Int Arch Occup Environ Health (1982) 49:293–303

International Archives of Occupational and Environmental Health

1,1,1-Trichloroethane Exposure, Biologic Monitoring by Breath and Urine Analyses

J. R. Caperos[1], P. O. Droz[2], C. L. Hake[3], B. E. Humbert[4], and A. Jacot-Guillarmod[1]

[1] Chemistry Institute of the University of Neuchâtel, Bellevaux 51, CH-2000 Neuchâtel, Switzerland
[2] Institute of Occupational Health and Industrial Hygiene, University of Lausanne, rue de la Clochatte, CH-1052 Le Mont-sur-Lausanne, Switzerland
[3] Department of Pharmacology, The Medical College of Wisconsin, Inc. 8701 Watertown Plank Road, Milwaukee, WI 53226, USA
[4] Interfood S. A., av. de Cour 107, CH-1001 Lausanne, Switzerland

Summary. Absorption and excretion of 1,1,1-trichloroethane, as well as the kinetics of formation and elimination of trichloroethanol (TCE) and trichloroacetic acid (TCA) were simulated by a mathematical model. The results of this model were compared with experimental ones on pulmonary elimination of the solvent and urinary excretion of the metabolites. The influences of duration and repetition of exposure on the pulmonary and urinary eliminations were studied. A tentative method of biologic monitoring is proposed. Theoretically, the most suitable method to estimate the exposure is by two determinations, before and after a work shift. Following this procedure, analysis of TCE in the urine is more sensitive than determination of 1,1,1-trichloroethane in the breath. As an indicator of exposure risk, TCA is not considered sensitive enough if variations in the inspired concentration occur.

Key words: 1,1,1-Trichloroethane – Kinetic model – Exposure monitoring – Biologic monitoring

Since its commercial introduction, 1,1,1-trichloroethane [methylchloroform (MC)] has in many cases replaced other halogenated solvents like trichloroethylene and tetrachloroethylene due to its believed lower toxicity. As a result, an increasing number of workers are exposed to its vapors.

With a view of setting up biologic monitoring methods, several researchers have studied the kinetic behavior of MC and its main metabolites, TCE and TCA, after experimental exposure [1, 8, 9, 10, 11, 14, 15].

Another approach to biologic monitoring makes use of kinetic models for extrapolating experimental results to industrial situations.

Offprint requests to: Dr. José R. Caperos (address see above)

0340-0131/82/0049/0293/$ 2.20

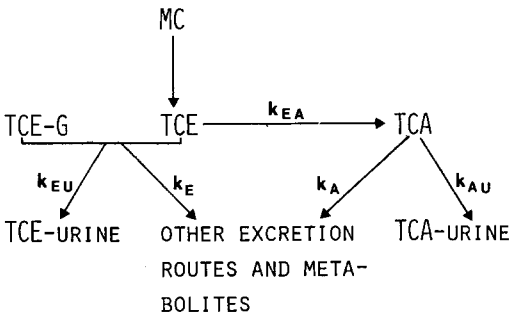


Fig. 1. Schematic pathways of the metabolism of 1,1,1-trichloroethane and elimination of its metabolites

Table 1. Rate constants of the formation and elimination of TCE and TCA

Rate constant	Numerical value
k_{EU}	0.02600 h^{-1}
k_{AU}	0.00685 h^{-1}
k_E	0.00820 h^{-1}
k_A	0.00685 h^{-1}
k_{EA}	0.01919 h^{-1}

Table 2. Tissue volumes, blood perfusions, blood volumes, and partition coefficients

	VRG	MG	FG	Pulmonary compartment
Tissue volume (l)	8.8	36.3	11.5	1.0
Blood volume (l)	3.19	0.63	0.18	1.4
Blood perfusion (%)	79.9	15.7	15.7	—
Partition coefficient	9.1	6.1	373	4.35

VRG: vessel-rich group; MG: muscle group; FG: fat group

In 1977, Fernandez et al. [7] developed a mathematical model to simulate the processes of absorption, distribution, metabolism, and excretion of solvents. This model is now used to study aspects of biologic monitoring of MC exposure [1, 8, 9, 10, 11, 12, 13, 14, 15].

