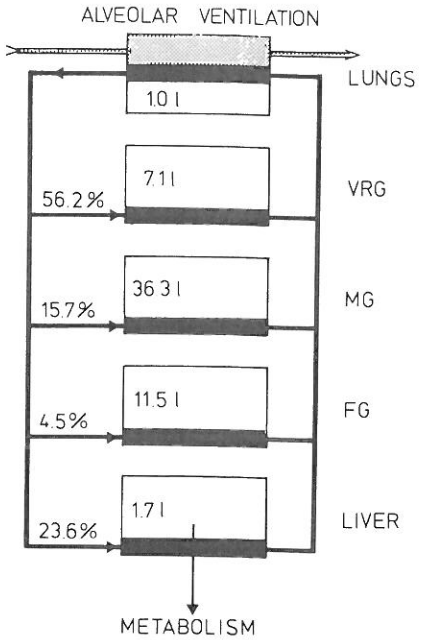

FIGURE 2 — Schematic presentation of the compartmental model used in the description of solvents distribution in the body. VRG = vessel-rich group, MG = muscle and skin group, FG = fatty tissues group. The blood perfusion (%) and tissues volumes (L) are also indicated.

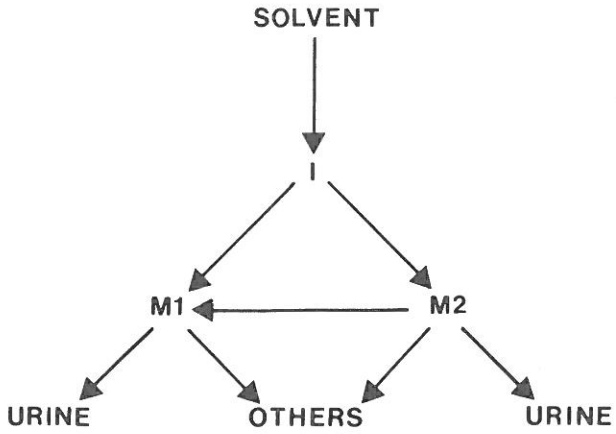

FIGURE 3 — Schematic presentation of the biotransformation and excretion pathways used to simulate the solvents metabolism. M1 = metabolite 1, M2 = metabolite 2, I = intermediate product, "others" stands for other excretion rates than urine.

Description of a simulation model

The simulation of the behavior of organic solvents can be separated into two parts: 1) the simulation of the solvent itself and 2) the description of the formation and elimination of the metabolites. To simulate the solvent's behavior, the body is considered to consist of five homogeneous compartments containing tissues of similar perfusion/volume ratio:[14,15]

1. A pulmonary compartment, responsible for exchange with the gaseous environment.
2. A group of vessel-rich tissues (VRG) containing the heart, the brain, the kidneys, etc.
3. A group of low perfused tissues (MG) representing mainly the muscles and the skin.
4. A group of poorly perfused fatty tissues (FG).
5. A tissue responsible for metabolic breakdown of the solvent (liver).

The description of the exchanges between air, tissues and blood is done on the basis of the following main hypotheses:

1. The solvent diffuses freely and instantaneously through the entire surface of the capillaries and alveolar walls.
2. The solvent in venous blood is in equilibrium with that dissolved in the corresponding tissue.
3. The concentration in arterial blood is in equilibrium with that of the alveolar air.

Figure 2 gives a schematic representation of the body for the distribution of the solvent.

The description of the metabolic phenomena is usually a more complex process and is variable from one solvent to the other. Figure 3 shows the basic schema which has been used to describe, in a way as simple as possible, the metabolism of some of the most widely used solvents.[5,6,16] The solvent is supposed to be transformed instantaneously into an unstable intermediate, which can give rise potentially to 2 metabolites. The latter can then transform into each other and/or be excreted into urine or other excreta. In order to describe the metabolism with the least experimental data as possible, the following assumptions are generally made:

1. All the reactions are considered to be of the first order type in the concentration ranges occurring during occupational exposures.
2. The transformation into metabolite 1 or 2 is considered as being much faster than the metabolites' kinetic behavior.
3. The distribution of each metabolite in the body takes place in one single volume.

It is to be noted that, as long as only excretion rates are needed, the volumes of distribution can be omitted.

TABLE II
Tissue Volumes, Blood Perfusions and Alveolar Ventilations for a 70 kg Standard Man at Rest

Compartment		Volume (L)	Perfusion (L/min)	
Lungs	air	2.85	6.0*	(11/22/36)**
	tissue	1.0	6.3	(9.2/13/19)**
VRG		7.1	3.5	
MG		36.3	1.0	(3.7/7.9/13)**
FG		11.5	0.28	
Liver		1.7	1.5	

* Alveolar ventilation BTPS
** Numbers in parentheses refer to workloads, respectively, light (0.6 L O_2/min), moderate (1.2 L O_2/min) and hard (2.0 L O_2/min)

TABLE III
Examples of Tissue-gas Partition Coefficients for Some Common Industrial Solvents[17]

