British Journal of Industrial Medicine 1989;46:447–460

Variability in biological monitoring of solvent exposure. I Development of a population physiological model

P O DROZ,[1] M M WU,[1] W G CUMBERLAND,[1] M BERODE[2]

From the School of Public Health,[1] University of California at Los Angeles, Los Angeles CA 90024, USA, and Institute of Occupational Health Sciences,[2] Lausanne University, 1005 Lausanne, Switzerland

ABSTRACT Biological indicators of exposure to solvents are often characterised by a high variability that may be due either to fluctuations in exposure or individual differences in the workers. To describe and understand this variability better a physiological model for differing workers under variable industrial environments has been developed. Standard statistical distributions are used to simulate variability in exposure concentration, physical workload, body build, liver function, and renal clearance. For groups of workers exposed daily, the model calculates air monitoring indicators and biological monitoring results (expired air, blood, and urine). The results obtained are discussed and compared with measured data, both physiological (body build, cardiac output, alveolar ventilation) and toxicokinetic for six solvents: 1,1,1-trichloroethane, trichloroethylene, tetrachloroethylene, benzene, toluene, styrene, and their main metabolites. Possible applications of this population physiological model are presented.

The development of quantitative biological indicators of solvent exposure is usually carried out by comparing blood, urine, or expired air levels of the solvents or their metabolites with some measure of the external exposure. Most studies, both experimental[1,2] and in workers,[3–5] show (1) highly significant relations between the biological indicators and external exposures and (2) a significant scatter around these relations. This second aspect is important in the development of biological indicators for several reasons:

If external exposure is to be measured by biological monitoring then the indicator showing the least residual variability when compared with exposure should be used;

If the internal exposure is the main focus then in certain cases indicators with higher variability might be preferred over others. This would be the case when the observed residual variability is related to corresponding variations in the internal exposure;

If internal exposure can be described by different parameters such as uptake, solvent concentration in a target organ, or amount of reactive metabolites formed then the choice of a biological indicator should depend also on the type of internal exposure considered.

Few studies have been designed to describe and understand individual variability in biological monitoring and this aspect has often been treated as secondary. With the goal of better describing and understanding variability, we have initiated a research project including both experiments on human volunteers and a theoretical approach based on simulation models. This report presents the development of a model for the second approach.

Physiological models have been applied with some success on several occasions to the description of volatile organics in the body.[6,7] They have nevertheless been restricted to the concept of a standard man and a standard environment, with some exceptions where known extreme deviations were investigated.[8,9] Workers and industrial environments are not constant and may be better described as the realisation of some probabilistic phenomena. For example, the body build of a worker, his liver and renal functions, and his exposure to solvents may all be thought of as results of observations following some joint statistical distribution. The main idea in building the present model was, therefore, to combine statistical simulation techniques with physiological models to simulate realistic groups of differing workers in variable industrial environ-

Accepted 30 August 1988

ments. The variability thus observed in the biological indicators may then be described and studied as a function of the input statistical distributions.

Method

PHYSIOLOGICAL MODEL DESCRIPTION

The simulation of solvent absorption, its distribution, and elimination in the body is done through the use of a physiological model containing seven compartments[7 10]: (1) lungs, (2) brain, (3) muscles and skin (MG), (4) fatty tissues (FG), (5) kidneys, (6) hepatoportal system (liver), and a last compartment (7) including the remaining perfused tissues (others). Solvent metabolism occurs only in the liver and is described by the "well stirred" model.[11] The rate of metabolism is a function of the organ clearance which is itself calculated from the intrinsic metabolic clearance and the blood perfusion. The unchanged solvent may be excreted by the lungs and kidneys according to blood-gas and blood-urine[12] partition coefficients (λ). The metabolism of the solvent is simulated using one or two metabolites each following a one compartment model that is usually typical of polar chemicals such as metabolites. One of the metabolites may be transformed into the other according to its intrinsic clearance. Their urinary excretion is calculated based on their renal clearance. Mathematical formulas are shown in the appendix.

SOURCES OF VARIABILITY CONSIDERED

Variability is assumed to result from either individual differences (body build, liver function, renal function) or to be linked to the workplace environment and the tasks performed by the worker (exposure, physical workload).

Individual variability—Variability within the same worker from day to day is considered to be much smaller than between workers' variability, and is therefore neglected for simplicity.[13] Between worker variability manifests itself in differences in body build (distribution), liver function (metabolism), and renal function (excretion). Body build is described by body height (BH) and body weight (BW) that are then used to calculate distribution volumes, blood perfusions, and alveolar ventilation. Liver function variability is simulated using three parameters, the intrinsic metabolic clearance ($CL_{int,s}$), the liver blood flow ($\dot{Q}_{liver}$), and the proportion of each metabolite formed (F_i). Renal function affects only the metabolite excretions and its variability is simulated by differences in renal clearance (CL_{mi}). The final urinary concentrations are integrated over a random urine voiding time ($T_{u,x}$) and expressed relative to creatinine excretion (which is itself a function of the volume of MG). For metabolites normally present in urine without exposure, a random background value is added in. Mathematical relations are presented in the appendix.

Environmental variability—The exposure concentration variability has three components: between workers (due to different tasks performed or different work practices), within worker from one day to the next, and within worker during the shift. The first concept allows for differences in long term mean exposure from one worker to another, the second for differences between eight hour time weighted averages (TWA) for the same worker, and the last for 15 minute average differences. Physical workload is taken as being constant during the workshift (lack of data), but fluctuations both between workers and within workers from one day to the next are allowed. Physical workload is described by the external workload (W) produced. The corresponding excess oxygen consumption $\Delta\dot{V}_{O2}$ due to workload is then calculated

Table 1 *Physicochemical and metabolic properties of solvents*

	Tissue-gas partition coefficient (37°C)								$CL_{int,s}$**
Solvent	*Water**	*Oil**	*Blood**	*Others†*	*Brain‡*	*MG§*	*FG‖*	*Kidney¶*	*(l/mn)*
Methylchloroform	0·88	373	4	9	11	6	260	6	0·025
Trichloroethylene	1·5	763	9	16	23	12	540	12	7·5
Tetrachloroethylene	0·94	2072	14	38	59	29	1450	29	0·0035
Benzene	2·8	498	7	15	17	10	350	10	7·5
Toluene	2·5	1460	16	30	44	23	1030	23	7·5
Styrene	4·9	5838	59	112	169	84	4100	86	7·5

*Measured experimentally.[18]
†Calculated according[18] to $\lambda_{others} = 0{\cdot}0172^* \lambda_{oil} + 2{\cdot}3^* \lambda_{water}$.
‡Calculated according[18] to $\lambda_{brain} = 0{\cdot}0281^* \lambda_{oil} + 1{\cdot}12^* \lambda_{water}$.
§Calculated according[18] to $\lambda_{MG} = 0{\cdot}0133^* \lambda_{oil} + 1{\cdot}36^* \lambda_{water}$.
‖Calculated according[18] to $\lambda_{FG} = 0{\cdot}7^* \lambda_{oil} + 0{\cdot}3^* \lambda_{blood}$.
¶Calculated according[18] to $\lambda_{kidney} = 0{\cdot}0138^* \lambda_{oil} + 1{\cdot}05^* \lambda_{water}$.
**Intrinsic metabolic clearance of the solvent (l/min).