Methods

The theoretical basis of the mathematical model has already been described in detail [7]. In order better to quantitate the amount of solvent metabolized, the model was modified according to Droz and Fernandez [3] to include the apparent metabolic clearance. The liver was not considered as a separate compartment, but a fixed amount of blood flow was considered to be totally cleared of solvent (0.025 l/min). This was calculated from results obtained during experimental exposures to trichloroethane [8] using the total amounts absorbed and metabolized.

Figure 1 shows the pathways of the metabolism of MC [10], which include hydroxylation to TCE and partial oxidation of TCE to TCA, similar to trichloroethylene. The first-order rate constants k_{EA}, k_A, k_{AU}, k_E, k_{EU} for the process in Fig. 1 are considered to be the same for the metabolism of trichloroethylene (TRI), and Table 1 gives their numerical values. This hypothesis is assumed to be realistic because most of the constants were estimated after absorption of TCE and TCA.

Table 3. Simulation of daily variations in the inspired concentration (parts/10^6)

Day	Model									
	1	2	3	4	5	6	7	8	9	10
Preceding exposure[1]	350	0	0	350	350	350	350	350	350	350
Monday	350	350	700	700	350	350	350	350	350	350
Tuesday	350	350	350	350	700	350	350	350	350	350
Wednesday	350	350	350	350	350	700	350	350	700	1,050
Thursday	350	350	350	350	350	350	700	350	350	350
Friday	350	350	350	350	350	350	350	700	700	1,050

1 Exposure concentration of the preceding week

Table 4. Simulation of hourly variations in the inspired concentration (parts/10^6)

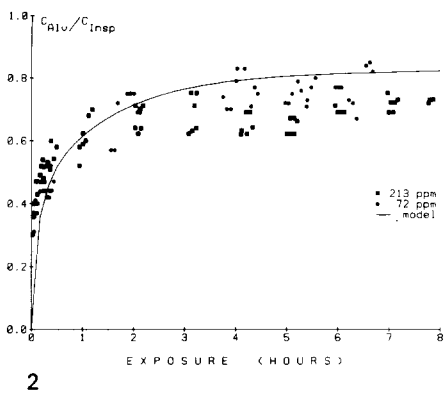
Model	Hours of exposure								
	1	2	3	4	5	6	7	8	9
11	150	150	150	150	0	550	550	550	550
12	550	550	550	550	0	150	150	150	150
13	600	100	600	100	0	600	100	600	100
14	150	550	150	550	0	150	550	150	550

Table 2 shows the tissue volumes, blood perfusions, blood volumes, and partition coefficients [2, 4, 6] entered into the computations. Previous values for the liver compartment [7] were added to the vessel-rich group (VRG) compartment as liver was not considered a separate compartment. The volume of alveolar air was determined by the functional residual capacity (2.43 l) plus half the tidal volume (0.25 l) [2]. The lung-tissue-gas partition coefficient was assumed to be the same as the blood-gas partition coefficient.

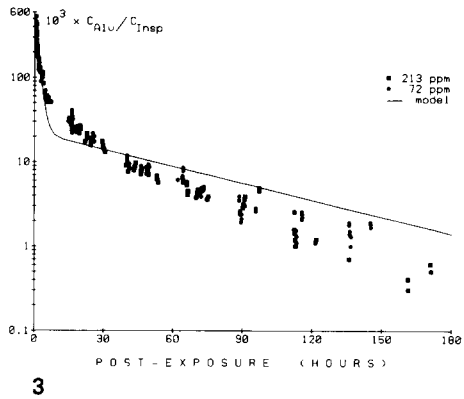
In the first part of the study we compared the simulated values with experimental data [8, 15]. To do so, we entered a cardiac output of 6.79 l/min, calculated with a cardiac index of 3.50 l/min/m^2 [2], and an estimated surface area [16] of our experimental subjects [8, 15] of 1.24 m^2. The alveolar ventilation corresponds to a value at rest of 5.45 l/min.

