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Differences following skin or inhalation exposure in the absorption and excretion kinetics of trichloroethylene and toluene

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ABSTRACT The concentrations of trichloroethylene in breath and blood and the urinary excretion of its metabolites following 30 minutes' direct immersion of one hand in the liquid, were compared with those obtained after four hours' inhalation exposure to the vapour of 100 ppm, described in a previous paper. The comparison shows that the end-tidal air concentrations during the first two hours of the post-exposure period were about twice as high in the case of skin exposure as in that of inhalation exposure, although the uptake of the solvent through the skin was only about one-third of the inhaled uptake. A kinetic approach suggested that differences in trichloroethylene movement in the body would be a principal cause of this discrepancy. The results of a similar series of experiments using toluene suggested that it is less readily taken up than trichloroethylene through the skin. It was concluded from the present investigation that analyses of not only breath but also of blood or urine are necessary for the evaluation of skin exposure, and also that trichloroethylene and toluene would rarely be absorbed through the skin in toxic quantities during normal industrial use.

Most organic solvents are highly volatile; this means that inhalation is the major route of absorption into the body. Some industrial solvents, however, have been known to penetrate human skin (Stewart and Dodd, 1964; Dutkiewicz and Tyras, 1967, 1968a, 1968b; Guillemin *et al.*, 1974). The reported absorption rates through the human skin for toluene, ethylbenzene, xylene, and styrene are very high (Dutkiewicz and Tyras, 1967, 1968a, 1968b). Animal experiments have also suggested that some hydrocarbons are likely to be absorbed in toxic quantities by skin contact (Tsuruta, 1975; Wahlberg, 1976). These investigations suggest that in some work conditions skin could be a major route of absorption in addition to that of inhalation.

As a measure of skin absorption of organic solvents their rates of decay in alveolar air have been analysed and compared with those following inhalation exposure (Stewart and Dodd, 1964; Guillemin *et al.*, 1974). It is doubtful, however, whether breath concentration alone is a reliable index of skin absorption. In fact, it has been suggested that substantial differences in pharmacokinetics of foreign compounds may arise when these substances are absorbed by different routes (Dollery *et al.*, 1971). For example, a difference in the metabolic fate of ethylbenzene following skin or inhalation exposure was reported by Dutkiewicz and Tyras (1967).

Excretion kinetics of benzene, toluene and trichloroethylene after inhalation exposure were reported previously (Sato *et al.*, 1974, 1977). The aim of the present investigation was to study the difference in absorption and excretion kinetics of trichloroethylene and toluene after skin contact or inhalation.

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Methods

TRICHLOROETHYLENE

Four healthy males, one member of the laboratory staff and three medical students, age range 21-34 years, volunteered for the skin absorption study. They each immersed a single hand up to the wrist for 30 minutes in liquid trichloroethylene in a large vial. The top of the vial was covered with a double polyvinylidene chloride synthetic membrane having an opening through which the hand was inserted. The opening was fitted snugly round the volunteers'

forearms with an elastic band. Leakage of the solvent vapour was prevented by placing the vial in a polyvinylidene chloride bag which was fixed to the lip of the vial and to the forearm about 10 cm above the wrist. To avoid any inhalation of trichloroethylene the volunteer wore a breathing mask with a non-rebreathing valve which was supplied continuously with abundant fresh air. Immediately after the exposure the skin was wiped with gauze. The solvent adsorbed to the skin was then rapidly evaporated by blowing warm air from a motor-driven drier. At predetermined intervals after the exposure the concentrations of trichloroethylene in breath and blood were determined: blood samples were collected from the cubital vein of the unexposed arm. The method of determination has been reported previously (Sato *et al.*, 1977). Metabolites of trichloroethylene in urine, i.e. total trichlorocompounds (TTC), trichloroacetic acid (TCA) and trichloroethanol (TCE), were measured according to the method of Tanaka and Ikeda (1968), where TTC = TCA + TCE.

The time-course of breath and blood concentration of trichloroethylene and urinary excretion of its metabolites were compared with those obtained from four hours' inhalation exposure to 100 ppm of trichloroethylene vapour, described in a previous paper (Sato *et al.*, 1977).