Solvent	Blood	Oil	Water	VRG[1]	MG[2]	FG[3]
Benzene	7	498	2.8	15	10	350
Toluene	16	1460	2.5	30	23	1030
m-Xylene	34	4321	2.2	80	60	3030
Styrene	59	5838	4.9	150	84	4100
Methylene chloride	8	157	6.5	17	11	260
Chloroform	11	424	3.8	16	11	300
Methylchloroform	4	373	0.9	9	6	373
Trichloroethylene	9	763	1.5	20	19	600
Tetrachloroethylene	14	2072	0.9	45	29	2070

[1]Estimated from heart tissue with heart/ H_2O = 0.0172 oil/ H_2O + 2.3.
[2]Calculated from MG/ H_2O = 0.0133 oil/ H_2O + 1.362.
[3]Calculated from FG = 0.7 oil + 0.3 blood.

Physiological, physicochemical and metabolic parameters

Three types of data are needed to completely solve the model described above:

1. Physiological: the tissues and blood volumes and the blood perfusions.
2. Physicochemical: the solubility or partition coefficient of the solvents in the various tissues and in blood.
3. Metabolic: clearance and excretion rates.

The physiological characteristics of the compartments described above can be found in medical tables and references.[14,15] Table II presents the tissue volumes and blood perfusions used in the model for a 70 kg standard man.[17] Also indicated are the values used when simulating physical workloads of different grades.

The physicochemical properties of the solvents, their tissues gas partition coefficients, have been reviewed on several occasions.[15,17,18] Missing data can be estimated through approximations using water and oil partition coefficients.[17] Table III summarizes some partition coefficients for the most widely used industrial solvents.

The metabolic clearance, or biotransformation rate of the solvent in the organism, can be estimated using different techniques based on solvent retention or metabolite output.[15,19] Table IV shows rate constants for the urinary excretion of a few important metabolites.

Validation of the model

The development of compartmental models describing the absorption, metabolism and excretion of solvents is based on numerous hypotheses. The first logical step, before any use of these models, is thus to validate the hypotheses by comparison of predicted results with data obtained in experimental or field studies.

Only a few solvents have been fully validated up till now. Nevertheless, the hypotheses emitted are such that the confirmation obtained in a few cases can be generalized to other untested solvents exhibiting the same general properties.

TABLE IV
Examples of Urinary Excretion Rate Constants for Some Common Metabolites

Metabolite	Originating Solvents	Urinary Excretion Rate Constant (h^{-1})	Reference
Phenol	Benzene	0.2	24
Hippuric acid	Toluene	0.11	26
Methyl hippuric acids	Xylenes	0.5	24
Mandelic acid	Styrene, ethylbenzene	0.113	6
Phenylglyoxylic acid	Styrene, ethylbenzene	0.113	6
Trichloroethanol	Trichloroethylene, methylchloroform	0.026	5
Trichloroacetic acid	Trichloroethylene, methylchloroform, tetrachloroethylene	0.00685	5

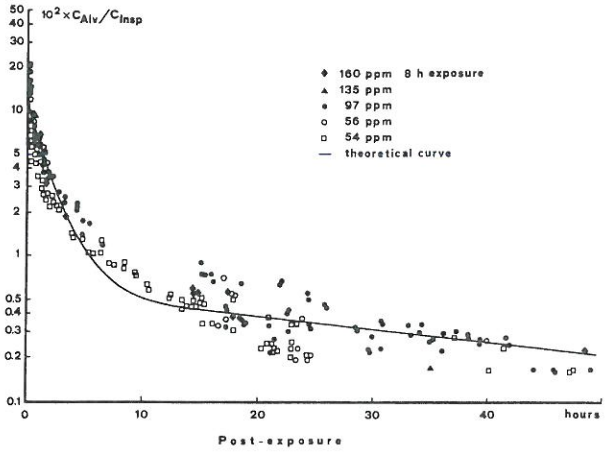

FIGURE 4 — Alveolar concentrations of trichloroethylene after 8 hours' exposure. They are expressed as the ratio to the exposure concentration. Comparison of the curve computed by the simulation model with experimental data obtained in controlled exposure studies with human subjects. (Figure taken from reference 5.)

Mainly the levels of solvents or metabolites in two principal biological media can be used in the validation: solvent in expired air, metabolites in urine (eventually in blood). Figure 4 shows the results obtained in such a comparison for trichloroethylene (TRI) in alveolar air.[5] The agreement between the theoretical curve predicted by the model and the experimental points is very satisfactory and indicates that the hypotheses concerning the solvent's distribution are realistic. Similar results have been shown for styrene,[6] methylchloroform (MC),[16] methylene chloride,[20] tetrachloroethylene (PER),[7] and benzene.[8] Figure 5 presents the results obtained for the urinary excretion of mandelic acid (MA) after experimental exposure to styrene.[6] Again the agreement is good indicating for this case that the simplified metabolic pathways assumed are a satisfactory model. Good comparative results have also been published for TRI[5] and MC.[16]

The validation can be extended to subacute situations with data obtained during one week repeated exposure. Such a comparison is shown in Figure 6 for trichloroethylene.[5,17,21] The agreement is very good indicating that the simple model used to simulate the metabolism is valid also under repeated conditions. Therefore, such models can be used to simulate industrial type repeated exposures.