We simulated a constant exposure of 8 h/day, 5 days/week, until the concentrations of MC, TCE, and TCA in the body were the same at the beginning of each week. Two weeks at 350 parts/10^6, the present threshold limit value (TLV), were required to arrive at a steady state. Additional simulations as listed in Tables 3 and 4 were also carried out. The conditions for these models were the same as previously described in detail [5, 7]. A slight physical activity by entering a cardiac output of 8.75 l/min and an alveolar ventilation of 7.01 l/min was taken into account. The excess of cardiac output, in comparison with the state at rest, is distributed to the muscle group (MG), only (muscle and skin, see Table 2).

To calculate the urinary concentrations of the two metabolites TCE and TCA, it was assumed that 1 ml/min of urine was formed. Furthermore, it was assumed that the bladder was emptied at 7 a.m., 12 noon, 5 p.m., and 10 p.m., and that exposure generally took place between 8 a.m.–12 noon and 1 p.m.–5 p.m.



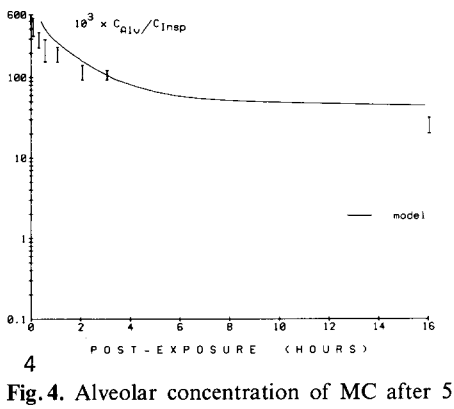
2



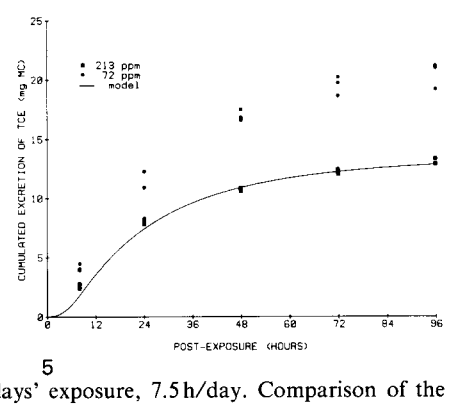
3

Fig. 2. Alveolar concentration of MC during 8-h exposure to 213 parts/10^6 or 72 parts/10^6, expressed as a fraction of the inspired concentration. Comparison of the theoretical curve ——— and experimental data

Fig. 3. Alveolar concentration of MC after 8-h exposure to 213 parts/10^6 or 72 parts/10^6, expressed as a function of inspired concentration



4



5

Fig. 4. Alveolar concentration of MC after 5 days' exposure, 7.5 h/day. Comparison of the theoretical curve ——— and experimental data

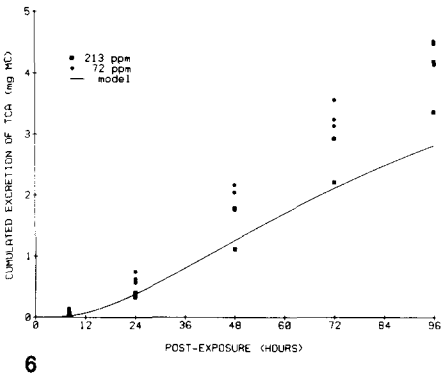
Fig. 5. Total amount of TCE excreted in urine after 8-h exposure to 213 parts/10^6 and 72 parts/10^6 MC. Experimental data are proportionally adjusted to 350 parts/10^6

Results and Discussion

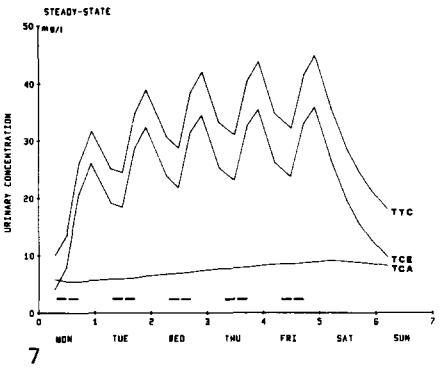
Comparison with Experimental Data

Figure 2 shows the comparison between the simulation and the experimental results [8] for alveolar breath concentrations during exposures to MC. Each exposure lasted 8 h at either 213 or 72 parts/10^6, and the results are expressed as a fraction of the inspired concentration C_{Alv}/C_{Insp}. As can be seen, there is satisfactory agreement between the simulated and experimental values, although some deviation exists towards the end of exposure.