TOLUENE

Skin exposure

Five male medical students, 21-24 years old, served as the subjects. The method of exposure was the same as described for trichloroethylene. During and after the exposure toluene concentrations in blood were determined by means of a vial-equilibration method (Sato *et al.*, 1975).

Inhalation exposure

Five male volunteers, all medical students aged 22-24 years, inhaled 100 ppm of toluene for two hours. The method of exposure has been reported elsewhere (Sato *et al.*, 1974). During and after the exposure blood concentrations of toluene were determined in the same way as for skin exposure.

Results

The time-course of breath and blood concentrations of trichloroethylene are shown in Table 1, and the urinary excretion data are shown in Table 2. The data of inhalation exposure reported previously in this journal (Sato *et al.*, 1977) are also presented in Tables 1 and 2 for comparison. As seen in Table 1, up to three hours after exposure the concentration in the end-tidal air was considerably higher following skin contact than it was after inhalation. This gave us the initial impression that the amount entering the body through the skin by 30 minutes' contact of one hand with liquid trichloroethylene was greater than the amount taken up through the lungs in the four-hour exposure by inhalation of 100 ppm vapour. However, with the exception of the first 15 minutes, the venous blood concentration following skin exposure was always lower than that following inhalation exposure. In addition, the amount of metabolites excreted in the urine following skin exposure was much smaller than that excreted following inhalation exposure (Table 2). These findings suggest that the processes of absorption and excretion may be quite different for the two penetration routes.

In the case of toluene exposure, when one hand was immersed in liquid toluene for one minute, hardly any toluene could be detected in the venous blood. Even after a 30-minute immersion, the maximum blood concentration was not more than a quarter of that achieved in the two-hour inhalation exposure to 100 ppm of toluene vapour (Fig. 1), which shows that toluene may be less easily absorbed than trichloroethylene. The skin exposure to toluene also differed from that to trichloroethylene in that the maximum concentration was maintained for 10-15 minutes after exposure had ended.

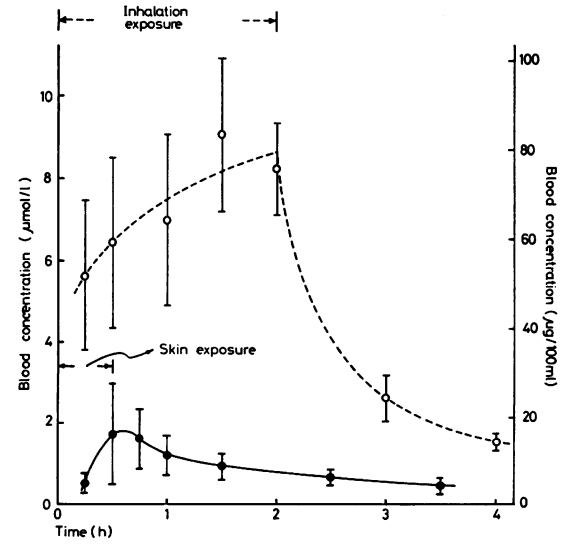

Fig. 1 *Time-course of toluene concentration in blood following skin (dots) and inhalation (circles) exposure. Vertical lines represent mean value ±SD (n = 5).*

Table 1 *Time-course of trichloroethylene concentration in breath and venous blood after skin (one hand for 30 min) and inhalation (100 ppm for 4 h) exposure*