Figure 7 presents the comparative results obtained while simulating a whole week of exposure for one styrene worker. The results obtained for uptake, MA and phenylglyoxylic acid (PGA) agree very well with the values measured.[22]

Although complete validation is still limited to a small number of chemicals, the basic hypotheses are probably realistic and the results obtained for new compounds can be used in first approximation.

Application of the model

As already mentioned above, compartmental models can be very useful tools in the discussion of BEIs. Two main contributions can be described:

1. Establishment of BEIs by simulation of industrial repeated exposure.

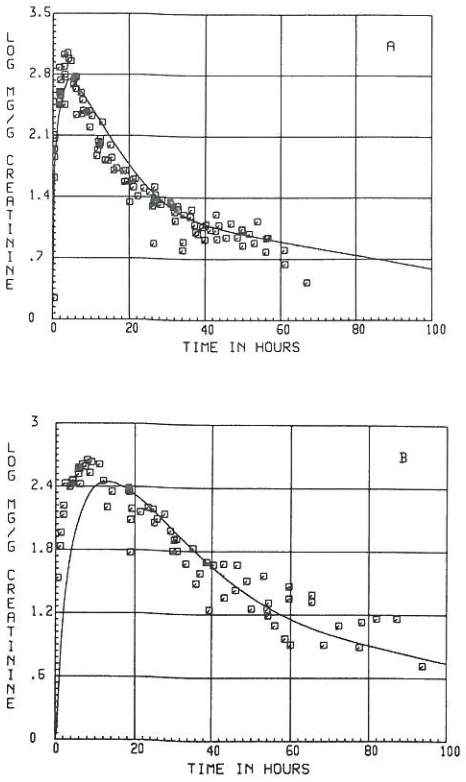

FIGURE 5 — Excretions of mandelic acid (A) and phenylglyoxylic acid (B) in urine after exposures at 100 ppm styrene for 4 hours (A) and 8 hours (B). The theoretical curve computed with the model is compared with experimental points obtained with controlled exposure of humans. (Figure taken from reference 6.)

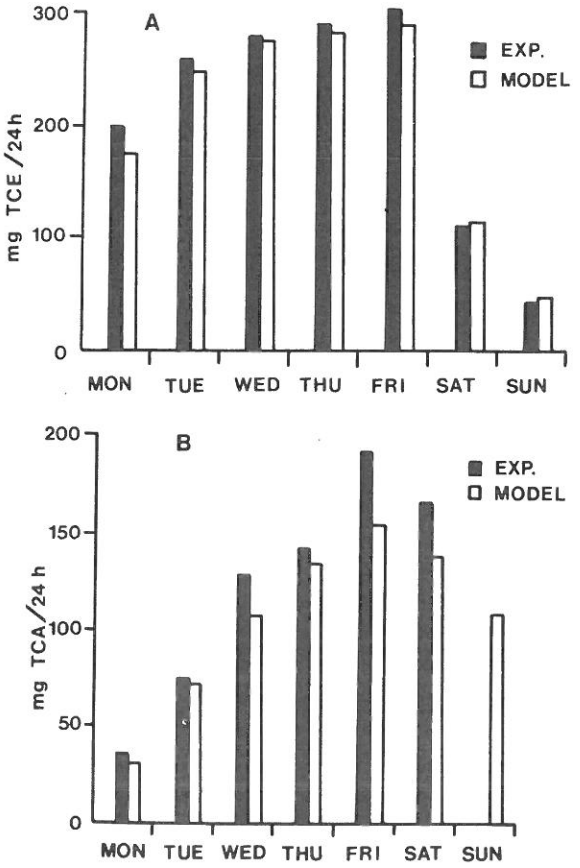

FIGURE 6 — Daily excretions of trichloroethanol (A) and trichloroacetic acid (B) in urine during a week exposure (5 days, 6 hours/day) at 100 ppm trichloroethylene. Experimental results obtained by controlled exposure of human subjects.[21]

2. Study of the distortion effect of various environmental or individual confounding factors on the TLV-BEI relationships.

Establishment of BEIs

The repetition of exposure to solvents 8 hours a day, 5 days a week lead to a steady state situation characterized by the fact that each following week gives identical results to the preceeding one. If the exposure concentration is equal to the TLV, then the concentration profiles obtained for the solvent (breath, blood) or the metabolites (blood, urine) can help to establish BEIs. Such profiles can easily be obtained using simulation models.

Table V shows the computed results obtained at the end of a steady-state week for 5 solvents at their respective TLVs;[4] only the results at the end of shift (30 minutes post-exposure) and on the next morning (15 hours post-exposure) are shown in the table as they are the only ones of practical interest. Table V also contains the levels proposed on the basis of experimental or field studies. Although there are some differences in certain cases, the general agreement is satisfactory.