Figures 3 and 4 show the concentration curves in the breath, expressed as C_{Alv}/C_{Insp} by use of the model and the corresponding experimental results at 213



6



7

Fig. 6. Total amount of TCA excreted in urine after exposure to 213 parts/10^6 and 72 parts/10^6 MC. Experimental data are proportionally adjusted to 350 parts/10^6

Fig. 7. Urinary concentrations of *TCE, TCA,* and *TTC* (total trichloro compounds) during a week of steady exposure at 350 parts/10^6 MC

Table 5. Alveolar air concentration (parts/10^6) of MC during a week of steady exposure at 350 parts/10^6 (model 1)

Day	Postexposure time				
	0 min 5 p.m.	30 min 5:30 p.m.	1 h 6 p.m.	2 h 7 p.m.	15 h 8 a.m. next day
Monday	300	127	76.6	32.5	10.0
Tuesday	302	130	79.1	35.0	12.1
Wednesday	304	131	80.9	36.7	13.5
Thursday	305	133	82.1	37.9	14.4
Friday	306	134	82.9	38.7	15.1

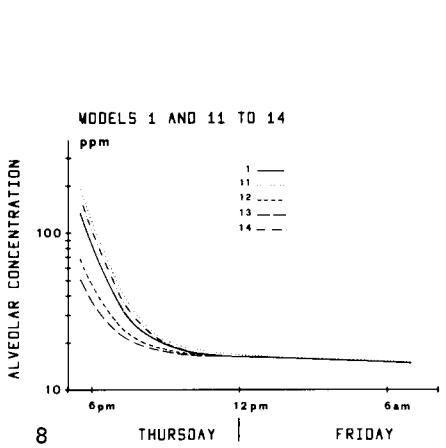
and 72 parts/10^6 over 8 h [8] and at 350 parts/10^6 over 5 days, $7\frac{1}{2}$ h each day [15]. The simulations with the model are of the same order of magnitude as the experimentally obtained results.

Figures 5 and 6 show the cumulative quantities of TCE and TCA eliminated during and after exposures to 72 and 213 parts/10^6 for 8 h. The experimental results have been proportionally adjusted to 350 parts/10^6 to permit a direct comparison. The urinary excretion of these metabolites is low [8], and there is little difference between the model and the experimental data.

Consequently, the results of the simulation model show satisfactory agreement with those obtained experimentally, which means that the model may be employed practically to simulate industrial situations.

Simulation of Repeated Exposures

Table 5 shows the concentrations of MC in alveolar air for each day of the week after 8-h exposures to 350 parts/10^6 every day. Figure 7 gives the corresponding



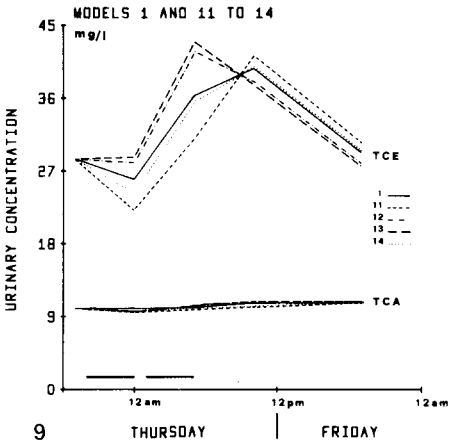


Fig. 8. Influence of hourly variations in exposure on Thursday during a week of steady exposure on the pulmonary elimination of MC

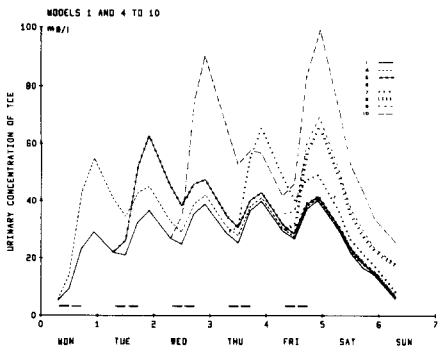
Fig. 9. Influence of hourly variations in exposure on Thursday, during a week of steady exposure on the urinary concentrations of *TCE* and *TCA*

