

Uptake of solvents in the blood and tissues of man

A review

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ÅSTRAND, I. Uptake of solvents in the blood and tissues of man: A review. *Scand. j. work environ. & health* 1 (1975) 199—218.

Key words: experimental physiology, exposure, uptake, ventilation, diffusion, solubility, circulation, blood, tissues, solvents, toluene, methylchloroform, styrene, white spirit, methylene chloride, trichloroethylene.

The uptake of solvents in the organism has been measured in a series of experiments performed in the Department of Occupational Medicine of the National Board of Occupational Safety and Health, Stockholm. This report summarizes the results obtained in studies concerning toluene, methylchloroform, styrene, white spirit, and methylene chloride (1, 2, 3, 4, 5). In certain instances a complementary addition was made from the results of a report on trichloroethylene, which is currently being prepared. The report is strictly limited to the physiological parts of the various studies, but the investigations also included analyses of psychomotor and cognitive functions of the exposed subjects (11, 12, 13, 14, 15).

PHYSIOLOGICAL PRINCIPLES

The uptake, via the lungs, of a gaseous solvent with a given concentration in ambient air depends on the following factors: (a) pulmonary ventilation, which supplies

the alveoli with fresh gas at each breath; (b) diffusion of the solvent through the alveolo-capillary membrane; (c) solubility of the solvent in blood; (d) circulation of blood through the lungs and other organs; (e) diffusion of the solvent through the tissue membrane; (f) solubility of the solvent in tissues.

Pulmonary ventilation

In healthy people the magnitude of pulmonary ventilation and blood circulation is mainly governed by metabolic rate. Under normal conditions the magnitude of the metabolic rate above a given basal level depends entirely upon the degree of physical exertion. The uptake of a gas in the lungs may therefore differ greatly at rest when compared to uptake during exercise.

Inspired gas is mixed almost completely with the air already in the alveoli. An alveolar air sample taken at the end of an expiration always consists of a mixture of air from different lung areas. During exposure the concentration of the solvent in such a sample is lower than the concentration in inspiratory air and greater than the concentration of gas in equilibrium with mixed venous blood. The exact concentration between these two extremes is mainly governed by the rate of air ex-

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change, i.e., alveolar ventilation, and by the rate of diffusion through the alveolo-capillary membrane. The concentration in alveoli, i.e., in the alveolar air sample, approaches the concentration in inspiratory air during extensive alveolar ventilation. When ventilation is slight, the concentration approaches the concentration in mixed venous blood.

Diffusion through the alveolo-capillary membrane

The permeability of a membrane depends on the physical and chemical properties of the membrane and of the diffusing gas (17, 26). The membrane between alveoli and blood is, however, generally not a limiting factor for the diffusion of the solvents referred to in this article. A diffusing solvent is taken up by the membrane, but this uptake is apparently very slight since the membrane only consists of two thin layers of cells. This uptake will henceforth be disregarded.

The rate of any diffusion from alveoli to blood is influenced by the size of the solvent molecules and by the difference in concentration between alveolar air and blood. For gases with similar properties in this respect, the amount which diffuses in one direction or the other is mainly governed by the solubility of the gas in blood, i.e., by the partition coefficient of the gas. Thus the concentration of the solvent in the blood leaving the lungs depends on the amount of solvent entering the alveoli, on the solubility of the gas in blood, and on the rate of the blood circulation.

Solubility in blood

The potential for uptake of a gas can be revealed with the aid of the partition coefficient of the gas for blood and air, i.e., the quotient between the concentration of the gas in blood and air at 37°C and in equilibrium. The concentration in blood is generally expressed as mg/kg; and in alveolar air, as mg/l. With a quotient of 10 the concentration in blood is 1 mg/kg of blood when the concentration in air is 0.1 mg/l of air. The higher the quotient, the greater the concentration in blood

compared to that in air. Also the higher the coefficient, the more rapid the diffusion up to equilibrium. Hence the concentration in alveolar air during the initial phase of exposure falls rapidly when the coefficient is high. Consequently, at the end of inspiration, the concentration is quite different from that at the end of expiration. A highly soluble gas will therefore achieve a low concentration in alveolar air in relation to that in inspiratory air. Similarly, a gas with a low coefficient will achieve a relatively high concentration in alveolar air.