Examples of urinary excretion data for steady state exposures at the TLV are shown in Figures 8 to 10 for three solvents: benzene, styrene and methylchloroform, respectively. The knowledge of such excretion patterns can be very useful for setting BEIs. Not only can those profiles give important information for the setting of a limit value, but they can be of considerable help in the de-

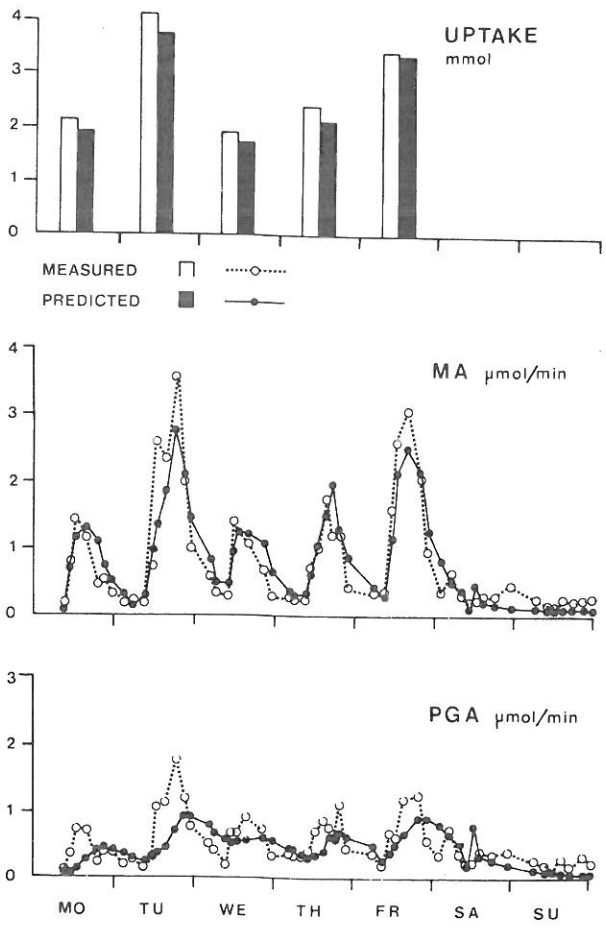

FIGURE 7 — Field validation of the simulation model. Simulation of one week of exposure to styrene, using exposure concentrations and ventilations, for one worker. Styrene uptakes, mandelic (MA) and phenylglyoxylic acid (PGA) excretion rates are compared with actual values.[22]

TABLE V
Solvent Breath Concentrations Obtained at the End of Shift (0.5 hr) and on the Next Morning (15 hr) at the End of a Steady-state Week of Exposure at the TLV

Solvent (TLV)		Model prediction (ppm)	Experimental (ppm)	Reference
Methylchloroform (350 ppm)	0.5 hr	120	273	25
	15 hr	16	17	25
Tetrachloroethylene (50 ppm)	0.5 hr	25	23	25
	15 hr	7	8	25
Trichloroethylene (50 ppm)	0.5 hr	7	3-4	25
	15 hr	0.6	0.3-0.4	25
Benzene (10 ppm)	0.5 hr	1.5		
	15 hr	0.2	0.12	3
Styrene (50 ppm)	0.5 hr	2		
	15 hr	0.3	0.06	4

cision of the sampling time, for example. Figures 8 and 9 tend to show that the day of sampling is not important for benzene and styrene; on the other hand, Figure 10 indicates an accumulation of TCE and TCA during the week.

Figure 10 also shows that for TCA the time of sampling during the day is without importance. However, for TCE, MA, PGA and phenol the time considered seems to be critical.

Thus, simulation models can do more than just give the level or limit value for a biological indicator. They allow a complete description and understanding of the processes, thus bringing invaluable information for the establishment of a sampling strategy.

Effect of confounding factors on BEIs

The relationships between TLVs and BEIs can be affected by numerous factors, environmental or individual. The quantitative knowledge of the influence of those factors, called here confounding factors, is of great importance for the application of biological monitoring.

Experimental and field studies are very useful for setting of BEIs. However, the study of the effect of confounding factors is very difficult using these two approaches: confounding factors very often arise simultaneously, making the separate analysis of their effects very complex if not impossible. The influence of those factors can thus be best undertaken using simulation models.[9,11,12]

As an example, a limited study of the effect of six important factors on breath and urinary concentrations will be presented here.[12] The confounding factors studied are presented in Table VI:

1. Repetition of exposure, very important in the process of extrapolation of isolated exposure results to repeated situations.
2. Intra- and interday exposure fluctuations, typical characteristics of industrial situations.
3. Physical workload, which has a large effect on uptake.[23]
4. Body build and metabolism, which can be representative of individual differences.

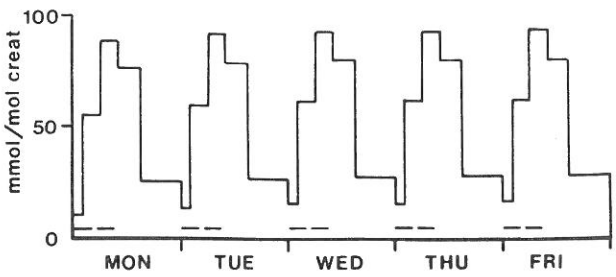

FIGURE 8 — Predicted profile of urinary phenol excretion during a steady-state week of exposure to 10 ppm benzene. Urine voiding times are: 07h00, 09h00, 13h00, 17h00, 22h00. Physical workload is light (600 ml O_2/min) — shows exposure periods (08h00-12h00, 13h00-17h00, 5 days).

