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British Journal of Industrial Medicine, 1977, 34, 56-63

A pharmacokinetic model to study the excretion of trichloroethylene and its metabolites after an inhalation exposure

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ABSTRACT For a better understanding of absorption, distribution, excretion, and metabolism of trichloroethylene the time-course of blood concentration of the vapour and urinary excretion of its metabolites was examined using a pharmacokinetic model. After a single experimental exposure in which four men inhaled 100 parts per million (ppm) of trichloroethylene for four hours an elimination curve showed three exponential components, that is, $x = 1.005e^{-16.71t} + 0.449e^{-1.710t} + 0.255e^{-0.2027t}$, where x is the blood concentration in mg/l and t the time in hours from 0 to 10. The overall rate constant for the disappearance of trichloroethylene was found to agree with the theoretical one, estimated by means of a mathematical model for the blood concentration data. A $D_{\infty} - X_t$ plot, developed from a mathematical model for urinary excretion, could also give a good estimate of rate constants for the transfer of trichloroethylene in the body. The rate constant thus estimated from urinary excretion was consistent with data on the blood concentration.

As industrial exposure to trichloroethylene vapour is liable to vary, air analysis does not necessarily give a real indication of the true exposure. A quantitative index of a worker's exposure can be estimated according to the amount of trichloroethylene being absorbed in his body (Roach, 1966; Elkins, 1967). Monitoring trichloroethylene levels in blood or expired air and measuring urinary metabolites of trichloroethylene are currently the most common techniques for determining the body burden of the vapour (Ahlmark and Forssman, 1951; Stewart *et al.*, 1962, 1970, 1974; Morgan *et al.*, 1970; Nomiya, 1971; Ogata *et al.*, 1971; Ertle *et al.*, 1972; Ikeda *et al.*, 1972; Müller *et al.*, 1972, 1974; Pfämi and Backman, 1972; Kimmerle and Eben, 1973; Lowry *et al.*, 1974). Estimation and prediction of the body burden of trichloroethylene, however, require precise information on the absorption, distribution, excretion, and metabolism of the vapour in the human body. Such information, obtained from a single experimental exposure, would lead to knowledge of the transfer of trichloroethylene in the body in

chronic exposure, which is a common situation in a work place (Sato and Nakajima, 1977).

In the current study a mathematical model was developed to simulate the processes of absorption, distribution, excretion, and metabolism of trichloroethylene, the rate constants for each process being estimated from the time-course data of the vapour concentration in blood and the urinary excretion of its metabolites.

Experiments

SOLUBILITY OF TRICHLOROETHYLENE IN TISSUES OF RATS

The blood/air and tissue/blood partition coefficients were determined according to the method of Sato *et al.* (1974) with minor modifications. Tissue excised from a freshly killed rat was stripped of capsular and vascular connective tissues and weighed. The tissue was then homogenised with a known volume of 0.9% saline. Five vials of equal size, each 16.5 ml on average and containing 1 ml of the tissue homogenates, were used as test vessels. 0.1 ml of a trichloroethylene solution in saline containing 10 μ l/l was put into the vials on which rubber and aluminium-foil stoppers were placed as quickly as

Received for publication 2 February 1976

Accepted for publication 15 June 1976

possible. Five other vials were treated in a similar manner to act as controls except that in these, there were no tissue samples. Both the test and control vessels were kept at a temperature of 37°C in a thermoregulated water bath with a shaker for about two to six hours. After equilibration of trichloroethylene vapour between the test material and overlying air was achieved, 1 ml of the gas phase was extracted by an air-tight syringe through the stopper and was introduced into a gas chromatograph. The tissue/air partition coefficient, which equals (concentration in tissue)/(concentration in air) by definition, was calculated from peak heights on the chromatogram in the same way as reported by Sato *et al.* (1974). The tissue/blood partition coefficient was expressed as the ratio of the tissue/air partition coefficient to the blood/air partition coefficient.