Table 2 *Pharmacokinetic parameters for metabolites*

Solvent	*Metabolite*	F_i	$CL_{m,i}$ *(ml/min)*	$V_{d,mi}$ *(l)*	CL_{mi} *(ml/min)*	$B_u(X, CV)$ *(mmol/mol creat)*
Methylchloroform	→ TCE	1·0	25	78	75	—
	↓					
	TCA	0·0	—	8·5	1·3	—
Trichloroethylene	→ TCE	0·51	25	78	75	
	↓					
	→ TCA	0·15	—	8·5	1·3	—
Tetrachloroethylene	→ TCA	1·0	—	8·5	1·3	—
Benzene	→ phenol	1·0	—	25	84	5·1 (1·1)
Toluene	→ HA	0·90	—	10·8	84	350 (0·6)
	→ o-cresol	0·0005	—	25	84	0·35 (2·0)
Styrene	→ MA	1·0	19	28	84	—
	↓					
	PGA	0·0	—	28	84	—

F_i = Proportion of i^{th} metabolite formed.
$CL_{int,mi}$ = Intrinsic metabolic clearance of metabolite m_i.
$V_{d,mi}$ = Volume of distribution of metabolite m_i.
CLmi = Renal clearance of metabolite i.
Bu(X, CV) = Normal excretion of metabolite without exposure (mean, coefficient variation).

assuming an efficiency independent of body build (see appendix).

DATA FOR FIXED COMPONENTS OF THE MODEL

Six solvents are considered here. Table 1 shows their tissues gas λ and intrinsic metabolic clearances $CL_{int,s}$. Trichloroethylene, benzene, and toluene, which are known to be highly metabolised, are considered to behave the same as styrene for which $CL_{int,s}$ is extrapolated from animal studies.[14 15] For tetrachloroethylene and methylchloroform $CL_{int,s}$ is estimated from the total amount of metabolite(s) excreted in urine.[16] Water, olive oil, and blood-gas λ are experimental measurements,[17 18] tissues-gas λ are calculated from them.[18] Blood urine λ is described by the blood water λ.[12] Table 2 shows the parameters describing the formation, distribution, and elimination of metabolites. The $CL_{int,s}$ of metabolites undergoing further transformation is calculated from their metabolic clearance CL and a mean liver blood flow of 1·5 l/min. The metabolic clearance is itself calculated from the corresponding rate constants and the volumes of distribution. The proportions of each metabolite formed (F_i) are estimated from various recovery studies in human volunteers.[19–21] Trichloroethanol (TCE), trichloroacetic acid (TCA), and phenol volumes of distribution and renal clearances are estimated from toxicokinetic studies[19 22] and using the relation between volume of distribution, clearance, and half life. O-cresol is assumed to behave as phenol and to have the same volume of distribution and the same clearance. Phenylglyoxylic acid (PGA) and hippuric acid (HA) are assumed to have the same clearance as mandelic acid (MA) which is determined from simultaneous blood and urine measurements.[23] Their volume of distribution is calculated from their known urinary excretion rates, PGA being considered as behaving as MA. The physiological parameters used in the model are described in table 3. The volumes are expressed as percentages of the lean body volume (LBV) and are estimated from data for a standard man (70 kg, 170 cm, LBV = 50·7 l).[24 25] The blood perfusions in table 3 are blood flows per volume of tissue and these are similarly estimated from the characteris-

Table 3 *Physiological parameters associated with compartments*

Compartment	*Volume (% LBV)*	*Unit perfusion (ml/min/ml)*	*Effect of physical workload on unit perfusion*
Lungs			
Tissue	0·91	$\dot{Q}_b^\circ = \Sigma\dot{Q}_i$	$\Sigma\dot{Q}_i$
Air	5·5	$\dot{V}_{alv}^\circ = 0{\cdot}8^* \dot{Q}_b^\circ$	$\dot{V}_{alv}^\circ + 22^* \Delta\dot{V}_{O2}$
Arterial blood	1·9	—	—
Others	1·0	2830	unchanged
Muscles and skin	69	33	$\dot{Q}_i + 7{\cdot}4^* \Delta\dot{V}_{O2}$
Fatty tissues	FBV	22	$\dot{Q}_i + \Delta\dot{V}_{O2}$
Brain	2·6	570	unchanged
Kidneys	0·53	4520	$\dot{Q}_i^* (1 - 0{\cdot}14^* \Delta\dot{V}_{O2})$
Splanchnic	5·8	520	$\dot{Q}_i^* (1 - 0{\cdot}19^* \Delta\dot{V}_{O2})$
Venous blood*	8·3	—	—

*Venous blood is distributed into the six tissue compartments according to their blood perfusion.

Table 4 *Description of sources of data for individual and physical variability*

Subjects (ref)	*BH[m] $\bar{X}$ (SD)*	*BW/BH2[kg/m2] $\bar{X}$ (SD)*	*CLint,x CV*	*$\dot{Q}$liver CV*	*Fi CV*
5634 white men [29]	1·77 (0·073)	25·3 (3·77)	—	—	—
160 workers[5]	1·72 (0·073)	25·1 (3·37)	—	—	—
58 workers*	1·69 (0·083)	24·7 (3·46)	—	—	—
40 workers†	1·68 (0·083)	27·2 (3·97)	—	—	—
59 patients[20]	—	—	0·27	—	—
20 twins[32]	—	—	—	—	0·25–0·45
73 patients[31]	—	—	—	0·17	—

BH = Body height.
BW/BH2 = Quetelet index.
CLint, x = Intrinsic metabolic clearance, x = antipyrine.
$\dot{Q}$liver = Liver blood flow.
Fi = Proportion of metabolite formed.
CLren, i = Renal clearance.
Tu, x = Urine voiding time (es = end of shift, nm = next morning).
W = Physical workload.
*Unpublished data.
†Unpublished data.

tics of a standard man. External physical workload produces an equivalent excess oxygen uptake $\Delta\dot{V}_{O2}$. The blood flow through the MG and FG is increased by a fixed amount proportional to $\Delta\dot{V}_{O2}$;[26] the perfusions of the kidneys and the liver are decreased proportionally to $\Delta\dot{V}_{O2}$.[27] Cardiac output is calculated as the sum of the blood flows to the various tissues. Alveolar ventilation at rest is computed from cardiac output using a ventilation/perfusion ratio of 0·8. With physical workload the alveolar ventilation increases by an amount proportional to $\Delta\dot{V}_{O2}$ to satisfy the increased oxygen uptake. Detailed calculations are shown in the appendix.

STATISTICAL DISTRIBUTIONS FOR RANDOM COMPONENTS

To simulate variability as realistically as possible, several sources of data were studied. These are briefly summarised in table 4, which shows the mean ($\bar{X}$) and standard deviation (SD), or the coefficient of variation (CV) when the mean is not relevant, for the variables needed in the simulation model. The parameters chosen for the random generators are shown in table 5. Their calculation from the sources presented in table 4 is detailed in the appendix.

Variability in body build is simulated using a gamma distribution for body height. A similar distribution is used for the Quetelet index (weight/height^2) which is used instead of body weight since it is less correlated with body height.[28] A gamma distribution was used for these two variables to take into account the skewness observed and to avoid generating exceedingly high values. Then weight is calculated from height and the value for the index. The parameters for the two gamma distributions are estimated from the NHANES II study[29] which gives results similar to the other studies of table 4 so far as mean and standard deviations are concerned.

For liver function, two tracers are considered to measure the variability of $CL_{int,s}$ and $\dot{Q}_{liver}$ respectively: antipyrine[30] and bromsulphalein.[31] The first shows a slow metabolism and therefore is an indicator of $CL_{int,s}$ variability, the second has a flow limited behaviour which makes it an indicator of $\dot{Q}_{liver}$ variability. For antipyrine a lognormal distribution is used to take into account the possible polymorphic genetic control of the intrinsic clearance[30]; for bromsulphalein a normal distribution seems satisfactory.[31] The variability in the proportions of metabolites formed F_i is estimated by looking at the variability in the ratio of antipyrine metabolites formation (3-hydroxymethyl-, N-dimethyl-, and 4-hydroxy- antipyrine).[32] Depending on the metabolite considered, the variability may be described by CV ranging from 0·25 to 0·45. A lognormal distribution is used because of the skewness generally observed in the distribution of the metabolites production.