Certain gases are highly soluble in water and insoluble in fat (lipids), whereas others are insoluble in water and highly soluble in fat. The concentration of a gas in the water and lipid phases of blood is governed by the partition coefficient between the lipid and water phases.

Blood circulation

The total blood flow per minute through the lung capillaries, i.e., the cardiac output, is of decisive importance for the transport of the solvent to the tissues. Diffusion equilibrium is achieved fairly rapidly if the blood circulation through the lungs is stopped. Net diffusion of a solvent from the lungs to the blood ceases when equilibrium is attained between the alveolar air and the mixed venous blood. Again it should be emphasized that at this stage the concentration of the solvent can be quite different in air and blood. Under such circumstances the transport will be zero even if the cardiac output is high. Additional prerequisites for a large transport of a solvent from the lungs to the tissues are therefore a high cardiac output and a large deficit in the saturation of the solvent in mixed venous blood.

Diffusion through the tissue membrane

In analogy with the preceding remarks, the uptake in a tissue from the blood is governed by the blood circulation through the tissue and the diffusion of the substance from the blood to the tissue. Again, it is a matter of membrane solubility, i.e., membrane permeability.

Solubility in tissues

Of great importance for the total uptake of a solvent is the composition and mass of the tissue. Generally speaking, about 60 % of the body weight of men and 50 % of that of women consists of water. Extracellular fluid constitutes about 30 % of the total body water. As adipose tissue contains very little water, the percentage of water in obese individuals is lower than in the nonobese. Total body fat varies considerably between individuals. Normally, it represents about 10 % or more of the body weight of men and 20 % or more of that of women.

The solubility of a substance in the tissue is expressed by the partition coefficient for the tissue concerned and blood. Evidently the coefficient for tissue/blood will depend on the composition of the tissue, particularly its content of fat and water, respectively. Tissue concentration is therefore generally expressed as mg/kg, as for blood.

After concluded exposure to a substance, the substance is eliminated from the body by various routes. The greater part of most substances is eliminated through the lungs. In this respect the same physical principles govern the magnitude and rate of elimination as in the case of uptake. However, the sequence is reversed, i.e., diffusion takes place from tissue via blood to alveolar air. Some elimination, depending on the properties of the substance, may also take place via the kidneys.

Certain solvents undergo biotransformation in the organism. This transformation usually takes place in the liver.

The physiological principles cited for the migration of a gas through the organism are mainly based on experience obtained with normally respired gases and anesthetic gases (9, 16, 25, 27).

OBSERVATIONS AND EXPERIENCES WITH SOLVENTS

The same design was used in all the series of experiments with solvents, the results from which are summarized in this report. Each subject was exposed during both rest and exercise. Each period of exposure lasted 30 min, and each subject was ex-

posed for four periods consecutively. Work intensity amounted to about 50, 100, or 150 W (300, 600 or 900 kpm/min). About 50 W can be regarded as light work; 100 W, as moderately heavy work; and 150 W, as heavy occupational work. The solvent was supplied to the subject in inspiratory air via a breathing valve and mouthpiece with very low breathing resistance. Whenever possible, the threshold limit value of the solvent was chosen as one of the concentrations in inspired air. Further details on the experimental design, analytical methods, and method errors are described in the different reports (1, 2, 3, 4, 5).

Concentration in alveolar air and pulmonary ventilation

During a 30-min period of exposure at rest with an alveolar ventilation of about 6—8 l/min, the alveolar concentration rose rapidly for the first 10 min; thereafter it tended to level off. This tendency applied to all the substances studied, i.e., toluene, methylchloroform, styrene, white spirit, methylene chloride, and trichloroethylene (1, 2, 3, 4, 5).