EXPERIMENTAL HUMAN EXPOSURE TO TRICHLOROETHYLENE

Four male Japanese medical students, 20 to 21-years-old, and weighing on average 61.6 kg, served as volunteers for the experiment in which they inhaled 100 ppm of trichloroethylene for four hours. After cessation of exposure the concentration of trichloroethylene in blood and exhaled air and the amount of its urinary metabolites, that is, trichloroacetic acid (TCA), trichloroethanol (TCE), and total trichlorocompound (TTC), was measured and the time-course of these data was obtained.

EXPOSURE CHAMBER

Air for inhalation containing 100 ppm of trichloroethylene was prepared by passing it through liquid trichloroethylene in a gas-washing bottle at a known rate and diluting this saturated air with fresh air, flowing in with a metered volume of ventilation. Several preliminary tests showed that this simple method of atmosphere generation was satisfactory. The experimental exposure was as follows: The volunteers entered the exposure chamber of 12.5 m³ capacity in which there was no trichloroethylene. To achieve a rapid build-up to the required concentration, a predetermined amount of liquid trichloroethylene was injected through a rubber stopper attached to the monitoring window of the chamber at a sheet of gauze hung behind the window. The injected trichloroethylene was vaporised and mixed thoroughly by an electric fan. Several minutes after injection when the concentration had reached the required level, the air stream saturated with trichloroethylene (2 l/min) was introduced into the chamber, accompanied by a constant rate of ventilation which had been adjusted beforehand so as to maintain the desired concentration, 100 ppm, of trichloroethylene. An electric fan mounted on the

chamber ceiling recirculated the air thus providing the homogenous exposure mixture. The atmospheric concentration was monitored by gas chromatography every 20 minutes during exposure.

DETERMINATION OF TRICHLOROETHYLENE IN BLOOD AND EXHALED AIR

The examiner entered the chamber towards the end of the four hours' exposure and collected blood samples from cubital veins of each subject when his exposure had ceased. Immediately after leaving the chamber the subjects exhaled the end-tidal air into a 100 ml glass syringe through an air tube attached to the end of the syringe. They held their breath for 10 seconds at a normal expiration, and then exhaled the residue into the syringe. Thereafter, blood and end-tidal air were collected at predetermined intervals for 10 hours. The concentration of trichloroethylene in blood was determined by a gas chromatographic equilibration method (Sato *et al.*, 1975a). The concentration in exhaled air was measured by injecting a portion of the sampled air directly into a gas chromatograph with an air-tight syringe (Sato, 1968).

DETERMINATION OF URINARY METABOLITES OF TRICHLOROETHYLENE

The subjects had to collect all urine excreted at preselected intervals after exposure. TCA, TCE, and TTC were determined according to the method of Tanaka and Ikeda (1968).

Results

SOLUBILITY OF TRICHLOROETHYLENE IN BODY TISSUES OF RATS

The partition coefficients of trichloroethylene for various body tissues are shown in Table 1, as well as those for triolein, cholesterol, lecithin, human blood, and human fat. The solubility coefficient of the vapour for fat is much higher than for other tissues: the tissue/blood partition coefficient was about 70 for fat, and 1-3 for most other tissues. The high solubility of trichloroethylene in fat compared with blood was also confirmed with human fat and blood. The fact that triolein has an extremely high affinity for trichloroethylene compared with lecithin and cholesterol suggests that fat content in the form of neutral fat in any tissue is a primary determinant for the level of solubility in that tissue. Fat tissue can be said therefore to play a very important role in the processes of absorption, distribution, and elimination of trichloroethylene. As in the case of other fat-soluble vapours such as benzene (Fiserova-Bergerova *et al.*, 1974; Sato *et al.*, 1974), toluene (Sato *et al.*, 1974), and tetrachloroethylene (Guberman

Table 1 Partition coefficients of trichloroethylene for various body tissues of rats

