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Pharmacokinetics of Trichloroethylene in Volunteers, Influence of Workload and Exposure Concentration

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Summary. Four male volunteers inhaled for 4 h 70 and 140 ppm trichloroethylene (TRI) at rest and also at rest combined with exercise. To estimate the amount retained in the body (dose), minute volume and concentration in exhaled air were determined. Concentrations of TRI, trichloroethanol (TCE) and trichloroacetic acid (TCA) were determined in blood. Exhaled air was analysed for TRI and TCE; urine for TCE and TCA.

During more than 60 h after exposure the concentration of TRI and TCE in blood and exhaled air were proportional to the dose, but the inter-individual variation was large; workload increased the dose, but no influence was found on the distribution and metabolism. The total recovery was 67%; 10% as TRI by the lungs and in urine 39% as TCE and 18% as TCA.

Key words: Trichloroethylene - Trichloroethanol - Trichloroacetic acid - Pharmacokinetics - Workload.

1. INTRODUCTION

There are numerous reports on the metabolism of trichloroethylene (TRI). Nevertheless the relation between uptake and excretion of TRI still requires investigation. The purpose of these experiments is to explore a balance of absorption and excretion and to develop a sensitive biological exposure test, usable in industry. Emphasis is laid upon amounts absorbed and excreted per unit of time. To increase the relevance of our findings for industry we studied our subjects at rest and at rest combined with exercise. Especially the following questions were of interest:

1. Is the dose absorbed proportional to the inhaled concentration?
2. What effect does work load during exposure have on dose?
3. Is there an influence of dose on distribution and metabolism?

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2. MATERIALS AND METHODS

2.1. Subjects

All experiments employed the same four male volunteers. They were in good health and glutamic-oxalacetic transaminase, glutamic-pyruvic transaminase and alkaline phosphatase in serum were within the normal range; the subjects were not allowed to smoke during exposure (two habitual smokers). After 3 h exposure they had a cold supper in the exposure chamber. The subjects were instructed not to drink alcohol during the first 24 h after exposure.

2.2. Exposure Conditions

The subjects were exposed to:
a) 70 ppm (376 mg/m^3), 4 h, rest
b) 70 ppm, 4 h, during exposure 2 x $\frac{1}{2}$ h 100 W workload on a bicycle ergometer
c) as (a), but 140 ppm (753 mg/m^3)
d) as (b), but 140 ppm.
Two subjects were exposed simultaneously, one 4 h at rest, the other at rest and workload after 45 and 150 min. During rest they were free to read or talk. The interval between exposures of same subjects was at least 3 weeks.

2.3. Exposure Chamber

The exposure chamber (TNO Research Institute for Environmental Hygiene, Indoor Air Pollution Division) (Duba, 1975) operates on the dynamic principle. A constant desired concentration of vapour was maintained in the room. The internal volume of the chamber was 21.8 m^3 (4 x 2.5 x 2.4 m). The air flow rate was 150 m^3/h. A liquid flow of TRI was supplied by a double-acting syringe pump (Sage) to an evaporator. The vapour with an auxiliary air flow was supplied to a venturi and mixed with the main air flow.

2.4. Actual Concentration

The concentration within the exposure chamber was recorded with a hydrocarbon analyser (HCA) by passing the TRI-air mixture with a constant flow (1.1 l/min) through the flame-ionisation detection system of the HCA. The apparatus was calibrated by gas chromatography. The concentrations in the chamber were homogeneous and constant within ±4% during the experiments.

2.5. Concentration of Exhaled Air during Exposure

In case of workload the subjects wore a modified gas mask from 5 min before workload continuously to 10 min afterwards. In case of only rest the subjects wore the gas mask 3 periods of 15 min. The gas mask (dead volume: 150 ml) had one inlet and one outlet. A prism-cornered Tedlar® bag (vol 3 l) was connected at one side directly to the outlet of the gas mask and the other side was connected through a 15 cm long Teflon tube (ID 5 cm) to the tube of a gas meter for volume registration. From the middle of the bag a constant volume (1.1 l/min) was drawn by the HCA with a small Teflon tube. In addition it was possible while sitting in the exposure chamber to connect a tube from outside to the inlet of the gas mask for inhalation of fresh air.

2.6. Dose

The amount absorbed by the lung is the difference between the amount inhaled and exhaled. So the dose absorbed per min is: $D = Ci \times MV \times \frac{Ci-Ce}{Ci}$, where D = quantity absorbed in mg/min, Ci = conc. in inhaled air in mg/l, Ce = conc. in exhaled air in mg/l, MV = minute volume in l/min, retention (R) = $\frac{Ci-Ce}{Ci}$, lung clearance (l/min) = MV.R.
Lung clearance indicates which volume of inspired air per min is cleared of vapour (van Rees, 1964).
The total dose during 4 h exposure was estimated by interpolating the doses as measured during the periods the gas mask was worn.