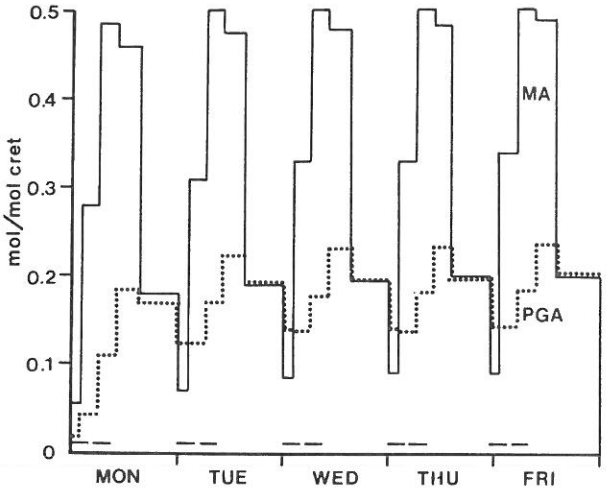

FIGURE 9 — Predicted profiles of urinary mandelic (MA) and phenylglyoxylic (PGA) acids excretions during a steady-state week of exposure to 50 ppm styrene. Urine voiding times are: 07h00, 09h00, 13h00, 17h00, 22h00. Physical workload is light (600 ml O_2/min) — shows exposure periods (08h00-12h00, 13h00-17h00, 5 days).

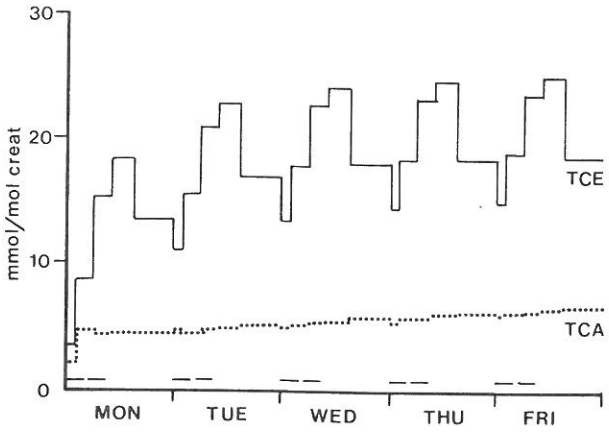

FIGURE 10 — Predicted profiles of urinary trichloroethanol (TCE) and trichloroacetic acid (TCA) excretions during a steady-state week of exposure to 350 ppm methylchloroform. Urine voiding times are: 07h00, 09h00, 13h00, 17h00, 22h00. Physical workload is light (600 ml O_2/min) — shows exposure periods (08h00-12h00, 13h00-17h00, 5 days).

TABLE VI
Description of the Factors Studied in the Simulations and Presentation of Their Associated Scenarios

Factor	Level	Scenarios
Repetition	Low	Isolated exposure.
	Standard	Steady-state repeated exposure.
Intraday fluctuations	Low	Standard with the monitored Wednesday morning at 0 ppm, the afternoon at 2 × TLV.
	High	Standard with the monitored Wednesday morning at 2 × TLV, the afternoon at 0 ppm.
Interday fluctuations	Low	Standard with no exposure on last Tuesday.
	High	Standard with 2 × TLV exposure on last Tuesday.
Physical workload	Low	Standard with rest during Wednesday exposure (V_{O2} = 300 ml/min).
	High	Standard with moderate physical workload during Wednesday exposure (V_{O2} = 1200 ml/min).
Body build	Low	Standard with half the amount of fatty tissue.
	High	Standard with twice the amount of fatty tissue.
Metabolism	Low	Standard with half metabolic clearance.
	High	Standard with twice metabolic clearance.

Standard exposure: steady-state repeated exposure (2 × 4 hr/day, 5 days/week) at TLV, light physical workload, standard man (V_{O2} = 600 ml/min).

This list is of course not exhaustive and other factors should be considered such as: renal clearance, interaction with other chemicals, solubility in the tissues, etc.

In order to simplify the analysis, three levels or scenarios have been chosen for each factor: standard, considered as being the reference; low, downward perturbation of the factor; and high, upward perturbation of the factor. The scenarios presented in Table VI represent very simplified or extreme cases and do not pretend to represent closely industrial situations.

Those scenarios have been applied to four typical solvents having very different properties especially with regard to blood solubility and metabolism. MC and PER have a very low metabolic clearance (2.5 and 15 ml/min, respectively) whereas benzene and styrene are highly biotransformed (1500 ml/min).[12] On the other hand, MC and benzene have relatively low blood solubilities, whilst PER and styrene are very soluble in blood (Table III). The metabolites of those solvents (phenol, MA, PGA, TCE, TCA) cover a wide range of pharmacokinetic properties with rate constants for their urinary excretion ranging from 0.2 h^{-1} (phenol) to 0.00685 h^{-1} (TCA).