	Mean	Standard deviation
<i>Five rats</i>		
Blood/air	25.82	1.70
Lung/blood	1.03	0.17
Heart/blood	1.10	0.31
Kidney/blood	1.55	0.48
Liver/blood	1.69	0.37
Muscle/blood	0.63	0.09
Brain/blood	1.29	0.28
Testis/blood	0.71	0.12
Spleen/blood	1.15	0.20
Fat/blood	25.59	1.08
<i>Five determinations</i>		
Blood/air (human) ¹	9.92	0.63
Fat/air (human) ²	674.40	34.08
Lecithin/air	387.90	27.97
Cholesterol/air	52.15	9.59
Cholesterol oleate/air	261.93	35.20
Triolein/air	848.24	31.33

¹Preserved blood from blood bank was used²The human fat tissue was obtained from a 23-year-old woman who died of acute myeloid leukaemia.

and Fernández, 1974). a three-compartment model can be applied to the transfer of trichloroethylene in the body, which is composed of (1) the tissue of the vessel-rich group (VRG) for example, brain, liver, kidney, etc.; (2) low perfused tissue of the muscle group (MG) for example, muscle and skin; and (3) poorly perfused tissue of the fat group (FG) for example, fat tissue and yellow bone marrow (Eger, 1963).

EXPERIMENTAL HUMAN EXPOSURE TO TRICHLOROETHYLENE

Elimination kinetics of trichloroethylene in blood

The decrease of trichloroethylene concentration in blood and exhaled air with time is shown in Fig. 1. Each decay curve was resolved into three exponential components, using the general expression as follows:

$$x = A_1 e^{-\alpha_1 t} + A_2 e^{-\alpha_2 t} + A_3 e^{-\alpha_3 t}, \quad (1)$$

where x is the concentration in mg/l, t the time in hours, and the values for A_i and α_i ($i = 1, 2$, and 3) are shown in the figure.

Sato *et al.* (1974) reported that when a solvent reaches an apparent equilibrium throughout the entire body after a sufficient time has elapsed, the transfer of the vapour in the body can be simulated by the model in Fig. 2, where the whole body is treated as a single body mass. When this model is applied to trichloroethylene, its intake and output to and from the entire body can be expressed in the following differential equation:

$$V \frac{dx}{dt} = -(\lambda_A a + b)x, \quad (2)$$

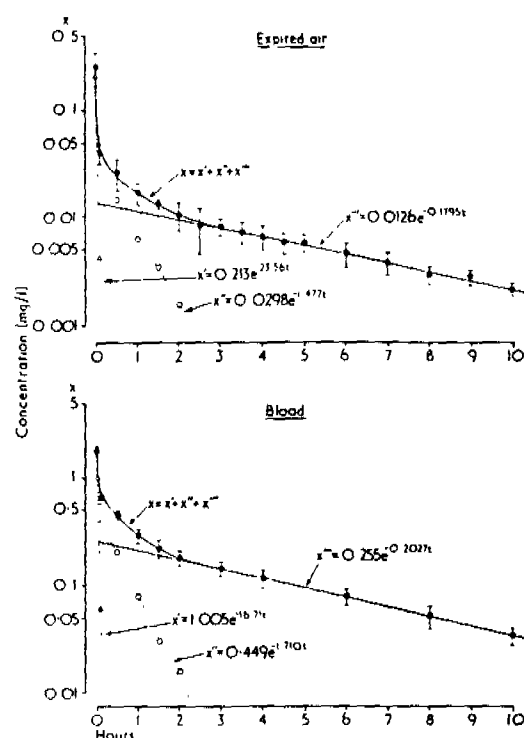


Fig. 1 Elimination curves of trichloroethylene.

where V is the distribution volume of trichloroethylene and τ equals the time elapsed after the trichloroethylene has reached apparent equilibrium period. In the equilibrium:

$$V = \lambda_1 V_1 + \lambda_2 V_2 + \lambda_3 V_3. \quad (3)$$

Solving (2) for x ,

$$x = x_0 e^{-\frac{\lambda_A a + b}{V} \tau}, \quad (4)$$

where x_0 is the concentration of trichloroethylene in blood just when it has reached the equilibrium, that is, $\tau = 0$. From equation 3, the rate constant for disappearance of trichloroethylene, $(\lambda_A a + b)/V$, becomes $(\lambda_A a + b)/(\lambda_1 V_1 + \lambda_2 V_2 + \lambda_3 V_3)$.