Table 6. Influence of daily fluctuations in the inspired concentration. Percentage deviations of the alveolar MC concentrations from the values obtained with model 1 (Table 5)

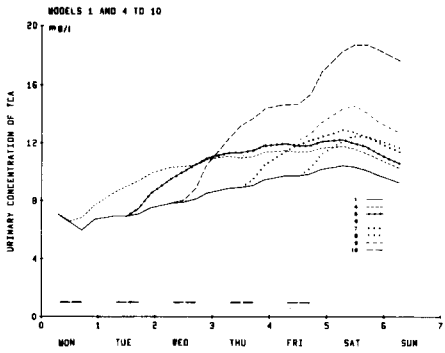
Day	Time	Model						
		4	5	6	7	8	9	10
Monday	8 a.m.	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	6 p.m.	92.2	0.0	0.0	0.0	0.0	0.0	0.0
Tuesday	8 a.m.	52.1	0.0	0.0	0.0	0.0	0.0	0.0
	6 p.m.	5.63	86.7	0.0	0.0	0.0	0.0	0.0
Wednesday	8 a.m.	29.6	43.2	0.0	0.0	0.0	0.0	0.0
	6 p.m.	3.77	5.51	87.3	0.0	0.0	87.3	174
Thursday	8 a.m.	18.1	26.5	38.7	0.0	0.0	38.7	77.5
	6 p.m.	2.54	3.71	5.42	86.0	0.0	5.42	10.8
Friday	8 a.m.	11.6	16.9	24.7	36.1	0.0	24.7	49.4
	6 p.m.	1.72	2.51	3.67	5.37	85.1	88.8	178
Saturday	8 a.m.	7.58	11.1	16.2	23.6	34.6	50.8	101

urinary concentrations of TCA, TCE, and total trichloro compounds (TTC) obtained by using model 1. It can be seen that the alveolar MC concentrations 15 h after the end of each exposure increase from Monday to Friday, this rise is much more pronounced than if it were judged only from the value 1 h after exposure.

Concentrations of TCA in the urine increase only slightly during the course of the week. The urinary excretion of TCE increases considerably at the beginning of the week, and reaches a plateau during the second half. Also, TCE concentration



10



11

Fig. 10. Influence of daily variations in the exposure concentration during one week on the urinary concentrations of *TCE*

Fig. 11. Influence of daily variations in the exposure concentration during one week on the urinary concentrations of *TCA*

varies considerably throughout the day: it is lower at 12 noon that at 7 a.m. (except on Monday), and increases from 12 noon till 10 p.m.

Hourly Variations in Exposure Concentration

Under industrial conditions exposure concentrations may fluctuate, hence it is important to simulate these situations.

Figures 8 and 9 give the results of computations with the models 1 and 11–14; they show the influence of hourly variations in the ambient air on the pulmonary elimination of MC and the urinary excretion of the metabolites TCE and TCA. It can be seen (Fig. 8) that variations in exposure concentration have a major influence on MC breath concentrations during the first few hours of postexposure. From hour 6 onward, the differences between the models are negligible and the alveolar air concentrations coincide with those obtained after exposure to a non-fluctuating (model 1) exposure concentration.

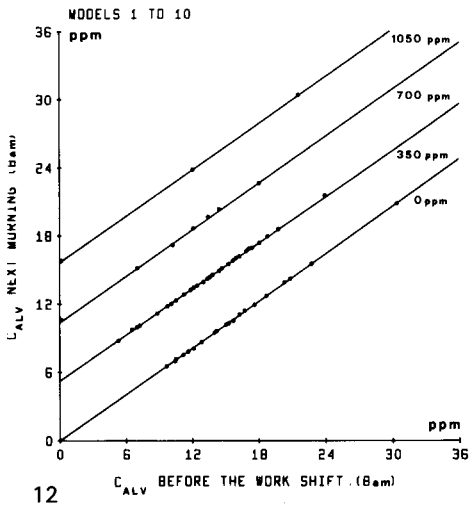
From Fig. 9 it is evident that fluctuations in the exposure concentration markedly influence the urinary TCE concentrations, but there is no effect on the levels of TCA in urine.

