THE SOLUBILITY OR DISTRIBUTION COEFFICIENT OF TRICHLORETHYLENE IN WATER, WHOLE BLOOD, AND PLASMA

BY

JOAN F. POWELL*

From the Nuffield Department of Clinical Medicine, The Radcliffe Infirmary, Oxford

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In a previous paper (Powell, 1945a) the elimination of trichlorethylene and its metabolite, trichloroacetic acid, was studied. The present investigation is concerned with the solubility properties of trichlorethylene, upon which its initial absorption and transference in the body depend.

Methods

To determine the solubility of trichlorethylene in water, whole blood, and plasma, similar techniques were used to those employed in determining the solubility of carbon tetrachloride (Powell, 1945b). Trichlorethylene-air mixtures were made up in gas cylinders under pressure. The trichlorethylene concentration varied between 500 and 8,000 vapour parts per million, that is, 0.26 to 3.9 mg. per 100 ml., the maximum pressure allowable being calculated from the saturated vapour concentration at 20° C. To produce higher concentrations, an Oxford vaporizer was used (Epstein and others, 1941).

Water was equilibrated with gas mixture by a simple bubbling technique. For the equilibration of blood and plasma, an apparatus containing a rotating tonometer was used. Blood was obtained from normal donors, unless otherwise stated, oxalate being used as an anticoagulant. Haemoglobin was measured by Haldane's carboxyhaemoglobin method. Plasma proteins were determined by the micro-Kjeldahl technique, and plasma fats by the method of Bloor (1928).

A slight modification was introduced in the estimation of trichlorethylene by treatment with pyridine and alkali (Haggood and Powell, 1945). It was found that the reaction could be made rather more sensitive by adding 1 ml. of 1 per cent. hydrochloric acid to the final orange-coloured solution. This gave a yellow colour which was measured with a filter transmitting at 430 m.μ.

Results

The results obtained by equilibrating water with trichlorethylene-air mixtures at 20° C. and 37° C. are shown in Table 1. The trichlorethylene absorbed is directly proportional to its concentration in the gas, the Ostwald solubility, or distribution coefficient, being 3.0 ± 0.1 at 20° C., and 1.55 ± 0.05 at 37° C. This relationship is maintained from a concentration of 0.26 mg. per 100 ml. to saturation.

As may be seen from Tables 2A and 2B, the distribution coefficient for whole blood varies between 18 and 22 at 20° C., and between 8 and 10 at 37° C. There is no direct relationship between haemoglobin content of whole blood and its trichlorethylene absorption. Three blood samples of haemoglobin 64 per cent., 90 per cent., and 110 per cent., were equilibrated at 22° C. with air containing

TABLE 1
SOLUBILITY OF TRICHLORETHYLENE IN WATER AT 20° C. AND 37° C.

Trichlorethylene (mg./100 ml.)			$\frac{^{\circ}\text{Water}}{^{\circ}\text{Air}}$	
Air	Water		20° C.	37° C.
	20° C.	37° C.		
0.26	0.77	0.42	3.0	1.6
0.55	1.70	0.90	3.1	1.6
1.08	3.12	—	2.9	—
1.23	3.75	1.78	3.1	1.5
2.10	6.38	—	3.0	—
2.22	6.88	3.72	3.1	1.6
11.0	34.5	—	3.1	—
15.8	49.5	—	3.1	—
†43.0	127	†122	3.0	1.5

† Concentration of trichlorethylene in saturated vapour at 37° C. is 84 mg. per 100 ml.

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0.55 mg. per 100 ml. The distribution coefficients were 19, 21, and 19 respectively. Further examples of this kind can be seen in Tables 2A and 2B.

It was found, however, that solutions of hæmoglobin in water absorbed trichlorethylene in proportion to their hæmoglobin content. To prepare these hæmoglobin solutions, washed erythrocytes were lysed with water and centrifuged at high speed to bring down cell envelopes and stroma. The results obtained with these solutions are illustrated in the figure. It was also found that red cell constituents other than hæmoglobin do not influence the uptake of trichlorethylene. Thus, a washed cell suspension of hæmoglobin 86 per cent. absorbed 3.12 mg. per 100 ml. in contact with air containing 0.28 mg. of trichlorethylene per 100 ml. An

TABLE 2A
SOLUBILITY OF TRICHLORETHYLENE IN BLOOD AT 20° C. AND 37° C.