Assuming that the eventual rate constant, α_3 in (1), is equal to this rate constant, we have

$$\alpha_3 = \frac{\lambda_A a + b}{\lambda_1 V_1 + \lambda_2 V_2 + \lambda_3 V_3}. \quad (5)$$

Since $\lambda_3 V_3 \gg \lambda_1 V_1, \lambda_2 V_2$ for trichloroethylene, equation 5 can be reduced to

$$\alpha_3 = \frac{\lambda_A a + b}{\lambda_3 V_3}. \quad (6)$$

The metabolic clearance for trichloroethylene was unknown. Substituting the value in Table 2 for α_3 , a , λ_A , λ_3 and V_3 in (6) resulted in $b = 104$.

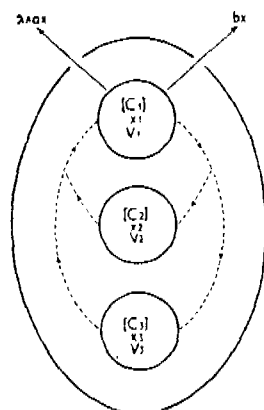


Fig. 2 A model for transfer of trichloroethylene in the body.

- a : Alveolar ventilation, l/hour.
 b : Metabolic clearance, l/hour.
 [C₁] : Compartment composed of VRG.
 [C₂] : Compartment composed of MG.
 [C₃] : Compartment composed of FG.
 x₁ : Concentration in [C₁], mg/l.
 x₂ : Concentration in [C₂], mg/l.
 x₃ : Concentration in [C₃], mg/l.
 λ₁ : Air/blood partition coefficient.
 λ₂ : VRG/blood partition coefficient.
 λ₃ : MG/blood partition coefficient.
 λ₄ : FG/blood partition coefficient.
 V₁ : Volume of VRG, l.
 V₂ : Volume of MG, l.
 V₃ : Volume of FG, l.

Broken lines with arrows show blood flow through each compartment.

Table 2 Values used in the present model

V ₁ , l	8 ¹
V ₂ , l	31 ¹
V ₃ , l	10 ¹
a, l/hour	336 ¹
b, l/hour	104 ¹
λ ₁	0.1 ¹
λ ₂	1.5 ¹
λ ₃	1.0 ¹
λ ₄	68.0 ¹
α, hour ⁻¹	0.2027 ²

¹Cited from Sato *et al.* (1974).

²Results obtained in the current investigation.

Excretion kinetics of urinary metabolites

The time-courses of urinary excretion of TCA, TCE, and TTC are shown in Table 3. The cumulative amount of each metabolite was plotted against time as shown in Fig. 3.

The major metabolic pathway of trichloroethylene in a living body is generally considered to be as

shown in Fig. 4 (Williams, 1959; Daniel, 1963; Byington and Leibman, 1965), where all the rate constants are assumed to be first-order rate constants. Let X_A, X_B, X_C, and X_D be the amounts of A, B, C, and D, respectively, at time t which equals the time that has elapsed after the cessation of the exposure. We then have for the model in Fig. 4,

$$\frac{dX_A}{dt} = -(k_1 + k_4)X_A, \quad (7)$$

$$\frac{dX_B}{dt} = k_1X_A - (k_2 + k_1 + k_j)X_B, \quad (8)$$

$$\frac{dX_C}{dt} = k_2X_B - k_3X_C, \quad (9)$$

$$\text{and } \frac{dX_D}{dt} = k_3X_C. \quad (10)$$

Solving (7) for X_A,

$$X_A = A_0 e^{-k_A t}, \quad (11)$$

where A₀ is the amount of A at t = 0, and k_A = k₁ + k₄. (k_A is the overall rate constant for loss of A from the body, and it has already been mentioned that k_A will be equal to (λ_{AA} + b)/V, when trichloroethylene will have reached an apparent equilibrium.)