2.7. Determination of TRI and Its Metabolites

For analysis of breath and blood the gas chromatographic technique described by Monster and Boersma (1975) was applied. In 2 ml blood TRI, TCE and TCA were determined simultaneously by means of the head-space technique. With this technique the non-glucuronidized as well as the glucuronidized fraction of TCE in blood were measured together. The concentration of TCA in total blood is about a factor 2 lower than in plasma (Paykoc and Powell, 1945), due to the high binding of TCA to plasma proteins (Sellers and Koch-Wezel, 1971). TRI and TCE in exhaled air were determined under the same gas chromatographic conditions as the headspace vapour of blood. TCA and TCE in urine were measured according to Weichardt and Bardodej (1970).

2.8. Time Course of the Experiments

Before entering the exposure chamber the subjects exhaled through a gas mask connected with the HCA for measuring base levels in exhaled air. In addition to the periods mentioned in 2.5. the subjects also wore the gas mask during the last 5 min of exposure; at the end of exposure the inlet of the gas mask was connected to fresh air. The subjects still remained in the chamber 10 min, then left the room without breathing. Blood samples were taken before entering the room, about 20 min before termination of exposure and 2, 20, 44, 68, 140 and 212 h after exposure. Exhaled air samples were collected during 1 min normal breathing at 30 min, 2, 20, 44, and 68 h after exposure. Urine was collected in timed samples for every voiding until 66 h after exposure, and also during 24 h on the 9th day after exposure.

2.9. TCA Excretion after 66 h

The amount of TCA excreted in urine after 66 h was estimated by the formula:

$$Q\ (66\ h \rightarrow \infty) = C\ (66\ h).\ \frac{Q\ (9th\ day)}{\Delta C\ (9th\ day)}$$

where $Q(66\ h \rightarrow \infty)$ = amount of TCA excreted in urine from 66 h after exposure till infinite, C (66 h) = concentration of TCA in blood at 66 h after exposure, Q (9th day) = amount of TCA excreted during 24 h at the 9th day after exposure, ΔC (9th day) = decrease in TCA blood concentration during the 9th day (determined from the TCA blood concentration curve), $\frac{Q\ (9th\ day)}{\Delta C (9th\ day)} = V_D$ = apparent distribution volume of TCA, referenced to TCA blood concentration.

2.10. Statistical Analysis

Statistical evaluation of blood concentrations of TRI, TCE and TCA (divided by dose) was done by an analysis of variance (three-crossed classification: time, condition, subjects). In the figures the corresponding residual error is shown.

Table 1
Retention (R), minute volume (MV), and lung clearance (LC), mean and SD of 9 x 5 min in 4 subjects exposed to 70 and 140 ppm TRI during 4 h at rest

Exposure concentration (ppm)	Subject	R (%)	MV ($l.min^{-1}$)	LC ($l.min^{-1}$)
65	A	49±2	7.7±0.8	3.80±0.46
68	B	46±3	10.7±0.7	4.84±0.38
70	C	45±1	8.5±1.0	3.70±0.34
76	D	43±3	11.6±0.9	4.85±0.40
140	A	48±4	8.9±0.7	4.20±0.48
138	B	42±4	10.4±1.6	4.35±0.45
142	C	40±4	9.8±0.9	3.93±0.57
140	D	37±3	12.3±1.3	4.52±0.64

3. RESULTS

3.1. Uptake

3.1.1. Absorption at Rest. After an initial decrease from 6.4 to 4.5 l/min in 5 min, mainly caused by a decrease in retention, lung clearance remained at the same level. Table 1 shows the mean retention, minute volume and lung clearance of each subject at rest (first 5 min excluded). There was no difference in lung clearance during exposure to 70 ppm compared to 140 ppm. The mean lung clearances were 4.30 l/min (3.80-4.85) and 4.23 l/min (3.93-4.52) respectively. So the dose absorbed during these two comparable exposures apparently was proportional to the inhaled concentrations.

3.1.2. Absorption during Exercise. Figure 1 shows the data of subject B at 140 ppm with workload. During exercise minute volume increased threefold. During the first 5 min retention was higher, thereafter lower than at rest. After exercise, retention did not increase fully to pre-exercise levels. During exercise lung clearance was 2.5 - 3-fold the rest value. Table 2 shows the effect of workload on minute volume and lung clearance. During the second workload mean lung clearance and retention were 15 ± 5% lower than during the first workload (probably due to a higher saturation of tissues during the second workload). There was no difference in lung clearance during workload between 70 and 140 ppm. In comparison with the situation at rest (Table 1) lung clearance and consequently dose per min was 2.5 times as high, mainly due to a threefold higher minute volume.