Daily Variations in Exposure Concentration

Models 4–10 simulate daily variations in exposure concentration. Table 6 shows the alveolar air concentrations calculated for each day at 8 a.m. and 6 p.m. as the percentage increase over those found during the steady-state week (model 11). Figures 10 and 11 give the influence on the urinary excretion of TCE and TCA, respectively.

The following can be deduced:

a) The alveolar air concentration at 6 p.m. is doubled when the exposure concentration is doubled, but does not remain so 15 h after exposure (8 a.m. the following morning);



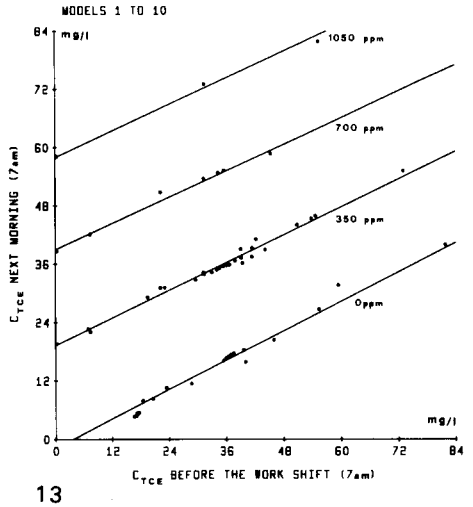


Fig. 12. Relation between exposure and alveolar air concentrations *(C_{Alv})* of MC before (8 a.m.) and after (8 a.m. the following morning) exposure

Fig. 13. Relation between exposure and urinary concentrations of TCE *(C_{TCE})*, the morning before and after the exposure

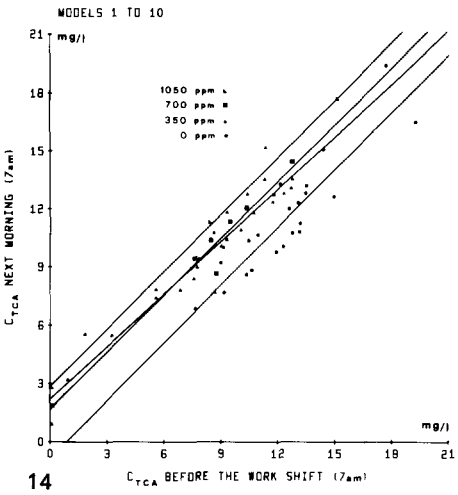
b) Elevated exposures influence the alveolar concentrations of MC at 8 a.m. for several consecutive days;
c) The influence of fluctuations in the exposure concentration on MC in the breath and TCE and TCA in urine depends also on the day of the week;
d) An increase in exposure concentration evokes a similar increase in urinary TCE concentration, this increase continues for several days;
e) The influence of varying exposure profiles on urinary TCA excretion is relatively low.

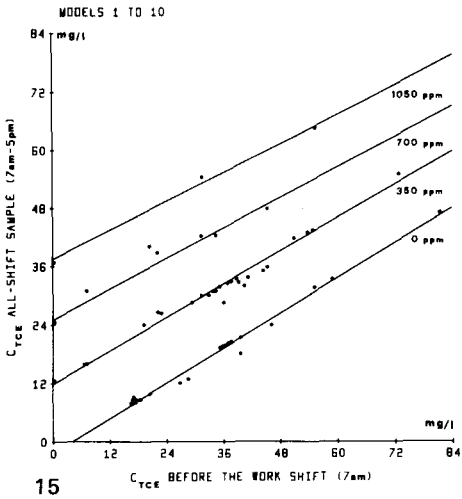
A Possible Method of Biologic Monitoring

In our model studies on uptake, distribution, and elimination of different solvents we have assumed that the elimination rates or concentrations of excreted products are proportional to the body weight of the solvent. We have, therefore, also calculated the interrelationship between absorption of MC and concentrations of unchanged MC in alveolar air of the metabolites, TCE and TCA, in urine at two theoretical sampling points, i.e., before and after the work shift. We have previously published similar calculations for TRI [5].