From (8), (9), and (11) we obtain

$$X_C = Q_3 e^{-k_3 t} - Q_2 e^{-k_B t} + Q_1 e^{-k_A t}, \quad (12)$$

where k_B = k₂ + k₁ + k_j (k_B is the overall rate constant for loss of B from the body.), B₀ and C₀ the amount of B and C at t = 0, respectively, and where

$$Q_1 = \frac{k_1 k_2}{(k_A - k_B)(k_A - k_3)} A_0,$$

$$Q_2 = \frac{k_2}{k_B - k_3} (B_0 + \frac{k_1}{k_A - k_B} A_0),$$

$$\text{and } Q_3 = C_0 + \frac{k_2}{k_B - k_3} B_0 +$$

$$\frac{k_1 k_2}{(k_B - k_3)(k_A - k_3)} A_0.$$

Substituting X_C in (10),

$$\frac{dX_D}{dt} = k_3 Q_3 e^{-k_3 t} - k_3 Q_2 e^{-k_B t} + k_3 Q_1 e^{-k_A t} \quad (13)$$

Solving (13) for X_D,

$$X_D = D_0 + C_0 + \frac{k_2}{k_B} B_0 + \frac{k_1 k_3}{k_A k_B} A_0 - Q_3 e^{-k_3 t} + \frac{k_3}{k_B} Q_2 e^{-k_B t} - \frac{k_3}{k_A} Q_1 e^{-k_A t}, \quad (14)$$

where D₀ is the amount of D at t = 0.

Let D_∞ be the total amount of D, that is, the total

amount of any one of TCA, TCE, or TTC excreted in urine, we have

$$D_{\infty} = k_3 \int_0^{\infty} X_{cdt} = D_0 + C_0 + \frac{k_2}{k_B} B_0 + \frac{k_1 k_2}{k_A k_B} A_0.$$

The equation (14) can therefore be reduced to

$$D_{\infty} - X_D = Q_3 e^{-k_3 t} - \frac{k_3}{k_B} Q_2 e^{-k_B t} + \frac{k_3}{k_A} Q_1 e^{-k_A t}. \quad (15)$$

Since $k_3 \ll k_A$ or k_B , we can see that when $D_{\infty} - X_D$ is plotted on a logarithmic scale against time, the slope of the line drawn through the second half of the points will be $-k_3$. When this line extrapolated to $t = 0$ and $[Q_3 e^{-k_3 t} - (D_{\infty} - X_D)]$ is replotted, the slope of the line drawn through the points at the tail end of this plot will give an estimate of the smaller one of the two rate constants, k_A and k_B , and the slope determined from the residual points an estimate of the larger one (Fig. 5).

The $D_{\infty} - X_D$ plots for TCA, TCE, and TTC resulted in the expressions as follows:

$$D_{\infty} - X_D(\text{TCA}) = 113.56e^{-0.0177t} - 59.30e^{-0.0618t} + 16.89e^{-0.2130t}$$

$$D_{\infty} - X_D(\text{TCE}) = 216.23e^{-0.0285t} + 75.23e^{-0.0961t}$$

$$D_{\infty} - X_D(\text{TTC}) = 303.24e^{-0.0224t} - 39.44e^{-0.8009t} + 79.34e^{-0.1890t}$$

The estimates of k_A thus obtained from TCA- and TTC-plots agree generally with the eventual rate constant, α_3 in (1), which was more directly determined from the time-course of blood or exhaled air concentration of trichloroethylene. The reason why the TCE-plot alone did not result in a three-exponential expression has not yet been fully elucidated, but may be due to the fact that the plotted values for TCA and TTC are directly measured but the value

for TCE is indirectly estimated, being expressed as the difference between these values for TCA and TTC.

Discussion

The quantitative study of the time-course of absorption, distribution, excretion, and metabolism of toxic substances is a useful tool in studying the characteristics of toxic effects induced by them (Levy and Gibaldi, 1972; Sato *et al.*, 1975b). The processes of uptake and washout of organic solvent vapours in a human body have recently been studied using an analogue or mathematical model, which simulates the processes and gives an adequate prediction (Fiserova-Bergerova *et al.*, 1974; Gubaran and Fernández, 1974).