Donor	Trichlorethylene (mg./100 ml.)			$\frac{^{\circ}\text{Blood}}{^{\circ}\text{Air}}$	
	In Air 0.55mg./100ml.) 1,000 v.p.p.m.	In Blood			
		20° C.	37° C.	20° C.	37° C.
(1.) Hæmo- globin 122%	0.28 0.56 1.10 2.06	5.30 11.3 20.7 41.0	2.55 — 11.3 20.8	19 20 19 20	9.1 — 10 10
(2.) Hæmo- globin 98%	0.28 0.56 1.10 2.06	5.85 12.0 23.0 41.2	2.41 5.75 9.94 18.5	21 21 21 21	8.7 10 9.0 9.0
(3.) Hæmo- globin 88%	0.26 0.55 1.08 2.10	4.65 10.6 21.0 39.0	— 4.30 9.70 —	18 19 20 19	— 7.8 8.8 —

TABLE 2B
SOLUBILITY OF TRICHLORETHYLENE IN BLOOD AT 20° C.

Donor	Trichlorethylene (mg./100 ml.)		$\frac{^{\circ}\text{Blood}}{^{\circ}\text{Air}}$
	Air	Blood	
4. Hæmoglobin 118%	0.29 0.60 1.10 17.1	6.10 13.3 22.8 36.0	21 22 21 21
5. Hæmoglobin 110%	1.23 2.22 5.28 10.7	23.1 43.3 95.6 194	19 19 18 18

equivalent hæmoglobin solution prepared in the above manner absorbed 3.33 mg. of trichlorethylene per 100 ml. from the same gas mixture.

In Table 3 the solubility of trichlorethylene in whole blood is compared with that in plasma. It is seen that red cells absorb relatively more trichlorethylene than does plasma, the distribution coefficient in the latter case ranging from 15 to 20.

TABLE 3
SOLUBILITY OF TRICHLORETHYLENE IN BLOOD AND PLASMA AT 20° C.

% Hb (Haldane)	Trichlorethylene (mg./100 ml.)			$\frac{^{\circ}\text{Blood}}{^{\circ}\text{Air}}$	$\frac{^{\circ}\text{Plasma}}{^{\circ}\text{Air}}$
	Air	Blood	Plasma		
64	0.55	10.2	9.40	19	17
118	0.30	6.10	5.95	20	20
122	0.28 2.06	5.30 41.0	4.65 39.0	19 20	17 19
88	1.08 2.10	21.0 39.0	15.9 34.3	20 19	15 16
112	5.28 10.7	95.6 194	85.3 180	18 18	16 17
98	0.56 1.10 2.06	12.0 23.0 41.2	10.3 19.0 37.6	21 21 20	18 17 18

TABLE 4
SOLUBILITY OF TRICHLORETHYLENE IN PLASMA AT 20° C.

Donor	Plasma		Trichlor- ethylene (mg./100 ml.)	$\frac{^{\circ}\text{Plasma}}{^{\circ}\text{Air}}$		
	fat (mg./100 ml.)	protein (g./100 ml.)				
			Air		Plasma	
Normal ..	570	7.2	} 2.13	42.4	20	
Normal ..	594	7.0		42.6	20	
Anæmia ..	480	7.9		46.0	22	
Leukæmia ..	510	6.0		30.5	14	
Anæmia ..	386	5.5		30.0	14	
Normal ..	720	8.1	} 0.55	12.0	22	
Normal ..	580	7.0		10.3	21	
Sprue ..	590	6.0		9.36	17	
Ileitis ..	360	7.3		9.01	16	
Normal ..	770	7.4	} 0.26	5.40	21	
Neoplasm ..	710	7.2		5.36	21	
Diabetes }	1,020	5.2		4.51	18	
Nephritis }						
Leukæmia ..	786	4.9		4.35	17	
Liver damage	504	5.6		3.70	14	
Nephrosis ..	620	5.1		3.15	12	

TABLE 5
SOLUBILITY OF TRICHLORETHYLENE AND CARBON TETRACHLORIDE IN FAT
EMULSIONS AT 20° C.