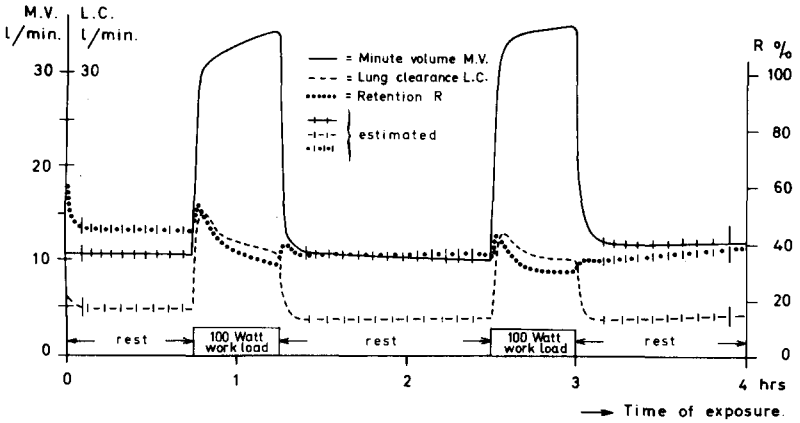


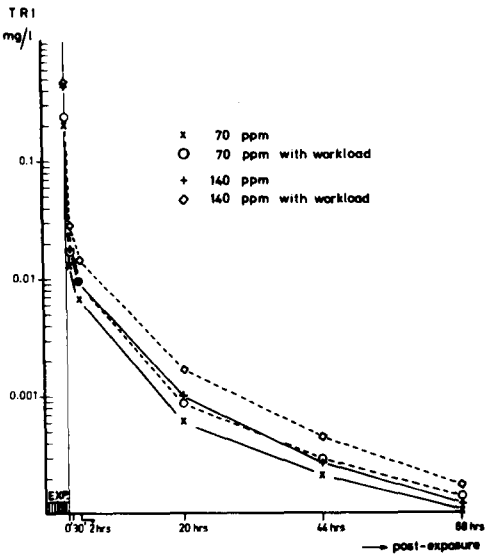
Fig.1
Minute volume, retention and lung clearance of subject B during exposure to 140 ppm trichloroethylene at rest combined with 2 x 100 W workload

Table 2
Mean and range of retention (R), minute volume (MV), and lung clearance (LC) during 2 x $\frac{1}{2}$ h 100 W workload in 4 subjects exposed to 70 and 140 ppm TRI during 4 h

Exposure concentration (ppm)	Workload	R (%)	MV ($l.min^{-1}$)	LC ($l.min^{-1}$)
70	1st exercise	39 (30-47)	30 (25-33)	11.6 (9.6-13.0)
(65- 76)	2nd exercise	35 (23-44)	29 (25-33)	10.2 (7.5-11.0)
140	1st exercise	41 (37-49)	29 (21-33)	11.4 (10.5-12.8)
(138-142)	2nd exercise	36 (33-42)	29 (21-33)	9.8 (8.7-10.9)

Table 3
Estimated dose for 4 subjects exposed to 70 and 140 ppm TRI, 4 h at rest, and 3 h at rest combined with 2 x $\frac{1}{2}$ h 100 W workload

Condition ppm	Dose (mg)				
	A	B	C	D	Mean
70 ppm rest	320	430	330	470	390
Rest + exercise	500	450	470	660	520
140 ppm rest	740	790	710	790	755
Rest + exercise	1050	1100	970	1100	1055



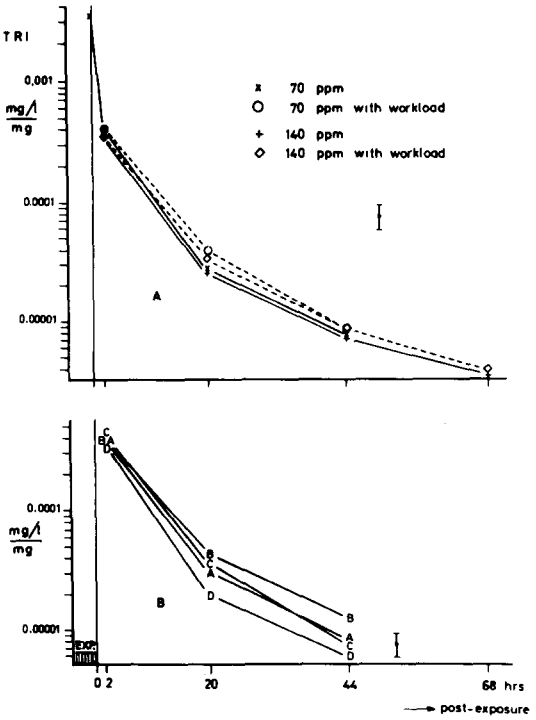


Fig.2 Fig.3

Fig.2
Mean trichloroethylene concentration in exhaled air (mg/l) of 4 subjects exposed during 4 h to 70 and 140 ppm at rest and at rest combined with workload