In Fig. 12 the values of alveolar air concentrations "before the work shift" and "next morning" as calculated from models 1–10 are presented. Each line corresponds to a distinct exposure concentration (0, 350, 700, and 1,050 parts/10^6). The abscissa gives the alveolar air concentration (C_{Alv}) measured just "before the work shift" (8 a.m.), and on the ordinate the values 15 h after the exposure (8 a.m. the "next morning") are shown.

Figures 13 and 14 give similar calculation data for the urinary metabolites TCE and TCA respectively. The concentration of TCE and TCA in the urine before the





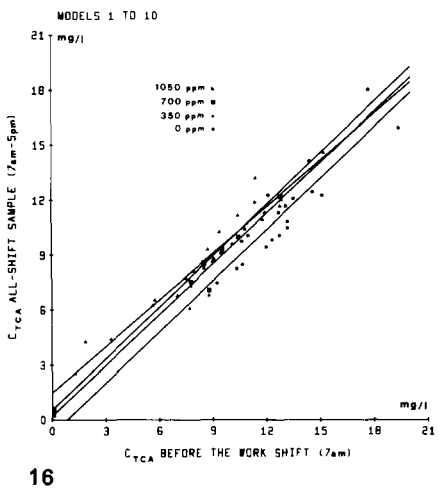


Fig. 14. Relation between exposure and concentrations of TCA *(C_{TCA})* in the urine, the morning before and after the exposure

Fig. 15. Relation between exposure and concentrations of TCE *(C_{TCE})* in the urine when samples are taken the morning before exposure or collected throughout the whole work shift

Fig. 16. Relation between exposure and concentrations of TCA *(C_{TCA})* in the urine when samples are taken the morning before exposure or collected throughout the whole work shift

work shift (7 a.m.) is given as a function of that in the urine collected throughout the whole work shift in Figs. 12–16.

Table 7 gives the constants a and b of the linear equations obtained by the regression analyses demonstrated in Figs. 12–16. The different concentration lines are hardly distinguishable for TCA: this biologic indicator is not sensitive enough to provide an estimate for the average exposure during that day. The concentration of TCE in urine is the most sensitive indicator, followed by the alveolar concentration. The sensitivity of these biologic indexes also varies with the concentration before exposure; in fact, a maximal sensitivity is obtained when the initial concentration is zero. Thus, biologic monitoring of exposure to MC by urine analysis of TCE before and after exposure seems to be the most suitable for giving an estimate of the average exposure over the entire day.

Table 7. Constants a and b of the linear regression equations and coefficients of correlation for the lines drawn in Figs. 12–16

Figure	Exposure concentration (parts/10^6)	a	b	Correlation coefficient
12 (MC)	0	0.684	0.0	1.000
	350	0.682	5.23	1.000
	700	0.684	10.4	1.000
	1,050	0.684	15.6	1.000
13 (TCE)	0	0.505	−1.74	0.995
	350	0.479	19.2	0.992
	700	0.449	39.3	0.994
	1,050	0.431	58.5	0.997
14 (TCA)	0	0.986	−0.858	0.891
	350	0.899	2.2	0.947
	700	0.975	1.71	0.984
	1,050	0.983	2.86	0.999
15 (TCE)	0	0.598	−2.48	0.993
	350	0.564	11.9	0.987
	700	0.522	25.1	0.993
	1,050	0.502	37.3	0.997
16 (TCA)	0	0.929	−0.704	0.915
	350	0.859	1.2	0.987
	700	0.921	0.235	0.988
	1,050	0.927	0.600	0.999

Conclusions

On the basis of the results of the foregoing simulations it is difficult to establish a valid correlation between average exposure or one day and urinary excretion of the metabolites (or pulmonary elimination of MC) on the basis of only one sample obtained either during or after the work shift. In theory, a much better estimate of exposure can be achieved on the basis of pair determinations, one before and one after a work shift. Using this method, the analysis of urinary TCE provides an even more accurate estimate than that of MC in the breath. The choice of the times for sampling the alveolar air or urine is very important. For a single alveolar air sample, a suitable time is at least 6 h after the end of the exposure (Fig. 8). Most representative urinary TCE samples are those taken in the mornings before (7 a.m.) and after the exposure (Fig. 13). The mathematical model used in this study is based on the assumption that MC is absorbed only through the lungs; however, some skin absorption is also possible. The amount of solvent penetrating the skin is difficult to estimate and depends on the area and type of skin exposed, the particular application to the skin's surface, and the total duration of skin contact.