The variability in renal clearance is described using the variability in creatinine clearance. The latter is estimated from blood creatinine and body build using the studies presented in table 4. The results obtained are in agreement with actual measurements.[33] A normal distribution is used here, the mean of which is the renal clearance of the metabolite considered. The variability in urine voiding times both at the end of shift ($T_{u,es}$) and for the morning sample ($T_{u,nm}$) are taken from the studies in table 4. Again a normal distribution is used for simulating these values. For metabolites normally present in urine (HA, o-cresol, phenol), a random background is added to urinary concentrations. It is sampled from lognormal distributions having the means and coefficients of variation shown in table 2. These distributions are based on before shift urinary metabolites concentrations obtained in a study of rotogravure printing workers (table 4).

Three lognormal distributions are used to describe exposure concentration variability. To stimulate industrial environments with a range of variabilities three levels are defined by their geometric standard deviation GSD: low (GSD = 1·2), medium (GSD = 2·0), and high (GSD = 3·0). The means, coefficients of variation, and geometric standard deviations considered are shown in table 5.

CLmi[l/min] $\bar{X}$ (SD)	*Tu, es[min] $\bar{X}$ (SD)*	*Tu, nm[min] $\bar{X}$ (SD)*	*W (watts) $\bar{X}$ (SD)*	*Description of data*
—	—	—	—	National Health Survey
101 (22)	—	474 (85)	43 (20)	Rotogravure/toluene
97 (23)	—	467 (68)	—	Dry cleaning/tetrachloroethylene
108 (25)	169 (54)	407 (118)	—	Polyester/styrene
—	—	—	—	Pooled data, antipyrine
—	—	—	—	Antipyrine metabolites
—	—	—	—	Bromsulphalein

The between worker variability in physical workload is estimated from the second study of table 4[5] assuming a negligible day to day component. A gamma distribution is chosen to take into account some positive skewness. In addition, a slight day to day fluctuation is simulated according to a normal distribution chosen mainly for simplicity as no data exist on day to day workload fluctuations in occupational settings. The workers are considered at rest when not working.

Results and discussion

PROTOCOL FOR THE SIMULATIONS

The exposure pattern chosen follows the normal work cycle: eight hours work interrupted by a one hour lunch break, five days a week, several weeks. Preliminary simulations showed that four weeks were sufficient to reach a steady state situation. In the fifth week Thursday (day 4) and Friday morning (day 5) are chosen for the monitoring. Three types of parameters are then calculated referring to: air monitoring, biological monitoring, and internal exposure.

Air monitoring—Time weighted average (TWA) exposure concentrations are calculated over eight hours on Thursday and over 40 hours during the entire week.

Biological monitoring—Two time points are considered: just after the end of work on Thursday (half an hour after exposure for blood and breath, end of shift for urine) and on Friday before shift. For breath the solvent concentration C_{alv} is calculated, for the blood the solvent C_{ven} and the metabolites C_{bm1}, C_{bm2} concentrations are computed, for urine the metabolites excreted corrected for creatinine C_{um1}, C_{um2} are calculated and the urinary solvent concentrations C_{usol}.

Internal exposure indices—The following indices can be calculated: uptake, mean solvent concentration in blood and in brain, mean metabolites concentration in blood, and "reactive intermediate" formation rate in liver.[14]

In one simulation run the numbers of workers simulated is usually 200. For each worker all the indicators described above are stored together with data describing the body build, the liver and renal function, the exposure, and the physical workload.

SIMULATION OF BODY BUILD

Body build is determined in the model by only two crude indicators: body height (BH) and weight (BW). It is therefore necessary to check that the predicted lean (LBV) and fat (FBV) volumes are in agreement with measured data. Figure 1 shows such a validation by comparing predictions by the model with the body fat volume measured by a density method in 25 sedentary male subjects (age 17–76, height 160–194 cm, weight 57–128 kg) and in 11 men engaged in

Table 5 *Simulation of individual and environmental variability*

	Distribution description	
Random variable	*Shape*	*Parameters*
BH (cm)	Gamma	$\bar{X} = 177, \alpha = 23, \beta = 1{\cdot}60, \gamma = 140$
BW/BH^2 (kg/m^2)	Gamma	$\bar{X} = 25{\cdot}3, \alpha = 11{\cdot}85, \beta = 1{\cdot}075, \gamma = 12{\cdot}5$
$CL_{int,i}$ (l/min)	Lognormal	CV = 0·27
Q_{liver} (l/min)	Normal	CV = 0·17
F_i	Lognormal	CV = 0·25–0·45
CL_i (l/min)	Normal	CV = 0·23
$T_{u,es}$ (min)	Normal	$\bar{X}$ = 180, SD = 75
$T_{u,nm}$ (min)	Normal	$\bar{X}$ = 420, SD = 120
Exposure (μmol/l)	Lognormal	$\bar{X}$ = TLV, CV = 0·18/0·78/1·53
Exposure (within worker)	Lognormal	$\bar{X}$ = TLV, CV = 0·18/0·78/1·53
Exposure (within day)	Lognormal	$\bar{X}$ = TLV, CV = 0·18/0·78/1·53
W (watts)	Gamma	$\bar{X} = 44, \alpha = 5{\cdot}0, \beta = 8{\cdot}8, \gamma = 0$
W (watts) (within worker)	Normal	CV = 0·10

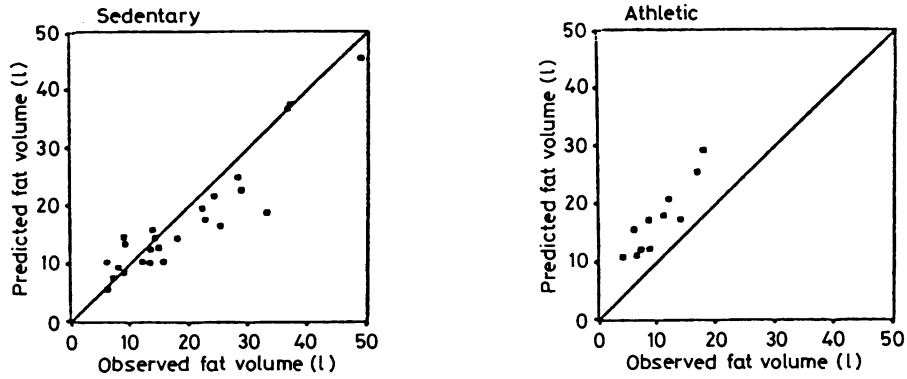

Fig 1 *Comparison of predicted and measured fat body volume in group of 25 sedentary men and of 11 athletic men. Diagonal line indicates one to one relationship.*

competitive sports (age 19–26, height 164–191 cm, weight 63–104 kg).[34] Figure 1a indicates a good agreement between predicted and measured values, with means respectively of 17·2 and 19·0 l. For athletic subjects, however, the agreement is much less, the predicted mean for this group is 17·2 l against 10·2 l measured. In fact in this case the model is mistaking muscle mass for fat. A third parameter should be introduced to take physical training into account. Nevertheless, such high level of training will concern only a small fraction of the workers and it is therefore not considered important for these simulations.

Body fat is certainly the most important body compartment for liposoluble solvents and it has therefore attracted some attention.[6,8,9] Figure 2 shows the cumulative distributions of fat body volumes and lean body volumes using the statistical distributions of table 4. This figure may be used to estimate the ranges of lean and fat volumes for a given fraction of a population of workers. It appears that FBW varies much more (CV = 35%) than LBV (CV = 11%). The mean FBV for this population is 19 l which is higher than the 12 l usually associated with standard man simulations. This is due to higher average body weight and height for workers than for a standard man. The investigation of the effect of body build on solvent behaviour is often done by halving or doubling the volume of fat.[8,9] In our simulations only 5% of the workers have a FBV outside this range. Therefore, most of the workers will show a much less extreme behaviour than previously predicted.