Fig.3A and B
Trichloroethylene concentrations in blood (as fraction of dose/l whole blood). Data points were calculated by dividing individual concentrations (mg/l) by individual dose (mg). A represents mean of 4 subjects in each condition and B the mean of each subject in 4 conditions. On the right side the residual error is indicated

3.1.3. Total Dose. Total doses are given in Table 3. The extra 2 x $\frac{1}{2}$ h 100 W workload increased the mean total dose over 4 h by about 40% (from 390 to 520 and from 755 to 1055 mg resp.). The mean dose at 140 ppm was about twice as high as at 70 ppm at rest as well as at rest combined with exercise (755 compared to 390 and 1055 compared to 520).

3.2. Concentrations in Blood and Exhaled Air

3.2.1. Trichloroethylene. The mean TRI concentrations in exhaled air in each exposure condition are presented in Figure 2. The exhaled concentrations decreased very sharply in the first minutes after exposure. After 5 min the concentration was about

Table 4. Anthropometric data of subjects

Subject	Body weight (kg)	Body height (cm)	Adipose tissue (%)	Age
A	70	180	12	30
B	80	180	26	28
C	62	165	14	34
D	67	186	9	27

10 times lower than during exposure. Thereafter the decline was much slower. As expected, during the whole period of 68 h after exposure the mean concentrations in exhaled air after rest combined with workload were higher compared to only rest. In order to compare the behaviour of the TRI concentrations in blood under different conditions and in different subjects, the individual concentrations were divided by the individual doses (TRI/dose). Figure 3A and B shows the behaviour of the mean TRI blood/dose *in each exposure condition* and *in each subject*. The elimination curves of the subjects show a greater spread than those of the conditions, particularly if measured more than 20 h after exposure. The TRI in blood/dose in blood appeared to be higher in the fattest subject (B: 26% fat) than in the leanest subject (D: 9% fat) (Table 4) particularly if measured more than 20 h after exposure. The elimination curves of TRI in exhaled air followed the same course in time as in blood, but the TRI concentration in exhaled air was generally 23 times lower than the concentration in blood (Monster and Boersma, 1975).

3.2.2. Trichloroethanol. TCE in blood and exhaled air had its maximum about 30 min after end of exposure; thereafter the concentration declined rapidly and exponentially with a half-life of 10 - 12 h. For comparison, concentrations were also divided by the individual dose. Figures 4A and B and 5A and B show the concentrations in blood and exhaled air of TCE divided by dose. Again the curves of the subjects (Figs.4B and 5B) show a greater spread than those of the conditions (Figs.4A and 5A). Note that subject A consistently had a higher TCE concentration than the other three subjects.
The curves of TCE concentration in exhaled air (Fig.5) followed the same exponential decline as those in blood (Fig.4), but the concentration generally was 15,000 times lower (Monster and Boersma, 1975).

3.2.3. Trichloroacetic Acid. The concentration of TCA in blood continued to rise even after the end of exposure; the increase persisted up to approximately 40 h after exposure. After about 60 h the concentration decreased exponentially with a half-life