With few exceptions, most pharmacokinetic models have been built on the assumption that blood perfusion alone is an effective medium of transport for all tissues in a living body (Kety, 1951). The mathematical model based on this perfusion-limited assumption, failed to simulate the time-course of elimination of inhaled benzene and toluene in men (Sato *et al.*, 1974). For the transfer of fat-soluble compounds direct diffusion between neighbouring tissues, each having different perfusion/partition properties and hence being filled and emptied at a different rate, was found to be a significant pathway in addition to perfusion (Perl *et al.*, 1965). Taking account of this intertissue diffusion, we have assumed that it takes no longer than three hours after exposure has ceased for trichloroethylene to reach an apparent equilibrium and then to be distributed throughout the body according to its partitioning characteristics between blood and

Table 3 Urinary excretion of TCA, TCE, and TTC

Interval of measurements (hours)	Midtime (hour)	Amount measured (mg) mean $\pm$ SD		
		TCA	TCE	TTC
0-1	0.5	0.21 $\pm$ 0.18	13.03 $\pm$ 3.25	13.24 $\pm$ 3.12
1-2	1.5	0.25 $\pm$ 0.08	11.00 $\pm$ 4.66	11.24 $\pm$ 4.73
2-4	3.0	0.57 $\pm$ 0.27	21.46 $\pm$ 10.34	22.03 $\pm$ 10.44
4-8	6.0	2.37 $\pm$ 1.57	36.28 $\pm$ 5.55	38.65 $\pm$ 6.35
8-12	10.0	1.32 $\pm$ 0.61	31.45 $\pm$ 7.15	32.77 $\pm$ 7.30
12-16	14.0	0.93 $\pm$ 0.26	26.70 $\pm$ 7.64	27.63 $\pm$ 4.33
16-24	20.0	2.15 $\pm$ 0.74	33.58 $\pm$ 5.75	35.73 $\pm$ 5.56
24-36	30.0	4.32 $\pm$ 1.31	39.70 $\pm$ 10.99	44.02 $\pm$ 11.01
36-48	42.0	8.17 $\pm$ 3.05	22.57 $\pm$ 7.76	30.74 $\pm$ 8.76
48-60	54.0	7.79 $\pm$ 1.84	17.03 $\pm$ 3.76	24.82 $\pm$ 2.28
60-72	66.0	7.83 $\pm$ 1.48	11.50 $\pm$ 4.95	19.33 $\pm$ 6.28
72-84	78.0	6.95 $\pm$ 2.64	6.52 $\pm$ 4.62	13.47 $\pm$ 4.10
84-96	90.0	4.34 $\pm$ 0.91	3.88 $\pm$ 1.58	8.22 $\pm$ 2.36
96-108	102.0	4.56 $\pm$ 1.22	6.00 $\pm$ 1.39	10.56 $\pm$ 2.44
108-120	114.0	3.32 $\pm$ 0.93	3.14 $\pm$ 1.85	6.45 $\pm$ 2.61
120-132	126.0	3.23 $\pm$ 1.18	2.17 $\pm$ 1.29	5.41 $\pm$ 1.88
132-144	138.0	4.00 $\pm$ 2.30	1.65 $\pm$ 0.54	5.66 $\pm$ 2.83
144-156	150.0	2.44 $\pm$ 0.32	0.88 $\pm$ 0.70	3.32 $\pm$ 0.69
156-168	162.0	1.44 $\pm$ 0.53	1.08 $\pm$ 0.80	2.52 $\pm$ 0.99
168-180	174.0	2.55 $\pm$ 0.32	1.17 $\pm$ 0.53	3.71 $\pm$ 0.76

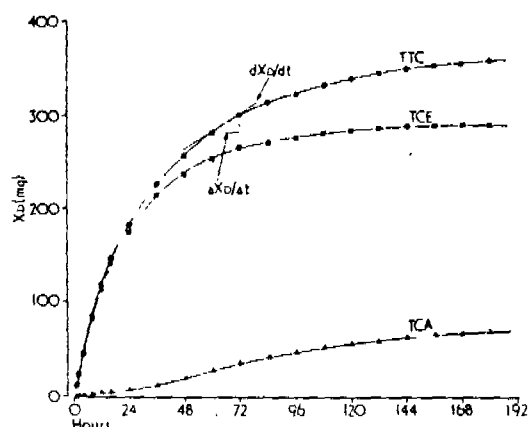


Fig. 3 Cumulative amount of metabolites excreted in urine.