SIMULATION OF PHYSICAL WORKLOAD

Both body build and physical workload affect blood flows and alveolar ventilation. Figure 3 illustrates the behaviour of the model for cardiac output, muscle

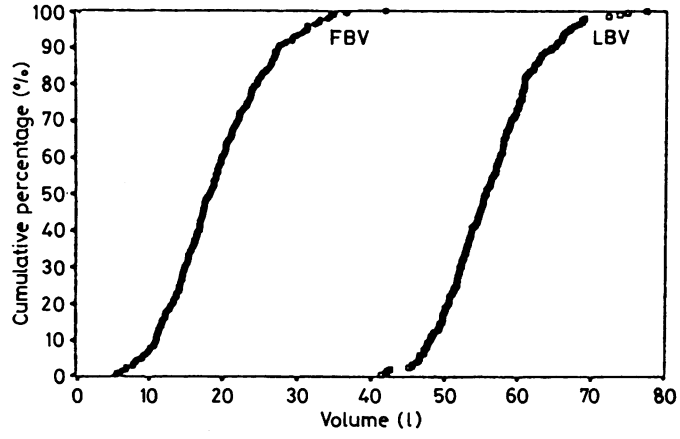

Fig 2 *Predicted cumulative distributions for fat (FBV) and lean (LBV) body volumes in group of 200 male workers.*

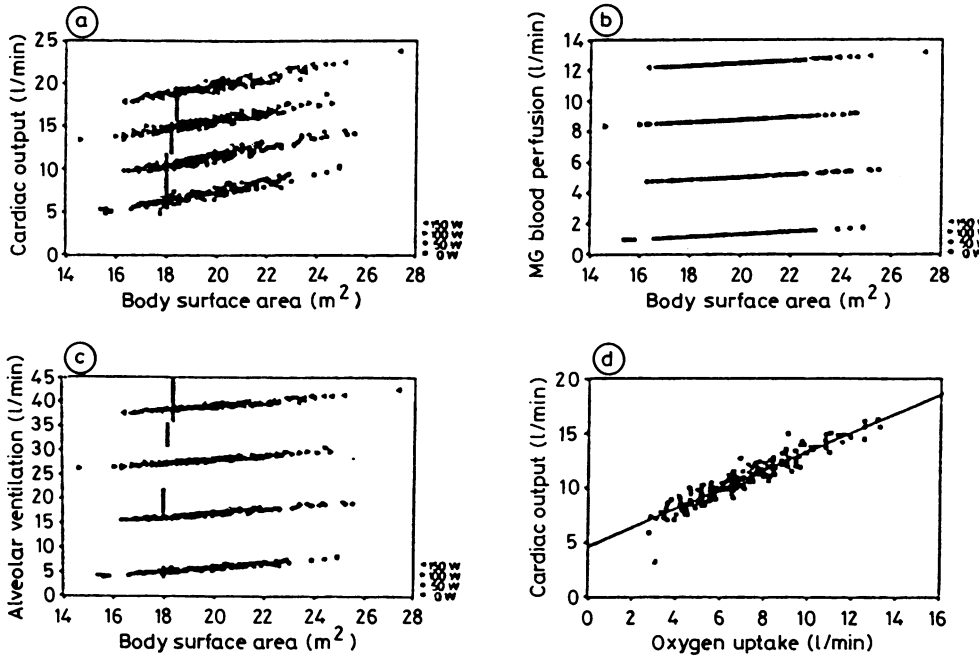

Fig 3 *Effect of body build (expressed as body surface area) and physical workload (Watts) on (a) cardiac output, (b) MG perfusion, and (c) alveolar ventilation simulated in four groups of 200 workers. Body surface area of a standard man (70 kg, 170 cm) is 1·6 m². Relation between cardiac output (Y) and oxygen uptake (X) in 200 workers with mean physical workload of 40 W (D). Regression line is Y = 8·7 X + 4·7. For plots (a) and (c), parentheses indicate ranges in young male volunteers.*[32]

blood flow, and alveolar ventilation as a function of body surface area for: 0, 50, 100, and 150 Watts of external physical workload. For cardiac output and alveolar ventilation, ranges of experimental values obtained in young male volunteers are also indicated.[26] For cardiac output there is a general agreement. For alveolar ventilation, the model is slightly underestimating the effect of physical workload. Muscle blood flow, according to the model (table 3), increases by about 4 l/min for each 50 W increment, which agrees with published data.[26] The plots in fig 4 indicate a linear increase in blood flow and alveolar ventilation

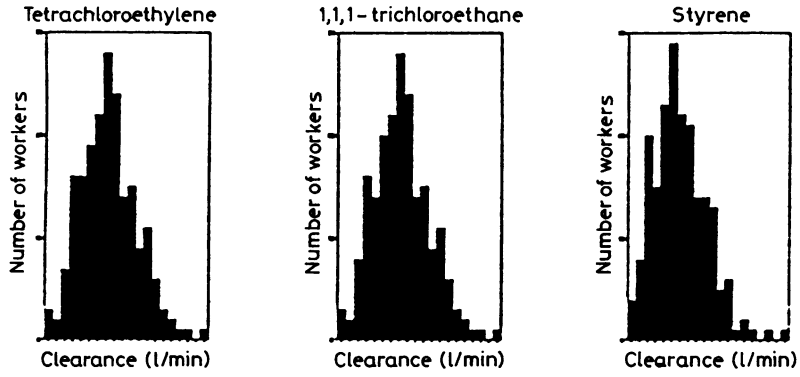

Fig 4 *Predicted distributions of metabolic clearance in a group of 200 workers for tetrachloroethylene (mean 0·0021, range 0·0012–0·0036 l/min), 1,1,1-trichloroethane (mean 0·0152, range 0·0088–0·0252 l/min), and styrene (mean 1·23, range 0·52–2·71).*

Table 6 *Comparison of biological indicators obtained after exposure at the TLV[40] with published data*

Biological indicators	Methylchloroform		Trichloroethylene		Tetrachloroethylene	
	Model $\bar{X}$ (CV)	Measured	Model $\bar{X}$ (CV)	Measured	Model $\bar{X}$ (CV)	Measured
						End of shift samples
Calv [μmol/m³]	4340 (0·03)	6850[41]	310 (0·13)	300[41]	1000 (0·06)	827[41]
Cven [μmol/l]	35 (0·02)	45[41]	6·0 (0·08)	3·8[41]	18 (0·05)	13[41]
Cbm1 [μmol/l]	87 (0·61)	102[41]	840 (0·40)	400[41]	29 (0·34)	34[41]
Cbm2 [μmol/l]	6·6 (0·25)	7·3[41]	32 (0·19)	33[40]	—	—
Cusol [μmol/l]	10 (0·05)	6·4[41]	1·4 (0·08)	—	1·3 (0·05)	—
Cum1 [mmol/mol]	8·4 (0·51)	12[41]	61 (0·19)	69[40]	2·9 (0·30)	4·8[40]
Cum2 [mmol/mol]	38 (0·29)	26[41]	175 (0·19)	159[40]	—	—
						Before shift samples
Calv [μmol/m³]	1270 (0·13)	1788[41]	78 (0·20)	15[40]	435 (0·07)	400[40]
Cven [μmol/l]	5·1 (0·13)	—	0·72 (0·20)	0·18[41]	6·1 (0·06)	5·3[40]
Cbm1 [μmol/l]	89 (0·61)	67[41]	815 (0·42)	400[41]	28 (0·38)	24[41]
Cbm2 [μmol/l]	3·4 (0·32)	3·3[41]	16 (0·37)	10[41]	—	—
Cusol [μmol/l]	1·2 (0·12)	—	0·12 (0·20)	—	0·43 (0·06)	—
Cum1 [mmol/mol]	8·7 (0·51)	8·7[41]	81 (0·19)	55[41]	2·8 (0·30)	2·9[41]
Cum2 [mmol/mol]	24·1 (0·20)	13[41]	110 (0·13)	91[41]	—	—

*AC Monster, St Louis, 1984.

with body surface area which is what is generally expected.[35] The effect of physical workload appears to be more pronounced on alveolar ventilation than on cardiac output. This will produce a decrease in the perfusion/ventilation ratio to about 0·5 for 100 W. This is what has been generally observed experimentally.[26]

The relation between cardiac output and oxygen uptake for a group of 200 workers simulated using parameters of table 4 is also shown in fig 3d. The linear least squares regression gives a slope of 8·7, higher than the usual range of 5–7, although data as high as 8 have been reported.[36] This possible discrepancy should slightly exaggerate the effect of physical workload on blood flow.