The results obtained are summarized in Figure 11. They are presented in terms of relative bias or effect produced by each factor on the solvents in breath, or metabolites in urine. Biological specimens are considered to be taken either at the end of shift (0.5 hour post-exposure for breath, last 4 hours exposure urine) or on the following morning (15 hours post-exposure for breath, night urine 10 pm to 7 pm).

The results for the solvents in breath are presented together as there was not much difference between the solvents,[12] except for two factors (work-load, metabolism) for which a classification is made between highly (styrene, benzene) and slowly (MC, PER) metabolized solvents.

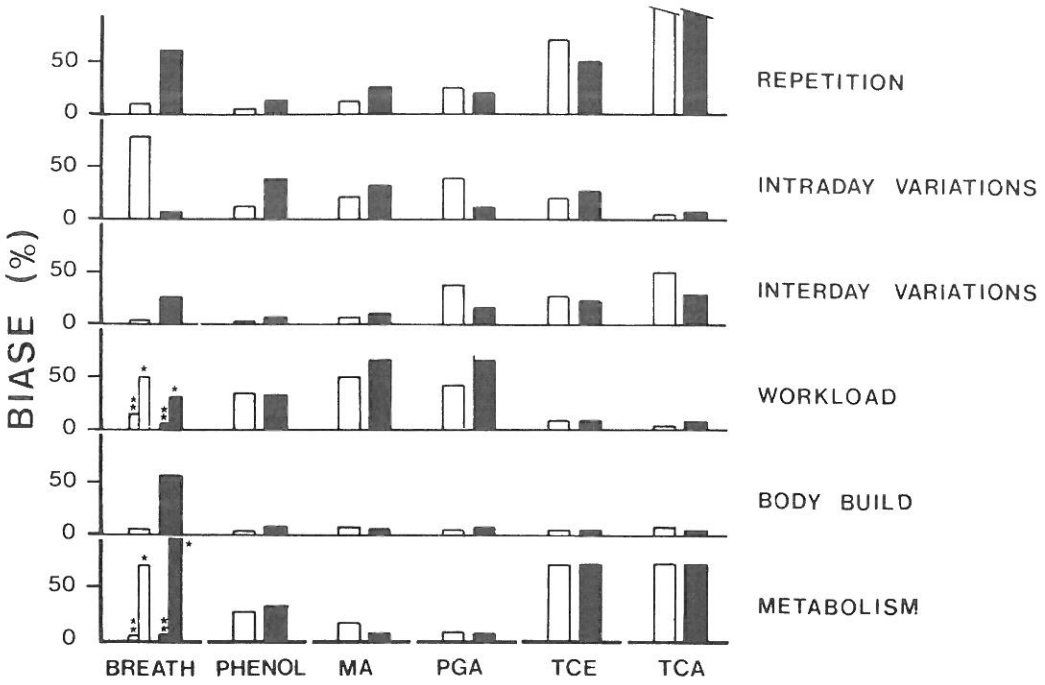

FIGURE 11 — Bias produced by the scenarios of Table VI concerning 6 factors. 4 solvents (5 metabolites) are considered: benzene (phenol), styrene (MA, PGA), methylchloroform (TCE, TCA), tetrachloroethylene (TCA). Average biases on breath (all solvents except for workload and metabolism), phenol, MA, PGA, TCE, TCA urinary excretions. White bar = samples taken at the end of shift (0.5 hour post-exposure for breath); black bar = samples taken on the next morning: 15 hours post-exposure for breath, 22h00-07h00 urine sample; * solvents with low metabolism; ** solvents with high metabolism.

The biases in Figure 11 are presented as unsigned values for simplicity. However, sometimes they would be negative, sometimes positive, an indication of possible under or overestimation depending on the cases.

The biases shown in Figure 11 are mainly conditioned by two characteristics of the solvents and metabolites:

1. Their kinetic characteristics at the time of sampling, which vary for the solvents as a function of post-exposure time and which are the excretion rate constants for the metabolites.
2. The metabolic clearance of the solvent itself.

Effect of repetition

A study of the effect of repetition of exposure is important firstly to establish biological limit values, and secondly to appreciate the bias which could arise if experimental single exposure data were used as a reference for industrial exposure monitoring. For the solvents in breath, the effect of repetition is important 15 hours after the exposure when the elimination kinetic is slow. For the metabolites, it is roughly parallel to the urinary excretion constants, TCA being the most affected with the slower kinetics. The use of single exposure data to interpret industrial exposures will therefore lead to high bias for solvents or metabolites showing slow kinetics at the time of sampling.

Effect of intra- and interday variations

In typical industrial situations, the exposure varies relatively widely during the shift and from one shift to the other. This can influence the levels of biological indicators after exposure. To study this effect, two extreme scenarios have been used:

1. Morning exposure of the day monitored with 0 ppm, afternoon exposure 2 × TLV (low), morning exposure 2 × TLV, and afternoon exposure 0 (high).
2. The day preceeding the monitored day has been simulated with the following exposures: 0 × TLV (low), TLV (standard), 2 × TLV (high).