Time in hours	*Trichloroethylene in breath; μmol/l (μg/100 ml)*		*Trichlorethylene in blood; μmol/l (μg/100 ml)*	
	Skin	*Inhalation**	*Skin*	*Inhalation**
0	—	1·943 ± 0·632 (25·53 ± 8·31)	15·457 ± 5·012 (203·11 ± 65·86)	13·011 ± 1·113 (170·97 ± 14·63)
0·08	2·181 ± 0·322 (28·66 ± 4·23)	—	—	—
0·17	—	0·302 ± 0·063 (3·97 ± 0·83)	—	4·896 ± 0·573 (64·33 ± 7·53)
0·25	0·810 ± 0·107 (10·64 ± 1·40)	—	8·098 ± 1·749 (106·41 ± 22·98)	—
0·5	0·441 ± 0·101 (5·80 ± 1·33)	0·200 ± 0·065 (2·63 ± 0·86)	2·593 ± 0·500 (34·07 ± 6·57)	3·278 ± 0·284 (43·07 ± 3·73)
0·75	0·276 ± 0·043 (3·63 ± 0·56)	—	—	—
1	0·184 ± 0·029 (2·42 ± 0·38)	0·129 ± 0·028 (1·69 ± 0·37)	1·682 ± 0·333 (22·10 ± 4·37)	2·203 ± 0·319 (28·95 ± 4·19)
1·5	0·148 ± 0·021 (1·94 ± 0·27)	0·101 ± 0·007 (1·33 ± 0·09)	—	1·658 ± 0·307 (21·79 ± 4·03)
2	0·110 ± 0·023 (1·45 ± 0·30)	0·079 ± 0·024 (1·04 ± 0·32)	1·187 ± 0·201 (15·60 ± 2·64)	1·336 ± 0·198 (17·56 ± 2·60)
2·5	0·086 ± 0·016 (1·13 ± 0·21)	0·062 ± 0·028 (0·82 ± 0·37)	—	—
3	0·054 ± 0·011 (0·71 ± 0·14)	0·061 ± 0·011 (0·80 ± 0·14)	0·831 ± 0·161 (10·92 ± 2·12)	1·068 ± 0·160 (14·04 ± 2·10)
3·5	0·049 ± 0·010 (0·64 ± 0·13)	0·054 ± 0·011 (0·71 ± 0·15)	—	—
4	0·041 ± 0·008 (0·54 ± 0·10)	0·049 ± 0·012 (0·64 ± 0·16)	0·730 ± 0·133 (9·59 ± 1·75)	0·865 ± 0·154 (11·37 ± 2·02)
4·5	0·037 ± 0·014 (0·49 ± 0·19)	0·043 ± 0·009 (0·56 ± 0·12)	—	—
5	0·033 ± 0·008 (0·44 ± 0·11)	0·042 ± 0·007 (0·55 ± 0·09)	—	—
5.5	0·031 ± 0·005 (0·41 ± 0·07)	—	—	—
6	0·030 ± 0·006 (0·40 ± 0·08)	0·033 ± 0·008 (0·44 ± 0·11)	0·481 ± 0·070 (6·32 ± 0·92)	0·583 ± 0·083 (7·66 ± 1·09)
6·5	0·027 ± 0·006 (0·36 ± 0·08)	—	—	—
7	0·027 ± 0·006 (0·35 ± 0·08)	0·027 ± 0·006 (0·36 ± 0·08)	—	—
7·5	0·021 ± 0·006 (0·28 ± 0·08)	—	—	—
8	0·021 ± 0·005 (0·27 ± 0·06)	0·021 ± 0·004 (0·28 ± 0·05)	0·333 ± 0·060 (4·37 ± 0·79)	0·392 ± 0·093 (5·15 ± 1·22)
8·5	0·017 ± 0·006 (0·22 ± 0·08)	—	—	—
9	0·016 ± 0·006 (0·21 ± 0·08)	0·021 ± 0·003 (0·27 ± 0·04)	—	—
9·5	0·015 ± 0·004 (0·20 ± 0·05)	—	—	—
10	0·016 ± 0·006 (0·21 ± 0·08)	0·016 ± 0·002 (0·21 ± 0·02)	0·244 ± 0·051 (3·21 ± 0·67)	0·259 ± 0·046 (3·40 ± 0·61)

Figures are mean ±SD (n = 4).
*These data have been reported previously (Sato *et al.*, 1977).