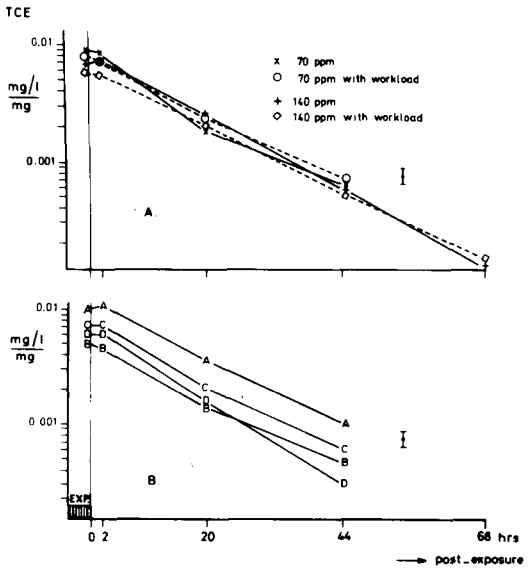


Fig.4

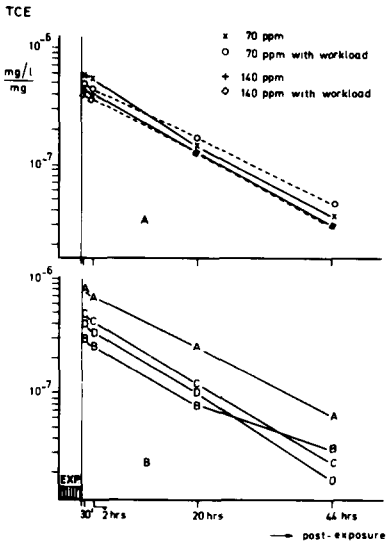


Fig.5

Fig.4 A and B. Trichloroethanol concentration in blood (as fraction of dose/l whole blood). Data points were calculated by dividing individual concentrations (mg/l TCE) by individual dose (mg TRI). A represents the mean of 4 subjects in each condition and B the mean of each subject in 4 conditions. On the right side the residual error is indicated

Fig.5 A and B. Trichloroethanol concentration in exhaled air (as fraction of dose/l exhaled air). Data points were calculated by dividing individual concentrations (mg/l TCE) by individual dose (mg TRI). A represents the mean of 4 subjects in each condition and B the mean of each subjects in 4 conditions

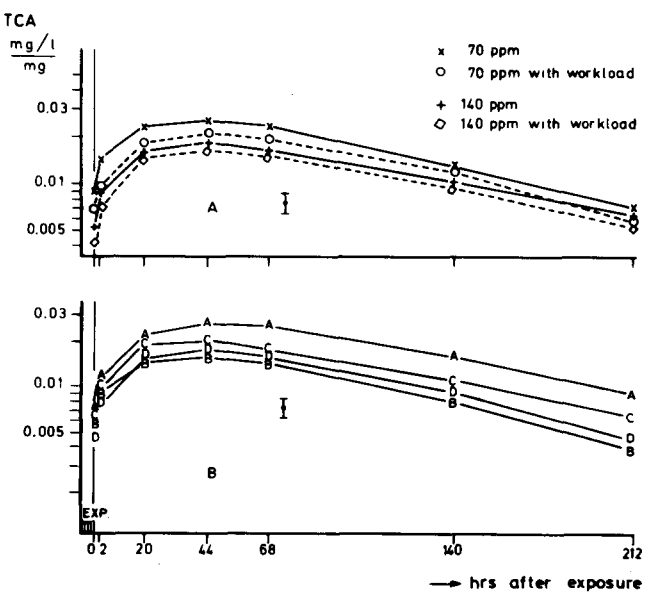


Fig.6 A and B Trichloroacetic acid concentration in blood (as fraction of dose/l whole blood). Data points were calculated by dividing individual concentrations (mg/l TCA) by individual dose (mg TRI). A represents the mean of 4 subjects in each condition and B the mean of each subject in 4 conditions. In the figure the residual error is indicated