The final decision which method may be used for biologically monitoring MC exposures, in addition to the above considerations, depends also on the expertise in the laboratory and the willingness of the workers to provide the samples.

Acknowledgements. We are grateful to the Fonds National Suisse pour la Recherche Scientifique for financial support. We thank Professeur J. Banderet and Mr. J. F. Jauslin of the Institute of Mathematics for their help with the calculations.

References

1. Åstrand I, Kilbom A, Wahlberg I, Ovrum P (1973) Methylchloroform exposure. I. Concentration in alveolar air and blood at rest and during exercise. Work Environ Health 10:69–81
2. Cowles AL, Borgsted HH, Gillies AJ (1971) Tissue weights and rates of blood flow in man for the prediction of anestheric uptake and distribution. Anesthesiology 35:523–526
3. Droz PO, Fernandez JG (1977a) Effect of physical workload on retention and metabolism of inhaled organic solvents. A comparative theoretical approach and its applications with regards to exposure monitoring. Int Arch Occup Environ Health 38:231–246
4. Droz PO, Fernandez JG (1977b) Solubility of organic solvents. I. Gas chromatographic determination of olive oil-gas partition on coefficients. Helv Chim Acta 60:454–458
5. Droz PO, Fernandez JG (1978a) Trichloroethylene exposure: Biological monitoring by breath and urine analysis. Br J Ind Med 35:35–42
6. Droz PO (1978b) Contribution à la recherche d'indices biologiques d'exposition aux solvants. Détermination de leurs coefficients de partage et étude de leur comportement dans l'organisme à l'aide de modèles de simulation. Doctoral thesis, University of Neuchâtel, Switzerland
7. Fernandez JG, Droz PO, Humbert BE, Caperos JR (1977) Trichloroethylene exposure. Simulation of uptake, excretion, and metabolism using a mathematical model. Br J Ind Med 34:43–55
8. Humbert BE, Fernandez JG (1977) Exposition au 1,1,1-trichloroéthane; contribution à l'étude de l'absorption, de l'excrémentation et du métabolisme sur des sujets humains. Arch Mal Prof 38:415–425
9. Monster AC, Boersma G, Steenweg H (1979a) Kinetics of 1,1,1-trichloroethane in volunteers; influence of exposure concentration and work load. Int Arch Occup Environ Health 42: 293–301
10. Monster AC (1979b) Difference in uptake, elimination, and metabolism in exposure to trichloroethylene, 1,1,1-trichloroethane and tetrachloroethylene. Int Arch Occup Environ Health 42:311–317
11. Monster AC, Houtkooper JM (1979c) Estimation of individual uptake of trichloroethylene, 1,1,1-trichloroethane and tetrachloroethylene from biological parameters. Int Arch Occup Environ Health 42:319–323
12. Sato A, Nakajima T (1979) A structure-activity relationship of some chlorinated hydrocarbons. Arch Environ Health 34:69–75
13. Stewart RD, Gay HH, Erley DS, Hake CL, Schaffer AW (1961) Human exposure to 1,1,1-trichloroethane vapor: relationship of expired air and blood concentration to exposure and toxicity. Am Ind Hyg Assoc J 22:252–262
14. Stewart RD, Gay HH, Schaffer AW, Erley DS, Rowe VK (1969) Experimental human exposure to methylchloroform vapor. Arch Environ Health 19:467–472
15. Stewart RD, Hake CL, Wu A, Graff SA, Forster HV, Lebrun AJ, Newton PE, Soto RJ (1975) Report no.: NIOSH-MCOW-ENVM-1,1,1-t-75-4, June
16. Tables scientifiques (1963) 6th edn. Documenta. Geigy, Basel, pp 642–643

Received March 30, 1981 / Accepted November 17, 1981