There was also a marked difference between the effects of trichloroethylene and toluene on skin. During immersion of the hand in trichloroethylene all subjects complained, not only of a burning sensation which increased in intensity with time, but also of a distinct pain towards the end of exposure; in one subject this pain was excruciating. On contact with toluene the subjects complained only of a mild burning sensation towards the middle of the exposure period. When the hands were removed from trichloroethylene a moderate degree of erythema which lasted for over an hour was noted on their backs;

Table 2 *Cumulative urinary excretion (X_D) of TCA, TCE and TTC after skin (one hand for 30 min) and inhalation (100 ppm for 4 h) exposure*

Time in hours	*TCA μmol (mg)*		*TCE μmol (mg)*		*TTC (mg)*	
	Skin	*Inhalation**	*Skin*	*Inhalation**	*Skin*	*Inhalation**
1	—	1·2 ± 1·2 (0·2 ± 0·2)	—	87·2 ± 22·1 (13·0 ± 3·3)	—	(13·2 ± 3·1)
2	3·7 ± 3·7 (0·6 ± 0·6)	3·1 ± 0·6 (0·5 ± 0·1)	60·4 ± 15·4 (9·0 ± 2·3)	161·1 ± 51·7 (24·0 ± 7·7)	(9·6 ± 2·5)	(24·5 ± 7·7)
4	4·9 ± 3·1 (0·8 ± 0·5)	6·1 ± 2·5 (1·0 ± 0·4)	115·4 ± 30·2 (17·2 ± 4·5)	305·4 ± 119·5 (45·5 ± 17·8)	(18·0 ± 4·3)	(46·5 ± 17·8)
6	11·0 ± 6·7 (1·8 ± 1·1)	—	168·5 ± 46·3 (25·1 ± 6·9)	—	(26·9 ± 5·9)	—
8	13·5 ± 8·6 (2·2 ± 1·4)	20·9 ± 11·7 (3·4 ± 1·9)	212·8 ± 53·0 (31·7 ± 7·9)	549·0 ± 153·0 (81·8 ± 22·8)	(33·9 ± 6·6)	(85·2 ± 23·1)
10	16·0 ± 8·6 (2·6 ± 1·4)	—	246·3 ± 55·0 (36·7 ± 8·2)	—	(39·3 ± 7·1)	—
12	19·0 ± 8·0 (3·1 ± 1·3)	28·8 ± 13·5 (4·7 ± 2·2)	294·0 ± 73·2 (43·8 ± 10·9)	759·7 ± 196·0 (113·2 ± 29·2)	(46·9 ± 9·9)	(117·9 ± 29·7)
16	—	34·4 ± 12·9 (5·6 ± 2·1)	—	938·9 ± 221·5 (139·9 ± 33·0)	—	(145·5 ± 33·4)
24	33·7 ± 10·4 (5·5 ± 1·7)	47·9 ± 17·8 (7·8 ± 2·9)	431·5 ± 124·8 (64·3 ± 18·6)	1164·4 ± 228·9 (173·5 ± 34·1)	(69·8 ± 17·8)	(181·3 ± 34·7)
36	55·8 ± 21·5 (9·1 ± 3·5)	74·2 ± 25·2 (12·1 ± 4·1)	519·5 ± 173·8 (77·4 ± 25·9)	1430·9 ± 263·8 (213·2 ± 39·3)	(86·5 ± 26·5)	(225·3 ± 39·8)
48	72·4 ± 24·5 (11·8 ± 4·0)	124·5 ± 38·0 (20·3 ± 6·2)	571·1 ± 182·6 (85·1 ± 27·2)	1582·6 ± 251·7 (235·8 ± 37·5)	(96·9 ± 27·9)	(256·0 ± 37·9)
60	96·9 ± 35·0 (15·8 ± 5·7)	172·4 ± 42·3 (28·1 ± 6·9)	605·4 ± 206·0 (90·2 ± 30·7)	1696·6 ± 255·7 (252·8 ± 38·1)	(105·8 ± 31·4)	(280·9 ± 38·4)
72	108·0 ± 38·7 (17·6 ± 6·3)	220·2 ± 40·5 (35·9 ± 6·6)	626·8 ± 210·1 (93·4 ± 31·3)	1773·8 ± 274·5 (264·3 ± 40·9)	(110·7 ± 31·8)	(300·2 ± 41·3)
84	128·8 ± 36·2 (21·0 ± 5·9)	262·6 ± 52·8 (42·8 ± 8·6)	651·7 ± 209·4 (97·1 ± 31·2)	1817·4 ± 289·3 (270·8 ± 43·1)	(117·9 ± 31·1)	(313·6 ± 41·4)
96	139·9 ± 41·7 (22·8 ± 6·8)	289·6 ± 47·9 (47·2 ± 7·8)	654·4 ± 208·1 (97·5 ± 31·0)	1843·6 ± 290·6 (274·7 ± 43·3)	(120·4 ± 30·7)	(321·9 ± 41·6)
108	165·0 ± 55·8 (26·9 ± 9·1)	317·2 ± 50·9 (51·7 ± 8·3)	655·7 ± 208·7 (97·7 ± 31·1)	1883·9 ± 288·6 (280·7 ± 43·0)	(124·1 ± 31·1)	(332·4 ± 40·3)
120	171·2 ± 60·1 (27·9 ± 9·8)	338·0 ± 46·6 (55·1 ± 7·6)	657·0 ± 208·7 (97·9 ± 31·1)	1904·7 ± 299·3 (283·8 ± 44·6)	(125·2 ± 30·9)	(338·9 ± 42·5)
132	184·7 ± 64·4 (30·1 ± 10·5)	357·7 ± 53·4 (58·3 ± 8·7)	658·4 ± 209·4 (98·1 ± 31·2)	1919·5 ± 304·0 (286·0 ± 45·3)	(127·3 ± 31·4)	(344·3 ± 42·8)
144	195·1 ± 64·4 (31·8 ± 10·5)	382·2 ± 52·8 (62·3 ± 8·6)	658·4 ± 208·7 (98·1 ± 31·1)	1930·2 ± 306·7 (287·6 ± 45·7)	(128·7 ± 31·1)	(349·9 ± 45·1)
156	205·5 ± 65·6 (33·5 ± 10·7)	396·9 ± 53·4 (64·7 ± 8·7)	661·1 ± 210·1 (98·5 ± 31·3)	1936·2 ± 308·1 (288·5 ± 45·9)	(130·6 ± 30·4)	(353·3 ± 45·0)
168	211·7 ± 68·7 (34·5 ± 11·2)	406·1 ± 52·1 (66·2 ± 8·5)	663·8 ± 212·8 (98·9 ± 31·7)	1943·6 ± 306·0 (289·6 ± 45·6)	(131·7 ± 30·3)	(355·8 ± 44·6)
180	—	421·5 ± 52·1 (68·7 ± 8·5)	—	1951·7 ± 307·4 (290·8 ± 45·8)	—	(359·5 ± 45·1)