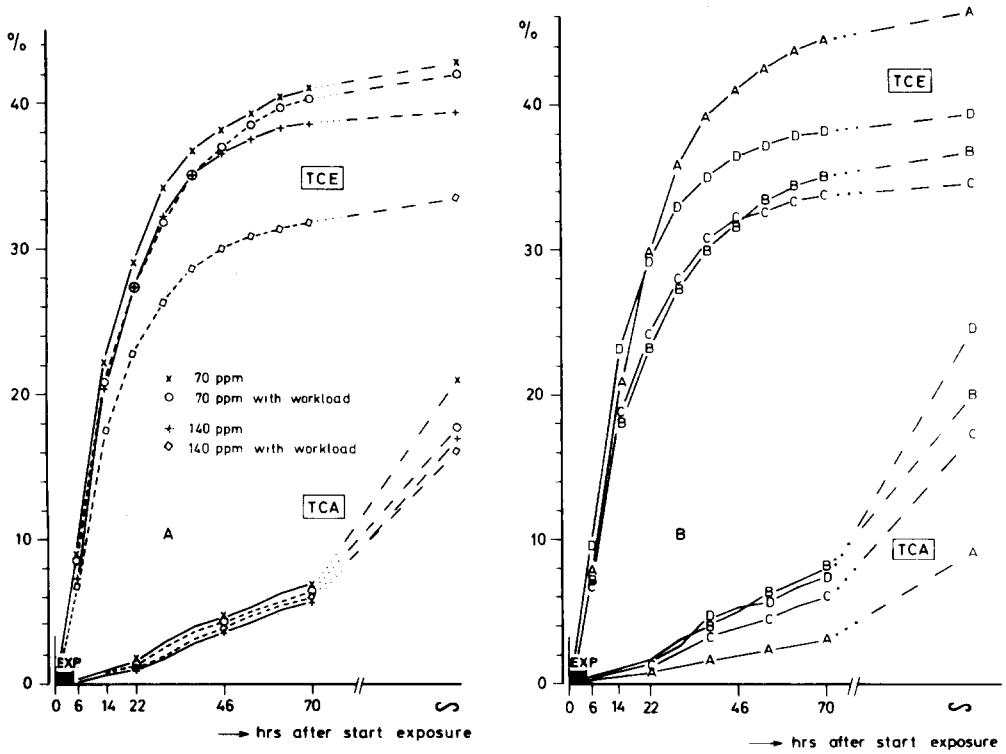


Fig.7
Cumulative percentage of the dose of TRI excreted per 8 h as TCE and TCA in urine (calculated as TRI). Data points were calculated by dividing amounts excreted by the individual dose. A represents the mean of 4 subjects in each condition and B the mean of each subject in 4 conditions

of 70 - 100 h. Figure 6A shows mean TCA blood concentrations divided by the dose in *each exposure condition* (TCA/dose). In the figure it is seen that as the dose in each consecutive condition was higher, the mean TCA/dose was lower, at least till 3 days after exposure. The mean TCA blood/dose *in each subject* is presented in Figure 6B. As with TCE subject A had a higher TCA blood concentration than the other three subjects. As with TRI and TCE the curves of TCA of the subject show a greater spread than those of the conditions.

3.2.4. Statistical Analysis of Blood Concentrations. There appeared distinct inter-subject differences for TRI, TCE and TCA ($P<0.001$). The conditions do not result in different height of the concentration/dose curves except for a tendency in the case of TCA ($P<0.1$). These results correspond to the finding that the curves of the subjects show a greater spread than those of the conditions.

3.3. Excretion of Trichloroethanol and Trichloroacetic Acid in Urine

Concentrations of TCE and TCA were determined in time-sampled urine specimens and calculated to amounts excreted per interval of 8 h. For each subject the 8 h amount (calculated as TRI) was expressed as a percentage of the TRI dose. Figure 7A shows the mean cumulative percentage of TCE and TCA excreted in urine *under each exposure condition*. The major portions of TCE (about 8 and 12% resp. of the total dose) were excreted during the periods 0 - 6 and 6 - 14 h after the start of exposure. TCE was almost totally excreted within 3 days after exposure. This is in agreement with the small half-life of TCE in blood (10 - 12 h). However, for TCA the maximum quantity (about 1%/8 h of the total dose) was excreted between 22 - 46 h after the start of exposure and excretion of TCA continued till at least 2 weeks after exposure. This is in accordance with the curve of TCA concentration in blood and the long half-life of TCA (75 - 100 h). The cumulative percentages of TCE and TCA excreted in urine *under each exposure condition* had the same sequence as the maximum concentrations in blood under each exposure condition (cf. Figs.4A and 6A with Fig.7A).
The mean cumulative percentage of dose excreted per interval of 8 h as TCA and TCE *in each subject* is shown in Figure 7B.

3.4. Total Recovery of Trichloroethylene

The total amount of TRI excreted in exhaled air after exposure was estimated from the course of the elimination curve of each subject under each condition multiplied by mean individual respiratory minute volume during exposure at rest. Table 5 shows that 10% (7 - 17%) of the dose was exhaled. The total amount of TCE excreted in urine for each subject was extrapolated from the measured amounts excreted within the 66 h after exposure. The mean percentage excreted as TCE (Table 5) was 40% (28 - 52%). The amount of TCE excreted in exhaled air was no more than 2% of the amount excreted in urine. Although only part of the TCA excretion was measured (till 66 h after exposure), the amount excreted after 66 h was estimated with the formula described under 2.9. The apparent distribution volumes referenced to TCA concentration in total blood in the subjects A, B, C and D were 3, 10, 8, and 12 l, respectively. The estimated mean percentage of dose excreted as TCA in urine was 18% (7 - 27%). There is a tendency that with increasing dose total recovery decreases.

Table 5
Percentage of dose excreted as TRI in exhaled air and as TCE and TCA in urine and total recovery (%) after exposure of 4 volunteers to 4 conditions

Subject	70 ppm TRI at rest				70 ppm TRI at rest and workload				140 ppm TRI at rest				140 ppm TRI at rest and workload			
	TRI	TCE	TCA	Total	TRI	TCE	TCA	Total	TRI	TCE	TCA	Total	TRI	TCE	TCA	Total
A	7	51	13	71	9	52	9	70	7	45	8	60	9	38	7	54
B	11	38	25	74	17	43	16	76	8	39	21	68	8	28	21	57
C	13	42	19	74	10	35	20	65	7	31	14	52	12	31	16	50
D	11	40	27	78	8	38	26	72	9	43	25	70	11	37	20	68