Table 1 shows the concentrations in alveolar air and arterial blood expressed in relative units so that a comparison of the different substances can be made. All the values listed were taken after 30 min of exposure. The "leveling off" alveolar concentration at rest differed considerably for different substances. Thus the level for methylchloroform amounted to about 50 % of the concentration in inspiratory air, for methylene chloride to about 30 %, for aliphatic components in white spirit and for trichloroethylene to 25 %, for toluene to about 20 %, and for styrene and the aromatic components of white spirit to about 15 %, respectively.

As previously mentioned, the concentration of a solvent in the alveoli is governed by the concentration of inspiratory air, alveolar ventilation, and by the blood/air partition coefficient. The concentration in arterial blood is governed by the concentration in the alveoli, the blood/air partition coefficient, and the concentration in mixed venous blood. The concentrations in the tissues are governed by the concentration in arterial blood, the blood flow, and the

Table 1. Alveolar and arterial concentrations after 30 min of exposure, as the percentages of the concentrations in inspiratory air, and the quotients between these concentrations. Exposure was made to toluene, methylchloroform, styrene, white spirit, methylene chloride, and trichloroethylene during rest and exercise. Mean values for 15 to 20 subjects are given at rest and during 50-W exercise and for 4 to 5 subjects during 100- and 150-W exercise. 150 W was always preceded by 100 W, and 100 W always by 50 W, without any pause between the exposure periods.

Solvent ^a (concentration in inspiratory air) mg/l	Rest			50 W			100 W			150 W		
	Alv. conc. ‰	Arter. conc. ‰	Quot.	Alv. conc. ‰	Arter. conc. ‰	Quot.	Alv. conc. ‰	Arter. conc. ‰	Quot.	Alv. conc. ‰	Arter. conc. ‰	Quot.
Toluene 0.375; 0.750	20	270	15	35	620	20	—	—	—	45 ^b	720 ^b	15 ^b
Methylchloroform 1.357; 1.900	50	240	5	70	355	5	85	385	5	85	405	5
Styrene 0.210; 0.630	15	260	15	20	970	50	20	1840	85	25	2525	105
Aliphatic white spirit 1.038; 2.075	25	165	5	50	365	10	55	490	10	60	665	10
Aromatic white spirit 0.212; 0.425	15	120	10	20	435	25	20	800	40	30	1370	50
Methylene chloride 0.870; 1.740	30	290	9	55	600	11	65	770	12	70	850	12
Trichloroethylene 0.537; 1.074	25	215	10	45	350	10	50	700	15	60	840	15

^a Two different concentrations were studied.

^b Two subjects.

tissue/blood partition coefficients, respectively. Many studies have been reported in which the mentioned partition coefficients for different solvents have been measured. Table 2 shows such coefficients measured in vitro. It should be noted that the coefficients are highly thermosensitive (7). Therefore the temperature at which the measurements were made is of decisive importance to the results.

The concentration of styrene in blood would according to table 2 be about 25 times greater than that of methylchloroform (32/1.4), about 4 times greater than that of methylene chloride (32/7), and about twice as great as that of toluene (32/15) at equilibrium between alveolar air and blood. The partition coefficients also imply that the alveolar concentration should be relatively high when the factor is low, and vice versa. In other words, with a small uptake by the blood, a relatively large amount of the solvent remains in the alveolar air.

An exposure of 30 min was probably not sufficient to produce equilibrium for any of the substances. A circumstance in which the blood continuously discharges the substances in the capillaries of different organs and tissues prevents the attainment of equilibrium in vivo.

The trend in results closely agrees with the solubility of the substances in blood, i.e., with the partition coefficients for blood and air (table 2). These coefficients show that methylchloroform is the substance least soluble in blood, followed by methylene chloride, trichloroethylene, and toluene. Styrene is the most soluble substance. According to the preceding discussion the alveolar concentration should be the highest for the least soluble substance, and vice versa. It should be emphasized that the partition coefficients given in table 2 were determined in vitro, and values given in table 1, in vivo.