SIMULATION OF METABOLIC CLEARANCE

The simulation of variability in metabolic clearance is based on the use of two tracers of liver microsomal oxidation (antipyrine) and liver blood flow (bromsulphalein). The hypothesis used is not that the solvents behave identically to these two tracers but that their variability will be similar. Other drugs may be considered as tracers. For the intrinsic metabolic clearance, kinetic data on drugs other than antipyrine indicate coefficients of variation of the same magnitude.[37] Liver blood flow studies using flow limited clearance drugs other than bromsulphalein give coefficients of variation ranging from 0·08 to 0·42.[38] Similar ranges of variability have been reported for liver blood flow determined by other techniques, such as inert gas clearance.[39] Therefore, although only two tracers are used formally in the development of the model, they seem to be generally representative.

Metabolic clearance for one solvent depends on the intrinsic clearance and the liver blood flow. Figure 4 shows the distributions of metabolic clearances for three solvents studied: styrene, tetrachloroethylene, and 1,1,1-trichloroethane. Benzene, toluene, and trichloroethylene would give results identical to styrene based on the hypothesis formulated above. For styrene, the mean CL is almost identical to the mean liver blood flow—that is, 1·5 l/min. The variability in intrinsic metabolic clearance will therefore have almost no effect on styrene, as well as on the other three similar solvents. The variability in metabolism will be most affected by blood flow variability and the factors affecting it such as physical workload and intake of food. For tetrachloroethylene and 1,1,1-trichloroethane the reverse is true and their behaviour is mainly linked to the intrinsic clearance as indicated by the low values obtained. Variability in liver function will therefore affect chemicals differently, depending on whether they have a high or low liver metabolic clearance.

MEAN BIOLOGICAL INDICATORS AT THE TLV

The simulation of repeated constant exposure at the TLV[40] with a constant light physical workload (50 W) for a group of variable workers gives for each biological indicator a statistical distribution which may be summarised by:

(*a*) the mean which indicates the average value that would be obtained in a group of workers exposed at the TLV;

(*b*) the coefficient of variation (CV) which describes the variability between workers that each biological indicator would have for a constant exposure at the TLV.

The results obtained (mean, CV) are presented in table 6 for the six solvents and their metabolites. For comparison, biological indicator levels found

Benzene		*Toluene*		*Styrene*	
Model $\bar{X}$ (CV)	*Measured*	*Model $\bar{X}$ (CV)*	*Measured*	*Model $\bar{X}$ (CV)*	*Measured*
66 (0·12)	50[42]	505 (0·16)	507[5]	106 (0·20)	—
1·1 (0·7)	—	17 (0·10)	11[40]	12 (0·14)	5[43]
—	—	—	—	25 (0·53)	—
—	—	—	—	150 (0·16)	—
0·60 (0·08)	—	3·5 (0·10)	2·8[12]	1·3 (0·13)	0·9[12]
—	—	1·2 (0·83)	1·6[5]	141 (0·30)	180[40]
12 (0·17)	60[40]	2100 (0·15)	1600[40]	927 (0·18)	595[40]
16 (0·20)	5[40]	131 (0·21)	85[5]	29 (0·24)	1·7[40]
0·11 (0·20)	—	2·1 (0·21)	—	1·7 (0·24)	0·2[40]
—	—	—	—	15 (0·85)	—
—	—	—	—	34 (0·42)	—
0·05 (0·20)	—	0·35 (0·21)	—	0·15 (0·24)	0·2[12]
—	—	0·69 (1·4)	—	113 (0.37)	90*
36 (0·25)	—	607 (0·33)	—	284 (0·16)	290*

equivalent to a repeated exposure at the TLV on the basis of experimental or field studies are also shown. In about 80% of the cases the agreement is within ±50%; in about half the comparisons it is within ±30%. The large deviations were observed for solvents in blood or expired air sampled before the shift. In these cases experimental data are usually obtained by extrapolation of single exposure of volunteers, and it is difficult to take into account the effects of exposure repetition and physical workload. In this case the differences observed in table 6 cannot be attributed only to the model but also to uncertainties

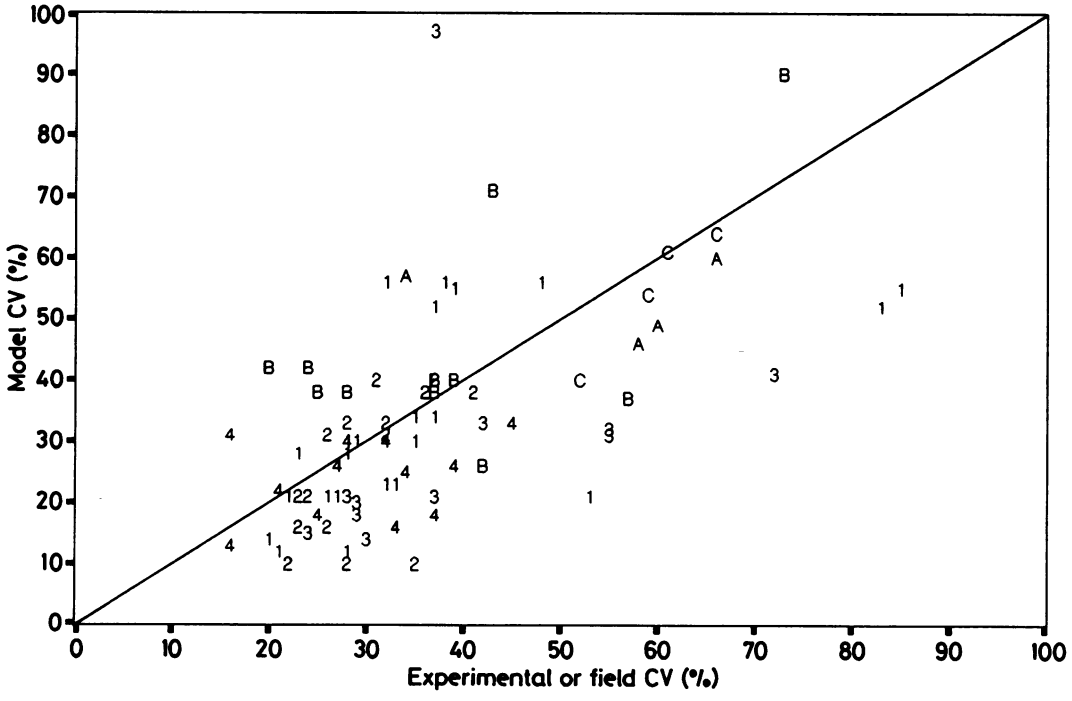

Fig 5 *Comparison of predicted and observed coefficients of variation (CV) of biological indicators for volunteers (numbers) and workers (letters) exposed to trichloroethylene (4), tetrachloroethylene (2, B), 1,1,1-trichloroethane (1, A), and styrene (3, C). Diagonal line indicates one to one relationship.*

in the experimental data.

The variability in the biological indicator results (CV) gives an idea of the effect of individual differences on biological monitoring. They qualitiatively follow the general tendencies reported previously.

COMPARISON OF VARIABILITY WITH EXPERIMENTAL AND FIELD RESULTS

Both experimental exposure data and results obtained during surveys of workers may be used to confirm the variability simulated by the model. The CV was chosen for comparison. The CV obtained by the model is adjusted to take analytical variability into account by adding the variances, assuming an analytical error with an average CV of 0·10. For field results, the CV is calculated from the residuals obtained by regressing in a log-log scale the exposure over the biological indicator.[45] Both daily and weekly exposures are considered where available. Biological indicators are breath, blood, or urinary levels in samples collected either at the end of the shift or before the shift. Figure 5 summarises the results calculated from experimental studies for trichloroethylene, tetrachloroethylene, and 1,1,1-trichloroethylene,[17] and from field studies for tetrachloroethylene,[3] (and unpublished data), 1,1,1-trichloroethane (A C Monster, St Louis, 1984), and styrene[4] (and unpublished data). The average predicted CV is 0·35 compared with a CV of 0·37 from the measured data. For the experimental studies, predicted CV is 0·30 and measured is 0·34. For the field studies they are respectively 0·49 and 0·46. The agreement between predicted and measured CV is satisfactory considering (1) that some CV are calculated on small numbers of subjects (as low as 4) therefore increasing the confidence range especially at high CV values and (2) that no attempt was made to match the model variable components to the characteristics of the groups measured or their environment. This agreement indicates that either the model is quite realistic or it allows one to simulate the major sources of physiological variability.