	Oleyl alcohol (450 mg./100 ml.)		Oleic acid (1,000 mg./100 ml.)		Arachis oil (900 mg./100 ml.)	
	Chlorhydro- carbon absorbed (mg./100 ml.)	Distribution coefficient	Chlorhydro- carbon absorbed (mg./100 ml.)	Distribution coefficient	Chlorhydro- carbon absorbed (mg./100 ml.)	Distribution coefficient
Carbon tetrachloride- air mixture (0.72 mg./100 ml.)	8.58	12	18.2	25	14.0	20
Trichlorethylene-air mixture (0.55 mg./100 ml.)	3.33	6.0	6.50	12	8.10	15

An attempt was made to determine whether the trichlorethylene distribution coefficient of plasma was related to its protein and fat content. The data given in Table 4 were used in the calculation, giving a value for b_1 , the partial regression coefficient for trichlorethylene solubility on protein of 2.750 ± 0.369 . The corresponding figure b_2 for fat was 0.00963 ± 0.00233 . The value for b_1 would occur by chance in less than 1 in 1,000 times, and that for b_2 in less than 1 in 100 times. The trichlorethylene absorption of plasma is almost certainly dependent, therefore, on its protein content and probably on its fat content.

This conclusion is supported by the results obtained on equilibrating fat emulsions in water at 20° C. with a gas mixture containing 0.55 mg. of trichlorethylene per 100 ml. Emulsions of oleyl alcohol, oleic acid, and arachis oil were used—these substances being considered as models for plasma cholesterol, fatty acid, and neutral fat respectively. No attempt could be made to assess the absorption of phospholipids, owing to the chemical instability of these compounds. The results are summarized in Table 5, together with a set of corresponding values for a carbon tetrachloride-air mixture containing 0.72 mg. per 100 ml. The distribution coefficients found for trichlorethylene were low compared with those given by plasma of equivalent fat content. On the other hand carbon tetrachloride-air mixture equilibrated with oleyl alcohol gave a distribution coefficient comparable with that of normal plasma. The more concentrated oleic acid and arachis oil emulsions gave very high distribution coefficients with carbon tetrachloride. Unfortunately no figures are available for comparison of these latter figures with those given by plasma containing an equivalent amount of

fat. Assuming that carbon tetrachloride absorption is proportional to the amount of fat present, oleic acid and arachis oil at lower concentrations will give roughly the same distribution coefficients as the oleyl alcohol emulsion.

Discussion

Trichlorethylene is more soluble in water than carbon tetrachloride, but less soluble than chloroform. In the case of whole blood, the distribution coefficient of both trichlorethylene and chloroform (Nicloux, 1929) is in the region of 20 at 20° C., and 9 at 37° C.—values markedly higher than those obtained for carbon tetrachloride (Powell, 1945b). This may be accounted for partly by the affinity of trichlorethylene and chloroform (Scotti-Foglieni, 1930) and the non-affinity of carbon tetrachloride, for hæmoglobin. Both chloroform and trichlorethylene are rather less soluble in plasma than in whole blood, this being in contrast with carbon tetrachloride, where the distribution coefficient at 20° C. is in the region of 4.5 for whole blood and 9 for plasma.

The results obtained with fat emulsions indicate that the plasma fat concentration cannot wholly account for the amount of trichlorethylene absorbed. Taking into consideration the affinity of trichlorethylene for hæmoglobin, it is reasonable to assume that the plasma proteins are also concerned with its uptake. The correlation between the distribution coefficient of plasma and its fat and protein content tends to confirm this.

In the case of carbon tetrachloride, fat emulsions roughly equivalent in fat content to normal plasma give distribution coefficients of 12. It seems, therefore, that plasma fat can wholly account for the carbon tetrachloride taken up, and that plasma

proteins and hæmoglobin do not influence the absorption. It seems possible that the affinity of all three chlorhydrocarbons for plasma fat involves a simple solution process, while the attachment of trichlorethylene and chloroform to protein may depend on an absorption process for which the non-polar carbon tetrachloride molecule is particularly unsuited.

Solubility of trichlorethylene in hæmoglobin solutions at 20° C.

Summary

The distribution coefficient of trichlorethylene between water and air is 3.0 at 20° C. and 1.6 at 37° C. The air concentration used varied between 0.26 and 15.8 mg. per 100 ml.

The distribution coefficient between blood and air is constant in a given specimen of blood throughout the above concentration range. The coefficient in a series of specimens ranged between 18 and 22 at 20° C., and between 7.8 and 10 at 37° C.

Hæmoglobin solutions in water absorb trichlorethylene in proportion to their hæmoglobin content.

The distribution coefficient of trichlorethylene between plasma and air varies between 16 and 20 at 20° C.

Evidence has been obtained that the absorption of trichlorethylene by plasma is correlated with its fat and protein content.

The absorption of carbon tetrachloride by the blood probably depends on the concentration of plasma fat alone, and is uninfluenced by plasma proteins and hæmoglobin.

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