Figure 11 tends to indicate that intraday variations in the concentration of exposure affect mostly components having fast kinetic behaviors at the time of sampling. For interday variations, the reverse seems to be true. This is a simplified interpretation and other parameters are probably of importance such as metabolic pathways, rate of formation of the metabolites, etc. Nevertheless, these results indicate that the effect of exposure fluctuation can be minimized by choosing the right indicator. But the rule seems to be that an indicator not sensitive to interday fluctuations will be sensitive to intraday fluctuations and vice versa.

Effect of physical workload

Physical workload has been studied using a man at rest (low), doing light workload (standard) and during moderate workload (high). Its effect mainly depends on the metabolic clearance. This is evident on the two groups of solvents (MC, PER and benzene, styrene) and on the metabolites. Another probably very important characteristic is the solvent solubility in blood. The very low influence of workload for inert solvents has to be put in relation with a relatively small increase in uptake.

Effect of body build

Body build, mainly fatty tissue volume, is an important factor in the behavior of solvents in the organism. The amount of fatty tissues varying widely between individuals, and also between male and female, three situations have been studied: slim subject (low), normal subject (standard), obese subject (high). Body build only influences the solvents in breath when sampled 15 hours after the exposure. No significant effect can be seen on the metabolites. Thus, large individual differences sometimes observed in metabolite excretions are therefore not due to fat content differences.

Effect of metabolism changes

The ability to metabolize solvents might vary between individuals due to genetic variations, sex, food habits, and/or intake of other chemicals. The results in Figure 11 show that the influence of changes in the metabolic rate have a large impact on breath concentrations of highly metabolized solvents, or on urinary concentrations of slowly metabolized solvents. These results can explain the high individual variability observed in some cases during experimental or field studies while looking at metabolites of low biotransformed solvents or at breath for highly metabolized solvents.

This short study of the effect of some confounding factors on biological monitoring results is a good example of the potentials of simulation models. Other important factors could be studied in the same way. Also more adequate and realistic scenarios could be chosen in order to achieve a finer analysis.

Conclusion

Simulation techniques using compartmental models are now developed enough to allow their application to the processes of BEIs' establishments. They can be considered as a very useful complement to the use of experimental or field studies.

Notably, they are powerful tools for the discussion of the effects of various factors such as environmental variability, individual differences, on the TLV-BEI relationships. The results obtained here indicate that for certain solvents or metabolites, BEIs should be applied with caution as their results and their interpretations can be the subject of large influence by various confounding factors.

Acknowledgments

We are grateful to Dr. M. Guillemin for helpful comments and discussions. This work was partly supported by the Fonds National Suisse de la Recherche Scientifique