Figures are mean ±SD (n = 4).
*These data have been reported previously (Sato *et al.*, 1977).

after toluene exposure only a slight degree of erythema was noted which subsided soon after the solvent adsorbed to the skin was wiped and blown away.

Discussion

It was suggested by Dutkiewicz and Tyras (1967) that the metabolism of ethylbenzene after skin absorption might differ from that after lung absorption. However no reason for this has been proposed.

The major metabolic pathway of trichloroethylene is generally considered to be as shown below (Williams, 1959; Daniel, 1963; Byngton and Leibman, 1965):

trichloroethylene $\xrightarrow{\text{step 1}}$ chloral hydrate $\xrightarrow{\text{step 2}}$ TCA, TCE $\xrightarrow{\text{step 3}}$ urinary TCA, TCE

The rate constant for disappearance of trichloro-

ethylene determined from the time-course of its blood or breath concentration has been reported to be in parallel with the rate of metabolism, i.e., the rate constant for step 1 (Sato *et al.*, 1977). The decays in blood and breath shown in Table 1 can be expressed in exponential forms as follows:

For the decay in blood,

$y = 1{\cdot}445e^{-0{\cdot}180t}$ (skin exposure);

$y = 1{\cdot}939e^{-0{\cdot}203t}$ (inhalation exposure);

and for the decay in breath,

$y = 0{\cdot}089e^{-0{\cdot}184t}$ (skin exposure);

$y = 0{\cdot}096e^{-0{\cdot}180t}$ (inhalation exposure);

where y is the concentration in μmol/l and t the time in hours which starts three hours after cessation of exposure.