4. DISCUSSION

4.1. Dose

There exist only a few reports on retention of TRI; higher and lower values have been reported than in our experiments: Soucek and Vlachova (1960), 58 - 70%; Bartonicek (1962), 51 - 64%; Nomiyama and Nomiyama (1971, 1974), 28 - 47% and 33 ± 10%; Fernandez et al. (1975), 74%. However, determination of retention as such does not give an adequate picture of the uptake, if the minute volume is not known at the same time. Therefore the use of lung clearance as a parameter is to be recommended for measuring respiratory uptake (van Rees, 1964) because it allows calculation of the dose absorbed per min.
The lung clearance measured in our experiment (4.3 l/min) is smaller than in the experiment of Fernandez et al. (1975) (4.6 l/min) sampling alveolar air, and higher than observed by Bartonicek (1962) (3.7 l/min) sampling exhaled air. The values used by Nomiyama and Nomiyama (1974) (1.8 l/min) concerning respiratory uptake can seriously be questioned, because they only measured retention. Retention and also dose per minute decrease with increasing saturation of the body until there is a dynamic equilibrium between uptake into and release from blood (to tissues and by metabolism). In the case of TRI this equilibrium is achieved very rapidly; we found that after 5 min exposure the lung clearance already has reached a constant level. This conforms to the results of Fernandez et al. (1975) who sampled alveolar air.

4.2. Workload

Only a few inhalation experiments have been carried out during workload. Zenz and Berg (1970) observed that in the postexposure phase expired air concentrations increase proportionally to workload.

From the data of Åstrand (1975) for TRI concerning exposure periods of 30 min with and without workload, it can be concluded that when ventilation increases in conjunction with physical exercise, concentration in alveolar air and blood will also increase until a new equilibrium is established. The doses mentioned were proportional to concentrations while the dose with 50 W workload was 2 times the dose at rest; with continuing work load the dose decreased; with increasing workload the increase in dose was smaller than the increase in ventilation. This is in agreement with our results that under comparable conditions the dose was proportional to concentration. We found that the dose during 100 W workload was 2.5 times higher than at rest; the dose during the second workload was about 15% lower than during the first workload (higher saturation of the body).

4.3. Concentrations in Blood, Exhaled Air and Urine

4.3.1. Trichloroethylene. Use of breath analysis for the purpose of estimating recent and time-weighted average exposure to TRI was recommended by Stewart et al. (1974) who pointed out that the optimal time for collection of a breath sample which will most accurately reflect the time-weighted exposure, is in the period 12 - 16 h following exposure. We found during more than 60 h after exposure that the concentration of TRI in blood as well as in exhaled air was proportional to the dose, but the inter-individual variation was large, probably attributable to differences in adipose tissues. Besides the concentration in exhaled air we also calculated the amount of TRI exhaled during the 1 min normal breathing, but this yielded no better correlation with TRI in blood.

4.3.2. Trichloroethanol (TCE). The time course of TCE in blood is comparable with other short term exposures as described by Kimmerle and Eben (1973), Müller et al. (1974, 1975), and Vesterberg and Åstrand (1976).

There was a tendency that with increasing dose the maximum concentration of TCE blood/dose decreased. This was also reflected in the percentage excreted in urine. For each subject, in observing different conditions, there was a linear relation between the maximum concentration of TCE in blood and the total amount excreted in urine. However, the slope of this relation varied widely between subjects. When the (lean) body mass is taken into account, the variation does not diminish.

4.3.3. Trichloroacetic Acid (TCA). The time course of TCA in blood is comparable to other short-term exposures as described by Müller et al. (1974, 1975) and Vesterberg and Åstrand (1976). Here also there was a tendency that with increasing dose the concentration of TCA blood/dose and the percentage excreted in urine decreased. This is in agreement with the results of Ikeda et al. (1972) who observed that in workers the amount of TCA excreted in urine was no longer proportional to the concentration if exposure exceeded 50 ppm, 8 h a day, 6 days a week. As with TCE the slope of the linear relation between the maximum concentration of TCA in blood and the total amount excreted in urine varied widely between subjects, also when taking into account the (lean) body mass. These individual differences also find expression in the individual distribution volume of TCA already mentioned under 3.4.

4.4. Recovery

An average of 10% (6 - 17) of the dose was eliminated as TRI after exposure by the lungs, whereas 57% (45 - 68) of the dose was eliminated in urine as TCE (39%: 28 - 51) and TCA (18%: 7 - 27). This accords with the data reported by Fernandez et al. (1975), Soucek et al. (1955), and Bartonicek (1962).