Comments

The physiological model developed here takes into account variability in exposure, physical workload, body build, liver function, and renal function. A limited number of factors were chosen in order to keep the model as simple as possible. Several other parameters may play a part in the solvent's behaviour in the human body, such as the variability in:

(*a*) solubility in blood and tissues which is known to be affected by the lipid content;[8]

(*b*) protein binding, mostly for the metabolites, which will affect not only their distribution volume but also their metabolism and renal clearance;

(*c*) physical workload efficiency, which is a function of body weight, physical fitness, and type of exercise; and

(*d*) physical activity after work.

These factors have been judged less significant, less generic, or more difficult to quantify than those simulated in the model. It seems that the factors used are sufficient to explain the variability observed and that taking into account the other variables will not change drastically the global variability. Nevertheless, they may be important for specific solvents or metabolites and they should therefore be studied further.

Other situations which are not considered here but have their importance in the variability observed under field conditions are the skin resorption and the acute effect of drugs or alcohol on metabolism. These aspects will need further study.

Physiological models have been useful in predicting the mean concentrations of solvents or metabolites in biological fluids under various exposure conditions. The model developed here has the added possibility of studying the variability expected for each biological level. Variability is one of the crucial points in biological monitoring development.

Models can never be completely validated, only some of their results can be confirmed. The results which are impossible to validate are usually the most interesting because not accessible experimentally. Therefore interesting results can only be speculative, but realistic, speculations. Such a model should be useful in improving our understanding of a complex system and to generate hypotheses. Such hypotheses could then be used and tested in experimental or epidemiological studies.

We are grateful to Dr P Harber, UCLA School of Medicine, for helpful discussions and advice. This work was supported by the Fonds National Suisse pour la Recherche Scientifique (project 5.804.084).

Appendix

LIST OF SYMBOLS

Symbol	Unit	Explanation
λ_x	—	Partition coefficient of x (b = blood, i = tissue i)
BH	cm	Body height
BW	kg	Body weight
$CL_{int,x}$	ml/min	Intrinsic metabolic clearance (s = solvent, mi = metabolite i)

Symbol	Unit	Explanation
$\dot{Q}_x$	l	Blood flow to x (b = lung, i = tissue i)
Q_x	l	Blood volume in x (b = lung, i = tissue i)
F_i	—	Proportion of i^{th} metabolite formed
CL	l/min	Metabolic clearance
CL_{mi}	ml/min	Renal clearance of metabolite i
W	Watts	Physical workload
$\Delta\dot{V}_{O2}$	l/min	Excess oxygen consumption
$T_{u,x}$	min	Urine voiding time (es = end of shift, nm = next morning)
C_{alv}	μmol/m³	Concentration of solvent in alveolar air
C_{ven}	μmol/l	Concentration of solvent in venous blood
C_{bmi}	μmol/l	Concentration of metabolite i in blood
C_{usol}	μmol/l	Concentration of solvent in urine
C_{umi}	mmol/mol	Concentration of metabolite i in urine
C_{insp}	μmol/m³	Concentration of solvent in inspired air
C_i	μmol/m³	Concentration of solvent in air in equilibrium with tissue i
ΔX	—	Change in variable X
$\dot{V}_{alv}$	l/min	Alveolar ventilation
V_x	l	Volume of x (i = tissue i)
F_{mi}	μmol/min	Formation rate of metabolite i
K_{2-1}	ml^{-1}	Rate constant for the transformation of M2 into M1
K_{i-u}	min^{-1}	Rate constant for urinary excretion of Mi
$V_{d,mi}$	l	Volume of distribution of metabolite i
R_{mi}	μmol/min	Urinary excretion rate of metabolite i
$\dot{V}^0_{alv}$	l/min	Alveolar ventilation at rest
$\dot{Q}^o_b$	l/min	Cardiac output at rest
B_u	mmol/mol	Normal excretion rate of metabolite w/o solvent exposure
α	—	Shape parameter in the gamma distribution
β	—	Dispersion parameter in the gamma distribution
γ	—	The origin in the gamma distribution
$\Gamma(\ )$	—	Gamma function

PHYSIOLOGICAL MODEL

The equations used have already been presented in preceding papers and are briefly summarised here.[7 10]

lung compartment:

$$\Delta C_{alv}/\Delta t = A\,\dot{V}_{alv}\,C_{insp} + A\,\lambda_b \sum_i C_i\dot{Q}_i + A\,C_{alv}[-\dot{V}_{alv} + \dot{Q}_b\,\lambda_b\,CL - \dot{Q}_b\,\lambda_b]$$

$$\text{with } A = 1/(V_{alv} + V_{lung}\,\lambda_b)$$

ith peripheral tissue:

$$\Delta C_i/\Delta t = \dot{Q}_i\,\lambda_b\,(C_{alv} - C_i)/(V_i\,\lambda + Q_i\,\lambda_b)$$

The solvent concentration in the liver tissue is not calculated, only the venous blood concentration is considered. The metabolic clearance CL is calculated assuming the well stirred model by Pang and Rowlands,[11] using

$$CL = \dot{Q}_{liver}\,CL_{int,s}/(\dot{Q}_{liver} + CL_{int,s})$$

where the intrinsic clearance is not a function of concentration at the low levels considered here. Tissue levels in the kidneys are calculated as for other peripheral compartments. Urinary excretion of the solvent is assumed to be a passive equilibration according to the blood-urine partition coefficient.[12] Therefore:

$$C_{usol} = \lambda_{water}/1000 \int C_{kidney}\,dt,$$

integrated over the corresponding urine voiding time.

METABOLITE FORMATION AND EXCRETION

The rate of formation of metabolite M2 is directly proportional to the solvent biotransformation rate:

$$F_{m2} = F_2\,CL\,\lambda_b\,C_{alv}/1000.$$

For the formation rate of M1, one has to take into account the formation from M2:

$$F_{m1} = F_1\,CL\,\lambda_b\,C_{alv}/1000 + F_{m2}\,K_{2-1}/K_{2-u}$$

The first order rate constants K_{2-1} (transformation of M2 into M1), K_{1-u} (urinary excretion of M1), and K_{2-u} (urinary excretion of M2) are calculated using the relations:

$$K_{i-u} = CL_{mi}/(V_{d,mi}*1000)$$

or

$$K_{2-1} = CL_{int,m2}/(V_{d,m2}*1000).$$

M1 and M2 concentrations in their respective distribution compartments are given by solving the following equations:

$$\Delta C_{bm2}/\Delta t = F_{m2}/V_{d,m2} - K_{2-u}C_{bm2} - K_{2-1}C_{bm2}$$

$$\Delta C_{bm1}/\Delta t = F_{m1}/V_{d,m1} - K_{1-u}C_{bm1}$$

M1 and M2 urinary excretion rates R_{m1} and R_{m2} are then calculated by:

$$R_{m1} = V_{d,m1}C_{bm1}K_{1-u}$$

$$R_{m2} = V_{d,m2}C_{bm2}K_{2-u}$$

Finally, M1 and M2 urinary excretions are expressed as a function of creatinine by making the urinary excretion rate of creatinine proportional to LBV, with a value of 1·8 g/24 h for a 70 kg, 170 cm man (LBV = 50·71 l). Creatinine excretion rate is considered independent of renal clearance, as changes in the latter will be followed by an inverse change in plasma creatinine.