These equations clearly show that there is no difference in the rates of metabolism between the two penetration routes. Step 2 proceeds so rapidly (Butler, 1948; Marshall and Owens, 1954; Mackay and Cooper, 1962) that chloral hydrate has not been found in blood in human trichloroethylene exposure (Kimmerle and Eben, 1973). Therefore, it can safely be said that this step can be in no sense a rate-limiting one in the metabolism of trichloroethylene. The $D_\infty - X_D$ plots of urinary excretion data against time t (Sato *et al.*, 1977), where X_D represents the cumulative amounts of TCA, TCE or TTC excreted in time t and D_∞ the total amount of the respective metabolite excreted after the exposure, are shown in Fig. 2. The curves approach straight lines, the slope of which gives an estimate of the rate constant for step 3 (Sato *et al.*, 1977). No major difference can be noted between the slopes for skin and inhalation exposures. It is very doubtful, therefore, that metabolism of trichloroethylene when absorbed through the skin is different from that when absorbed through the lungs.

The inhalation exposure was continued for four hours, but the skin exposure for only 30 minutes. It is supposed, therefore, that the body tissues under the inhalation conditions were nearer to equilibrium with the arterial concentration at the time of end-exposure than under the skin exposure conditions, that is, the tissues in the inhalation experiment would have taken up a much greater quantity at the end of exposure than the tissues in the skin contact experiment. This may be a major reason why the amounts of metabolites following skin exposure were so minimal compared with those after inhalation exposure, although a very high end-tidal concentration (and therefore a very high arterial concentration) of trichloroethylene was achieved after the 30-minute skin exposure of one hand. If the skin exposure had been continued for four hours (as in the inhalation exposure experiment) the uptake and hence the total urinary excretion of metabolites would have been considerably greater.

The end-tidal concentrations of trichloroethylene

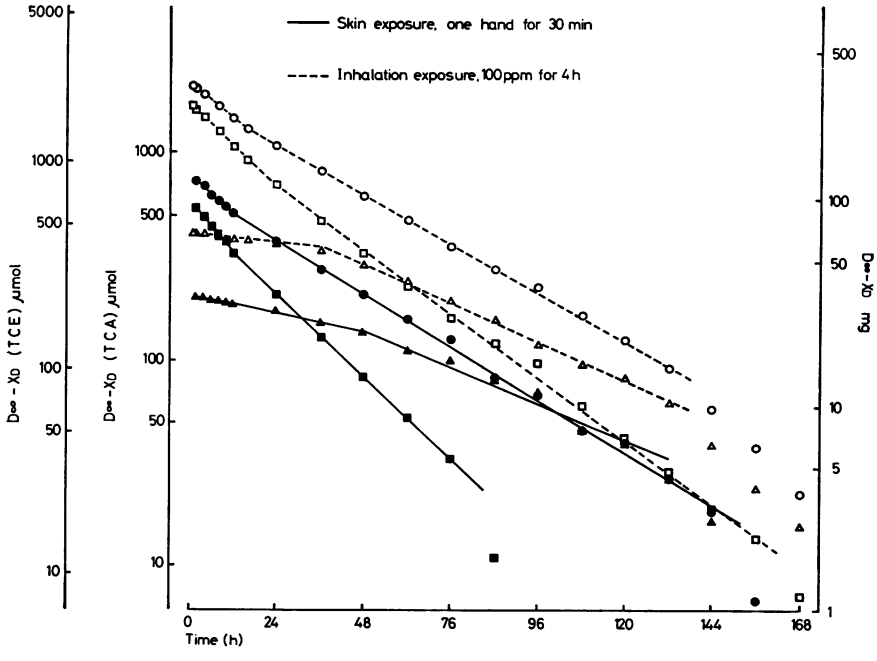

Fig. 2. *Semi-logarithmic plots of* $D_\infty - X_D$.
▲,△: *TCA*
■,□: *TCE*
●,○: *TTC*