Soucek et al. (1955, 1960) suggest for the remaining part the metabolites chloroform and monochloroacetic acid. We did not find chloroform in exhaled air, although the detection method used was sensitive enough. Nor did we find monochloroacetic acid in blood or urine, but the detection limit of the method we used was high (20 mg/l).

4.5. Biological Monitoring

The difference in behaviour of TCE and TCA in blood and urine and also the large inter- and intraindividual variations make estimation of the magnitude of previous exposure to TRI a difficult affair.

The study reported is part of a larger program; in future papers the results of 5-day exposure to TRI, and 1-day exposure to 1,1,1-trichloroethane and tetrachloroethylene will be reported. In reviewing the data of the total series, and the literature, the applicability of biological monitoring in workers exposed to chlorinated hydrocarbon solvars will be discussed more fully.

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REFERENCES

Åstrand, I.: Uptake of solvents in blood and tissues of man: a review. Scand.J.Work environm.Hlth 1, 199-218 (1975)

Bartonicek, V.: Metabolism and excretion of trichloroethylene by human subjects. Brit.J.industr.Med. 19, 134-141 (1962)

Duba, W.C.: Studium der mentalen Belastung bei kurzfristiger Einatmung von Trichloräthylen in einem Expositionsraum. II. Beschreibung des Expositionsraums. Staub-Reinhalt.Luft 35, 410-412 (1975)

Fernandez, J.G., Humbert, B.E., Droz, P.O., Caperos, J.R.: Exposition au trichloréthylène. Bilan de l'absorption, de l'excrétion et du metabolisme sur des sujets humains. Arch.Mal.prof. 35, 397-407 (1975)

Ikeda, M., Ohtsuji, H., Imamura, T., Komoike, Y.: Urinary excretion of total trichloro-compounds, trichloroethanol, and trichloroacetic acid as a measure of exposure to trichloroethylene and tetrachloroethylene. Brit. J.industr.Med. 29, 328-333 (1972)

Kimmerle, G., Eben, A.: Metabolisme, excretion and toxicology of trichloroethylene after inhalation. II. Experimental human exposure. Arch.Toxicol. 30, 127-138 (1973)

Monster, A.C., Boersma, G.: Simultaneous determination of trichloroethylene and metabolites in blood and exhaled air by gas chromatography. Int.Arch. Occup.Environ.Hlth 35, 155-163 (1975)

Müller, G., Spassovski, M., Henschler, D.: Metabolism of trichloroethylene in man. II. Pharmacokinetics of metabolites. Arch.Toxicol. 32, 283-295 (1974)

Müller, G., Spassovski, M., Henschler, D.: Metabolism of trichloroethylene in man. III. Interaction of trichloroethylene and ethanol. Arch.Toxicol. 33, 173-189 (1975)

Nomiyama, K., Nomiyama, H.: Metabolism of trichloroethylene in human, sex difference in urinary excretion of trichloroacetic acid and trichloroethanol. Int.Arch.Arbeitsmed. 28, 37-48 (1971)

Nomiyama, K., Nomiyama, H.: Respiratory retention uptake and excretion of organic solvents in man. Int.Arch.Arbeitsmed. 32, 75-84 (1974)

Paykoc, Z.V., Powell, J.F.: The excretion of sodiumtrichloracetate. J.Pharmacol.Exp.Ther. 85, 289-293 (1945)

van Rees, H.: De respiratoire opname van niet-inerte gassen en dampen. Proefschrift, Leiden (1964)

Sellers, E.M., Koch-Weser, J.: Kinetics and clinical importance of displacement of warfarin from albumin by acidic drugs. Ann.N.Y.Acad.Sci. 179, 213 (1971)

Soucek, B., Teisinger, J., Vlachova, D.: Chloroform jako metabolit trichloroethylene. Pracov.Lék. 7, 143 (1955)
Soucek, B., Vlachova, D.: Excretion of trichloroethylene metabolites in human urine. Brit.J.industr.Med. 17, 60-64 (1960)
Stewart, R.D., Hake, C.L., Peterson, J.E.: Use of breath analysis to monitor trichloroethylene exposures. Arch.environm.Hlth 29, 6-13 (1974)
Vesterberg, O., Åstrand, I.: Exposure to trichloroethylene monitored by analysis of metabolites in blood and urine. J.occup.Med. 18, 224-226 (1976)
Weichart, H., Bardodej, Z.: Die Bestimmung von Trichloressigsäure und Trichloräthanol im Urin von TRI-Arbeitern. Zbl.Arbeitsmed. 20, 219-221 (1970)
Zenz, C., Berg, B.A.: Influence of submaximal work on solvent uptake. J.occup.Med. 12, 367-369 (1970)

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