BODY BUILD CALCULATIONS

Body weight and body height are used to divide body volume into lean body volume (LBV) and fat body volume (FBV). The following hypotheses are made: (1) densities of LBV and FBV are respectively 1·1 and 0·9,[46 47] (2) total body water (TBW) represents 72% of the lean body mass,[48] and TBW may be predicted from BH and BW using the following equation describing adult men[49]:

$$TBW\ [l] = -12{\cdot}86 + 0{\cdot}1757BH + 0{\cdot}331BW$$

A lower limit of 1·5 l for FBV has been decided to avoid low results for extreme combinations of BH and BW. LBV obtained is then shared between the different body tissues in the same proportions as in the standard man.[24 25] Blood and alveolar air volumes are also made proportional to LBV. FBV represents the volume of FG compartment. The volumes of distribution of the metabolites are considered proportional to LBV as they are relatively polar chemicals which do not distribute significantly in fat. Blood flows to the tissues are made proportional to the tissue volumes,[24 25] cardiac output is then the sum of the all blood flows. Alveolar ventilation at rest is calculated from cardiac output with a perfusion/ventilation ratio of 0·8. Body surface area (SA) may be calculated from BH and BW by the equation[8]:

$$SA\ [m^2] = 0{\cdot}0072\ BW^{0{\cdot}425} * BH^{0{\cdot}725}$$

PHYSICAL WORKLOAD

External physical workload W produced is expressed in Watts. The excess oxygen uptake due to W is considered independent of body size and is calculated from the following equation[50]:

$$\Delta\dot{V}_{O2}\ [l/min] = 0{\cdot}01\ W$$

Excess oxygen uptake is then used to calculate blood flows and alveolar ventilation as described in table 3. The following assumptions were made: (1) W has a constant effect on MG and FG blood flows independent of the tissue volume,[26] (2) W has an effect proportional to the basal flow rate or the tissue volume for liver and kidneys,[27] (3) the excess alveolar ventilation is directly proportional to W according to[50]:

$$\dot{V}_{alv} = \dot{V}^{\circ}_{alv} + 22\,\Delta\dot{V}_{O2}$$

and (4) brain and other tissues are unaffected by W.[26]

ESTIMATION OF INPUT STATISTICAL DISTRIBUTIONS

Body height

The observed data from HNANES II study[29] suggests modelling body height by a gamma distribution[47] that allows description of moderately skewed distributions. Body height is assumed to follow a gamma distribution with parameters α, β, and γ:

$$\Pr\{BH = x\} = [(x-\gamma)^{\alpha-1} \exp(-(x-\gamma)/\beta)]/[\beta^{\alpha}\Gamma(\alpha)],\ (\alpha > 0, \beta > 0, x > \gamma)$$

where α is the shape parameter, β the dispersion parameter, and γ the origine. γ may be estimated by the smallest observed BH (140 in the NHANES II study). Once the estimate of γ is determined, the three parameter estimation problem can be reduced to a two parameter problem by subtracting 140 from each observation and treating γ as 0. Among the several estimation methods of α and β, an approximation to the maximum likelihood estimate discussed in Johnson and Kotz is used[51]:

$$\hat{\alpha} = \bar{X}/[2*(\bar{X} - GM)] - 0{\cdot}083 \text{ and } \hat{\beta} = \bar{X}/\alpha$$

with $\bar{X}$ and GM respectively arithmetic and geometric means. From the NHANES II study, the arithmetic and geometric means, with 140 subtracted from each observation, are 37·05 and 36·25 respectively. Therefore, in the simulations BH is drawn from a gamma distribution with parameters 23, 1·6, 140.

Quetelet index

The same approximation method as for BH is used to estimate the parameters of a gamma distribution. Based on the arithmetic and geometric means (12·76 and 12·23), after subtracting the minimum value 12·58 from each observation, the three parameters α, β and γ in the gamma distribution are estimated as 11·85, 1·08, and 12·50 respectively.

Workload

A gamma distribution with $\gamma = 0$ is assumed for W. Based on the arithmetic and geometric means of 44·33 and 39·97 from a study of 160 workers (table 4, 5), α and β are estimated as 5·0 and 8·8 using the approximation method discussed for BH.

Exposure

Exposure concentration is assumed to have a lognormal distribution. The mean solvent of all workers is set to be at the TLV.[40] For each of the variability components (between workers, within worker between days, and within worker during shift), three levels of variability are used according to their geometric standard deviation GSD: low (GSD = 1·2), medium (GSD = 2·0), and high (GSD = 3·0). They may be transformed into

coefficient of variation (CV) as 0·18, 0·78, and 1·53 respectively with the following formula:

$$CV = (\exp(\ln GSD)^2 - 1)^{1/2}$$

Program description

A Fortran 77 program is written for the simulation. It includes two random number generators from the International Mathematical and Statistical Library (IMSL): GGAMR of gamma distribution for generating body height, Quetelet index, and person's workload and GGNML for normal random variates for within day during shift workload. Also a Fortran subroutine[52] is used to generate a Latin hypercube sample consisting of logarithm of exposure concentration, CL_{mi}, $T_{u,es}$, $T_{u,nm}$, logarithm of $CL_{int,s}$, logarithm of F_i, and $\dot{Q}_{liver}$. This simulation is carried out in a digital microVax II 630QB computer. For a simulation of 200 men for a five week period, it took about 3·5 hours to complete.

References

1 Monster AC. Difference in uptake, elimination, and metabolism in exposure to trichloroethylene, 1,1,1-trichloroethane and tetrachloroethylene. *Int Arch Occup Environ Health* 1979;**42**:311–7.

2 Guillemin M, Bauer D. Biological monitoring of exposure to styrene by analysis of combined urinary mandelic and phenylglyoxylic acids. *Am Ind Hyg Assoc J* 1978;**39**:873–8.

3 Monster AC, Regouin-Peeters W, Van Schijndel A, Van Der Tuin J. Biological monitoring of occupational exposure to tetrachloroethylene. *Scand J Work Environ Health* 1983;**9**:273–81.

4 Guillemin M, Bauer D, Martin B, Marazzi A. Human exposure to styrene IV. Industrial hygiene investigations and biological monitoring in the polyester industry. *Int Arch Occup Environ Health* 1982;**51**:139–68.

5 Droz PO, Berode M, Boillat MA, Lob M. Biological monitoring and health surveillance of rotagravure printing workers exposed to toluene. In: Dillon K, Ho MH, eds. *Biological monitoring of exposure to chemicals*. Vol I. *Organic compounds*. New York: J Wiley, 1987:111–31.

6 Guberan E, Fernandez J. Control of industrial exposure to tetrachloroethylene by measuring alveolar concentrations: theoretical approach using a mathematical model. *Br J Ind Med* 1974;**31**:159–67.

7 Fernandez JG, Droz PO, Humbert BE, Caperos JR. Trichloroethylene exposure. Simulation of uptake, excretion and metabolism using a mathematical model. *Br J Ind Med* 1977;**34**:43–55.

8 Fiserova-Bergerova V, Vlach J, Cassady JC. Predictable "individual differences" in uptake and excretion of gases and lipid soluble vapours simulation study. *Br J Ind Med* 1980;**37**:42–9.

9 Droz PO. The use of simulation models for setting BEIs for organic solvents. *Annals of the American Conference of Governmental Industrial Hygienists* 1986;**12**:339–50.

10 Droz PO, Guillemin MP. Human styrene exposure: V. Development of a model for biological monitoring. *Int Arch Occup Environ Health* 1983;**53**:19–36.

11 Pang KS, Rowland M. Hepatic clearance of drugs. I. Theoretical considerations of a "well-stirred" model and a "parallel tube" model. *J Pharmacokinet Biopharm* 1977;**5**:625–53.

12 Imbriani M, Ghittori S, Pezzagno G, Capodaglio E. Toluene and styrene in urine as biological exposure indexes. *Annals of the American Conference of Governmental Industrial Hygienists* 1986;**12**:351–5.