References

1. Halprin, W.E.: Medical Screening in the Workplace: Proposed Principles. Presented at the *Conference on Medical Screening and Biological Monitoring for the Effects of Exposure in the Workplace*, Cincinnati OH (1984).
2. Zeilhuis, R.L.: Recent and Potential Advances Applicable to the Protection of Workers' Health — Biological Monitoring II. In: *Assessment of Toxic Agents at the Workplace*, pp. 84-94. A. Berlin, R.E. Yodaiken and B.A. Henman, Eds. Martinus Nijhoff Publishers (1984).
3. Lauwerys, R.R.: *Industrial Chemical Exposure: Guidelines for Biological Monitoring.* Biomedical Publications, Davis, CA (1983).
4. ACGIH: *Threshold Limit Values for Chemical Substances and Physical Agents in the Work Environment and Biological Indices with Intended Changes for 1984-85.* Cincinnati OH (1984).
5. Fernandez, J.G., P.O. Droz, J.E. Humbert and J.R. Caperos: Trichloroethylene Exposure: Simulation of Uptake, Excretion and Metabolism using a Mathematical Model. *Brit. J. Ind. Med. 34*:43-55 (1977).
6. Droz, P.O. and M.P. Guillemin: Human Styrene Exposure. V. Development of a model for biological monitoring. *Int. Arch. Occup. Environ. Health 53*:19-36 (1983).
7. Guberan, E.: Proposed Biological Threshold Limit Values for Industrial Exposure to Trichloroethylene Vapor. *Scand. J. Work Environ. Health 3*:80-90 (1977).
8. Fiserova-Bergerova, V., J. Vlach and K. Singhal: Simulation and Prediction of Uptake, Distribution, and Exhalation of Organic Solvents. *Brit. J. Ind. Med. 31*:56-52 (1974).
9. Fiserova-Bergerova, V.: Simulation Model as a Tool for Adjustment of Biological Exposure Indices to Exposure Conditions. In: *Biological Monitoring of Exposure to Chemicals*, Vol. 1, *Organic Compounds.* John Wiley & Sons, New York (in press).
10. Droz, P.O. and J.G. Fernandez: Trichloroethylene Exposure. Biological Monitoring by Breath and Urine Analyses. *Brit. J. Ind. Med. 35*:35-42 (1978)
11. Fiserova-Bergerova, V.: Predictable "Individual Differences" in Uptake and Excretion of Gases and Lipid Soluble Vapours — Simulation Study. *Ibid. 37*:42-49 (1980).
12. Droz, P.O., M. Guillemin: Occupational Exposure Monitoring Using Breath Analysis. *J. Occup. Med.* (in press).
13. Fiserova-Bergerova, V.: Toxicokinetics of Organic Solvents. *Scand. J. Work Environ. Health* (to be published).
14. Eger, E.I.: *Anesthetic Uptake and Action.* The Williams & Wilkins Company, Baltimore, MD (1974).
15. Fiserova-Bergerova, V.: *Modeling of Inhalation Exposure to Vapors: Uptake, Distribution and Elimination*, Vol. I and II. CRC Press, Boca Raton, FL (1983).
16. Caperos, J.R., P.O. Droz, C.L. Hake et al: 1,1,1-Trichloroethane Exposure. Biological Monitoring by Breath Analyses. *Int. Arch. Occup. Environ. Health 49*:293-303 (1982)
17. Droz, P.O.: *Contribution a la Recherche d'Indices Biologiques d'Exposition aux Solvants.* Thesis. Institut de Chimie de l'Universite de Neuchatel, Switzerland (1978).
18. Stewart, A., P.R. Allott, A.L. Cowles, W.W. Mapleson: Solubility Coefficients for Inhaled Anaesthetics for Water, Oil and Biological Media. *Brit. J. Anaesth. 45*:282-293 (1973).
19. Droz, P.O. and J.G. Fernandez: Effect of Physical Workload on Retention and Metabolism of Inhaled Organic Solvents. A Comparative Theoretical Approach and its Application with regards to Exposure Monitoring. *Int. Arch. Occup. Environ. Health 38*:231-246 (1977).
20. Hake, C.L.: Simulation Studies of Blood Carboxyhemoglobin Levels Associated with Inhalation Exposure to Methylene Chloride. Presented at the *18th Annual Meeting of the Society of Toxicology*, New Orleans, LA (1979).
21. Muller, G., M., Spassowski and D. Henschler: Trichloroethylene Exposure and Trichloroethylene Metabolites in Urine and Blood. *Arch. Toxicol. 29*:335-340 (1972).
22. Droz, P.O., J. Sollenberg, R. Bjurstrom and O. Vesterberg: Occupational Styrene Exposure: Monitoring of Uptake and Analyses of Metabolites in Urine. II. Comparison of a computer model with analyses data. Presented at the *International Conference on Organic Solvents Toxicity.* Stockholm, Sweden (1984).

23. Astrand, I.: Effect of Physical Exercise on Uptake, Distribution and Elimination of Vapors in Man. In: *Modeling of Inhalation Exposure to Vapors: Uptake, Distribution, and Elimination.* Vol. II, pp. 107-130. V. Fiserova-Bergerova, Ed. CRC Press, Boca Raton, FL (1983).

24. Piotrowski, J.: *The Application of Metabolic and Excretion Kinetics to Problems of Industrial Toxicology.* U.S. Dept. HEW, Washington DC (1971).

25. Monster, A.C.: In: *Biological Monitoring and Surveillance of Workers Exposed to Chemicals,* pp. 111-150. Mc-Graw Hill, New York (1984).

26. Riihimaki, V.: Conjugation and Urinary Excretion of Toluene and m-Xylene Metabolites in a Man. *Scand. J. Work Environ. Health* 5:135-142 (1979).

Annals of the
American Conference
of Governmental
Industrial Hygienists

Volume 12

International Symposium on Occupational Exposure Limits

AMERICAN CONFERENCE OF GOVERNMENTAL INDUSTRIAL HYGIENISTS
CINCINNATI, OHIO
1985

The Annals series will present the latest state-of-the-art information on research and practical applications of science in the field of occupational health. Each issue will be the proceedings of an important symposium, conference, or meeting sponsored by the American Conference of Governmental Industrial Hygienists or other leading professional organizations in, or allied with, the occupational health field. Contents will deal with subjects of current interest. The Annals series will become a valued addition to the international scientific literature.

Volume 1: Dosimetry for Chemical and Physical Agents (1981)
Volume 2: Agricultural Respiratory Hazards (1982)
Volume 3: Protection of the Sensitive Individual (1982)
Volume 4: ACGIH Transactions — 1982 (1983)
Volume 5: Industrial Hygiene — The Future (1983)
Volume 6: Computerized Occupational Health Record Systems (1983)
Volume 7: Some Pioneers of Industrial Hygiene (1984)
Volume 8: ACGIH Transactions — 1983 (1984)
Volume 9: Threshold Limit Values — Discussion and Thirty-Five Year Index with Recommendations (1984)
Volume 10: Evaluating Office Environmental Problems (1984)
Volume 11: ACGIH Transactions — 1984 (1984)

Library of Congress Catalog Card No.: 85-73089

Printed in the United States of America

ISBN: 0-936712-62-7

CODEN: ACGHD2 12 1-389 (1985)