tissues. The value of 104 l/hour for metabolic clearance was estimated by treating the whole body in the equilibrium as a single body mass. So far there is no proof for these assumptions, but they would be supported indirectly if the quantities predicted agreed with the quantities measured by other methods. About 70-80% of the absorbed trichloroethylene was reported to be excreted in urine as metabolites and the remaining 20-30% to be eliminated unchanged in expired air (Bartoniček, 1962; Nomiyama and Nomiyama, 1971; Ogata *et al.*, 1971). Assuming that the loss of trichloroethylene absorbed in man through other pathways is negligible, the ratio, P , of the amount metabolised to the total amount absorbed is given as follows:

$$P = \frac{\text{amount metabolised}}{\text{total amount absorbed}} = \frac{bx}{(\lambda_{AA} + b)x} = \frac{b}{\lambda_{AA} + b} \quad (16)$$

Substitution of $b = 104$ for b in (16) resulted in $P = 0.75$, which is not very different from the one measured more directly by other investigators. Therefore, the assumptions that trichloroethylene

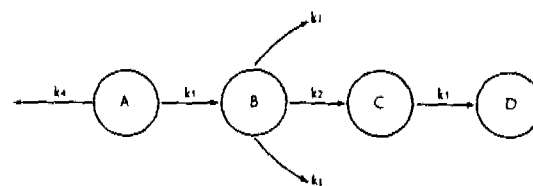


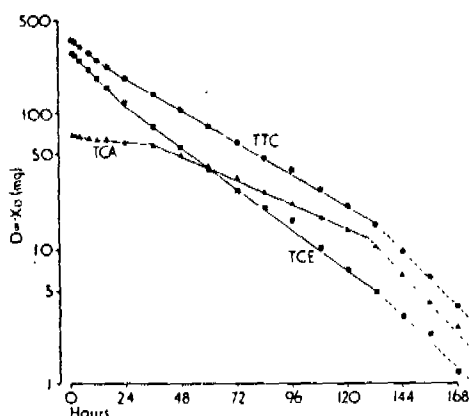
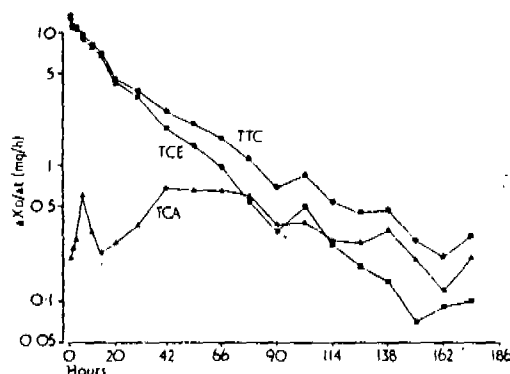
Fig. 4 Metabolic pathways of trichloroethylene.

- A : Trichloroethylene in the body.
 B : A metabolite of trichloroethylene in the body, possibly chloral hydrate. $\rightarrow$ TCA
 C : A metabolite of trichloroethylene in the body, which is to be excreted and applies to any one of TCA, TCE, and TTC.
 D : C excreted in urine (TCA, TCE, or TTC).
 k_1 : Rate constant for the step $A \rightarrow B$, which is another quantity from the metabolic clearance b in Fig. 1.
 k_2 : Rate constant for the step $B \rightarrow C$.
 k_3 : Rate constant for the step $C \rightarrow D$.
 k_4 : Rate constant for the loss of A through other pathways than $A \rightarrow B$. (k_4 corresponds approximately to the elimination through the lungs, but is not identical to a in Fig. 1.)
 k_i, k_j : Rate constant for the pathways for disposal of B other than the $B \rightarrow C$ step.