13 Consolazio CF, Johnson RE, Pecosa LJ. *Physiological measurements of metabolic functions in man*. New York: McGraw-Hill, 1969:453–80.

14 Andersen ME, Clewell HJ, Gargas ML, Smith FA, Reitz RH. Physiologically based pharmacokinetics and risk assessment process for methylene chloride. *Toxicol Appl Pharmacol* 1987;**87**:185–205.

15 Ramsey, JC, Andersen ME. A physiologically based description of inhalation pharmacokinetics of styrene in rats and humans. *Toxicol Appl Pharmacol* 1984; **73**:159–75.

16 Droz PO, Fernandez JG. Effect of physical workload on retention and metabolism of inhaled organic solvents. A comparative theoretical approach and its applications with regard to exposure monitoring. *Int Arch Occup Environ Health* 1977;**38**:231–46.

17 Droz PO, Fernandez JG. Solubility of organic solvents. I Gas chromatographic determination of olive oil gas partition coefficient. *Helvetica Chimica Acta* 1977;**60**:454–8.

18 Droz PO. *Contribution à la recherche d'indices biologiques d'exposition aux solvants. Détermination de leurs coefficients de partage et étude de leur compartement dans l'organisme à l'aide de modèle de simulation*. Neuchâtel:Neuchâtel University, 1977. (Thesis.)

19 Fernandez JG, Humbert BE, Droz PO, Caperos JR. Exposition au trichloroéthylène. Bilan de l'absorption, de l'excrétion et du métabolisme chez des sujets humains. *Archives des Maladies Professionelles de Médecin du Travail* 1975;**36**:396–407.

20 Humbert BE, Fernandez JG. Exposure to 1,1,1,-trichloroethane: study of its absorption, excretion and metabolism in humans. *Archives des Maldies Professionnelles de Médecine du Travail et de Sécurite Sociale* 1977;**38**:415–25.

21 Woiwode W, Drysch K. Experimental exposure to toluene: further consideration of cresol formation in man. *Br J Ind Med* 1981;**38**:194–7.

22 Piotrowski JK. *Exposure tests for organic compounds in industrial toxicology*. Cincinnati: National Institute for Occupational Safety and Health, 1977:66–8. (DHEW (NIOSH) publ No 77–144.)

23 Berode M, Droz PO, Boillat MA, Guillemin M. Effect of alcohol on the kinetics of styrene and its metabolites in volunteers and in workers. *App Ind Hyg* 1986;**1**:25–8.

24 Davis NR, Mapleson WW. Structure and quantification of a physiological model of the distribution of injected agents and inhaled anaesthetics. *Br J Anaesth*

1981;53:399–405.
25 Cowles AL, Borgstedt HH, Gillies AJ. Tissue weights and rates of blood flow in man for prediction of anaesthetic uptake and distribution. *Anesthesiology* 1971;35: 523–6.
26 Astrand I. Effect of physical exercise on uptake, distribution and elimination. In: Fiserova-Bergerova V, ed. *Modeling of inhalation exposure to vapors: up-take, distribution and elimination.* Vol II. Boca Raton: CRC Press, 1983:107–30.
27 Rowell B. Human cardiovascular adjustments to exercise and thermal stress. *Physiol Rev* 1974;54:75–159.
28 Womersley J, Durnin JVGA. A comparison of skinfold method with extent of "overweight" and various weight-height relationships in the assessment of obesity. *Br J Nutr* 1977;38:271–84.
29 National Centre for Health Statistics. *National Health and Nutrition Examination Survey 1976–1980.* Hyattsville Maryland: NCHS, 1981.
30 Alvan G. Individual differences in the disposition of drugs metabolised in the body. *Clin Pharmacokinet* 1978;3:155–75.
31 Bradley SE, Ingelfinger FJ, Bradley GP. Hepatic circulation in cirrhosis of the liver. *Circulation* 1952;5:419–29.
32 Penno MB, Dvorchik BH, Vessell ES. Genetic variation in rates of antipyrine metabolite formation: a study in uninduced twins. *Proc Natl Acad Sci USA* 1981;78:5193–6.
33 Bauer JH, Brooks CS, Burch RN. Clinical appraisal of creatinine clearance as a measurement of glomerular filtration rate. *Am J Kidney Dis* 1982;2:337–46.
34 Womersley J, Durnin JVGA, Boddy K, Mahaffy M. Influence of muscular development, obesity, and age on the fat-free mass of adults. *J Appl Physiol* 1976;41:223–9.
35 Fiserova-Bergerova V, Hughes HC. Species differences on bioavailability of inhaled vapors and gases. In: Fiserova-Bergerova V, ed. *Modeling of inhalation exposure to vapors: uptake, distribution and elimination.* Vol II. Boca Raton: CRC Press, 1983:97–106.
36 Yamaguchi I, Komatsu E, Miyazawa K. Intersubject variability in cardiac output—O_2 relation of men during exercise. *J Appl Physiol* 1986;61:2168–74.
37 Breimer DD, Danhof M. Interindividual differences in pharmacokinetics and drug metabolism. In: Breimer DD, ed. *Towards better safety of drugs and pharmaceutical products.* Amsterdam: Elsevier/North-Holland Biomedical Press, 1980:117–42.
38 George CF. Drug kinetics and hepatic blood flow. *Clin Pharmacokinet* 1979;4:433–48.
39 Mathie RT. Hepatic blood flow measurement with inert gas clearance. *J Surg Res* 1986;41:92–110.
40 American Conference Governmental Industrial Hygiene. *Threshold limit values and biological exposure indices for 1987–88.* Cincinnati: ACGIH, 1987.
41 Monster AC. Trichloroethylene, tetrachloroethylene, 1,1,1,-trichloroethane. In: Aitio A, Riihimaki V, Vaino H, eds. *Biological monitoring and surveillance of workers exposed to chemicals.* New York: Hemisphere Publishing Corporation, 1984:111–50.
42 Drummond L, Luck R, Afacan AS, Wilson HK. Biological monitoring of workers exposed to benzene in the coke oven industry. *Br J Ind Med* 1988;45: 256–61.
43 Bartolucci GB, De Rosa E, Gori GP, Corona PC, Perbellini L, Brugnone F. Biomonitoring of occupational exposure to low styrene levels. *Annals of the American Conference of Governmental Industrial Hygienists* 1985;12:275–82.
44 Imbrian M, Ghittari S, Pezzagno G, Huang J, Capodaglio E. 1,1,1,-trichloroethane (methyl chloroform) in urine as biological index of exposure. *Am J Ind Med* 1988;13:211–22.
45 Droz PO, Wu MM, Cumberland WG. Variability in biological monitoring of solvent exposure. II Application of a population physiological model. *Br J Ind Med* (in press).
46 Behnke AR, Osserman EF, Welham WW. Lean body mass: its clinical significance and estimation from excess fat and total body water determinations. *Arch Intern Med* 1953;91:585–601.
47 Fidanza F, Keys A, Anderson JT. Density of body fat in man and other animals. *J Appl Physiol* 1953;6:252–6.
48 Widdowson EM. Chemical analyses of the body. In: Brozek J, ed. *Human body composition. Symposium of the Society of the Study of Human Biology.* London: Pergamon, 1965.
49 Watson PE, Watson ID, Batt RD, Phil D. Total body water volumes for adult males and females estimated from simple anthropometric measurements. *Am J Clin Nutr* 1980;33:27–39.
50 Cotes JE. *Lung function assessment and application in medicine.* 3rd ed. London: Blackwell, 1975:296–325.
51 Johnson NL, Kotz S. *Continuous univariate distributions I. Distributions in statistics.* New York: J Wiley, 1970:184–90.
52 Iman RL, Shortencarier MJ. *A Fortran 77 program and user's guide for generation of Latin hypercube and random samples for use with computer models.* Springfield: National Technical Information Service, 1984. (US Nuclear Regulatory Commission, NUREG/CR-3624.)