following skin exposure were significantly higher than those observed in the inhalation exposure for the first two hours following exposure, suggesting that the decay in the alveolar air alone cannot be a reliable index of absorption through the skin. A possible explanation for this may be that shown schematically in Fig. 3. Trichloroethylene absorbed through the lungs is transferred in the body as follows; (a)→(b)→(c)→(d), while when absorbed through the skin; (c)→(d)→(a)→(b). That is, being absorbed through the lungs trichloroethylene achieves a high concentration in the arterial blood (a) leaving the lungs and is first carried (b) to the body tissues, while when absorbed through the skin, all trichloroethylene absorbed first reaches (c and d) the lungs where a portion is eliminated according to its partition characteristics between blood and air before it is distributed (a and b) among the tissues. Thus in skin exposure, an appreciably large proportion of absorbed trichloroethylene is eliminated unchanged through the lungs.

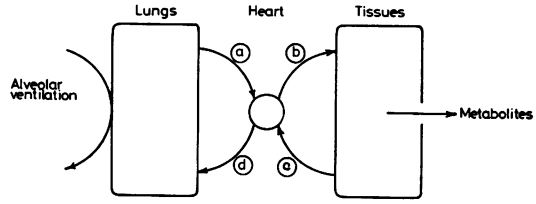

Fig. 3 *A schematic representation of trichloroethylene movement in the body.*

The absorption rates of some liquid solvents through the skin were calculated from the loss of solvents applied locally to the human skin (Dutkiewicz and Tyras, 1967, 1968a, 1968b). The reported values were very high, for example, 14-23 mg/cm²/h for toluene. Dutkiewicz and Tyras (1968b) concluded from these results that the exposure of both hands to liquid toluene for only 1·5 minutes would lead to the absorption of as much toluene as from eight hours' inhalation exposure to the vapour of 0·1 mg/l (26 ppm). In our experiment, however, even after immersion of one hand for 30 minutes in liquid toluene the blood concentration achieved was far from being comparable to that following two hours' inhalation exposure to 100 ppm of toluene vapour. There is no doubt that toluene, when in contact with the skin in its liquid form, can diffuse into the skin at an appreciable rate, but it is not certain that the solvent entering the skin in this manner would be entirely carried away from that region to other tissues by the circulation or to the neighbouring tissues by direct diffusion. One portion of the solvent entering the outer densely packed horny layer may penetrate further into the dermis and on into the systemic circulation, while the other may escape out of the epidermis into the surrounding air because of its high volatility. In fact, the finding in our experiment that the maximum blood concentration of toluene was maintained for a while after the end of skin exposure suggests that toluene entering the skin would probably be confined there for an appreciable time. The value, therefore, reported as the rate of skin absorption may not be the absorption rate but simply the rate of penetration into the horny layer.

Comparing the decay in the alveolar air following human skin exposure to five chlorinated hydrocarbons with the results obtained from inhalation exposure, Stewart and Dodd (1964) concluded that no liquid solvents other than carbon tetrachloride would be likely to be absorbed through the skin in toxic quantities during normal industrial use. We agree with this conclusion. Trichloroethylene is definitely more easily absorbed than toluene. However, trichloroethylene is such an irritating agent in its liquid form when in contact with the skin that the 30 minutes' total immersion of one hand in it may be a gross exaggeration of likely industrial exposure. Uptake through the skin is also related to the type of skin exposed and the area of skin exposure as well as to the duration of skin exposure (Stewart and Dodd, 1964). Therefore, if a very large area of skin were in contact with liquid solvents, there might be a possibility of a significant amount being absorbed through the skin even in a short exposure.

In conclusion, trichloroethylene and toluene would rarely be absorbed through the human skin in toxic quantities during normal industrial use. In order to obtain a reliable index of absorption through the skin, analyses of not only breath but also of blood or urine are necessary.

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