Table 3 Urinary excretion of TCA, TCE, and TTC

dX_d/dt , mg/hour			X_d , mg			$D_\infty - X_d$, mg			$ Q_3 e^{-k_3 t} - (D_\infty - X_d) $, mg		
TCA	TCE	TTC	TCA	TCE	TTC	TCA	TCE	TTC	TCA	TCE	TTC
0.21	13.03	13.74	0.21	13.03	13.24	68.51	277.74	346.25	43.06	67.59	49.73
0.25	11.00	11.24	0.45	24.02	24.48	68.25	266.75	335.01	41.36	62.50	45.06
0.29	10.74	11.02	1.02	45.48	46.53	67.69	245.29	312.98	38.12	52.35	35.74
0.60	9.07	9.67	3.39	81.76	85.18	65.33	209.01	274.33	33.25	36.84	20.86
0.33	7.87	8.19	4.71	113.20	117.90	64.00	177.56	241.57	27.85	23.93	9.83
0.23	6.68	6.91	5.64	139.91	145.53	63.08	150.87	213.94	22.50	13.78	2.07
0.27	4.20	4.47	7.79	173.49	181.27	60.93	117.29	178.21	13.36	8.13	1.11
0.36	3.31	3.67	12.11	213.18	225.29	56.61	77.59	134.19			
0.68	1.88	2.56	20.28	235.76	256.03	48.44	55.02	103.45			
0.65	1.42	2.07	28.06	252.79	280.85	40.65	37.99	78.64			
0.65	0.96	1.61	35.89	264.29	300.17	32.83	26.49	59.31			
0.58	0.54	1.12	42.84	270.81	313.64	25.88	19.97	45.84			
0.36	0.32	0.68	47.18	274.68	321.86	21.54	16.09	37.62			
0.38	0.50	0.88	51.74	280.68	332.42	16.98	10.09	27.07			
0.28	0.26	0.54	55.05	283.82	338.87	13.66	6.95	20.61			
0.27	0.18	0.45	58.29	285.99	344.28	10.43	4.78	15.21			
0.33	0.14	0.47	62.29	287.64	349.93	6.43	3.13	9.55			
0.20	0.07	0.28	64.73	288.53	353.25	3.99	2.25	6.23			
0.12	0.09	0.21	66.16	289.61	355.77	2.55	1.17	3.71			
0.21	0.10	0.31	68.71 ¹	290.77 ¹	359.48 ¹	0	0	0			

¹The value is equal to D_∞ .

Fig. 5 Semilogarithmic plots of $D_{\infty} - X_D$.Fig. 6 Semilogarithmic plots of $\Delta X_D/\Delta t$ against midpoint time.

will have reached an apparent equilibrium throughout the body in three hours after exposure has ceased and that the whole body can then be treated as a single body mass, should not be unreasonable. The rate constants for the disappearance of trichloroethylene estimated from the time-courses of urinary excretion of TCA and TTC based on these assumptions agreed with those determined from the time-course of blood concentration of trichloroethylene.

The method of estimating rate constants for absorption, metabolism, and elimination of drugs from urinary excretion data was reported by Wagner (1967). The method described above applies Wagner's method for trichloroethylene with several modifications. As is clear in (13), the plot of dX_D/dt on a semilogarithmic scale against time is also expected to give an estimate of k_a , k_{11} , and k_{12} . The value of $\Delta X_D/\Delta t$ in Table 3, an estimate of dX_D/dt , was plotted on a semilogarithmic paper (Fig. 6). Com-

parison of the $D_{\infty} - X_D$ plot (Fig. 5) and $\Delta X_D/\Delta t$ plot (Fig. 6), shows that the former is clearly more linear.

TCA accounts for about 20% of TTC, and TCE for about 80% in the present single exposure as is shown in Table 3. The fact that k_3 for TCA is smaller than that for TCE, however, suggests that TCA has a longer biological half-life than TCE, which will lead to the prediction that the proportion of urinary metabolites excreted as TCA increases in a chronic exposure (Sato and Nakajima, 1977).

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