When alveolar ventilation increased in conjunction with physical exercise, the con-

centration in alveolar air rose (table 1). Alveolar ventilation at 50 W amounted to about 23 l/min, at 100 W to about 35 l/min, and at 150 W to about 60 l/min. At the heaviest work intensity the concentrations of different solvents, expressed as percentages of the levels in inspiratory air, were as follows: for methylchloroform, 85 %; for methylene chloride, 70 %; for the aliphatic components of white spirit, 60 %; for trichloroethylene, 60 %; for toluene, 45 %; for aromatic components in white spirit and for styrene, 30 and 25 %, respectively (example: fig. 1).

Stimulating respiration by the administration of carbon dioxide at rest and during physical exercise made it possible to study the effect of increased pulmonary ventilation alone, apart from the effect of increased pulmonary ventilation plus increased blood circulation. The measurements were made with a modest increase in alveolar ventilation (from 5 to 20 l/min) and cardiac output (from 5 to 10 l/min) (fig. 2).

At rest pulmonary ventilation increased to about 21 l/min with the administration of carbon dioxide, whereas cardiac output remained unchanged. Alveolar concentration rose to about the same level as was attained during 50 W of physical exercise (fig 2). Accordingly, the increase was mod-

est for styrene and for the aromatic components of white spirit, whereas it was relatively great for methylchloroform, toluene, and for the aliphatic components of white spirit. Increased pulmonary ventilation alone tended to be as important to the alveolar and blood concentrations of all the substances studied as the exercise-induced increase in both pulmonary ventilation and blood circulation.

Increased pulmonary ventilation leads to an increased inhalation of a substance. Alveolar concentration rises more for a relatively insoluble substance than for a relatively soluble one. Concentration in the alveoli rises because a proportionally smaller amount of the substance supplied diffuses into the blood. A relatively insoluble substance also achieves "equilibrium" with arterial blood more rapidly. When the supply is further increased by enhanced alveolar ventilation, the blood concentration rises and a new "equilibrium" is established. A highly soluble substance is apparently unable to attain "equilibrium" during a 30-min period; blood levels rise continuously. Because of the higher rate of diffusion, the alveolar concentration measured remains almost unchanged at a low level for a long period of time — the extra supply of solvent to the alveolar air is quickly removed by the blood. This

Table 2. The relation between the concentration in blood and gas, in oil and gas, in fat and gas, and between oil and blood in equilibrium. The relations are given for some anesthetic gases and some solvents. The values are taken from the literature (references within parentheses) and are based on measurements in vitro between 25 and 40°C. In reference 18 the coefficients were given at 35°C; in reference 20, at 37°C; in 22, at 37—38°C; in 23, at 40°C; in 24, at 25°C; in 26, at 37°C; and in 28 and 29, at 37°C. The values were based upon concentrations for blood, oil, and fat as mg/kg and for air as mg/l. Oil is a substance that resembles subcutaneous fat.

Anesthetic gas or solvent	Blood/gas	Oil/gas	Fat/gas	Oil/blood
Ethylene	0.140 (20)	1.28 (20)	1.28 (22)	
Cyclopropane	0.415 (20)	11.2 (20)	9.2 (22)	
Fluorocarbon FX-80	0.4 (18)			150 (18)
Nitrous oxide	0.468 (20)	1.4 (20)	1.41 (22)	
Methylchloroform	1.4 (23)	139 (24)		100 (24,23)
Halothane	2.3 (20)	224 (20)	138 (22)	
Methylene chloride	7.0 (23)	75 (24)		
Benzene	7.72 (29)			406 (28)
Trichloroethylene	9.15 (20)	220 (24)	960 (22)	
Chloroform	10.3 (20)	265 (20)	500 (22)	
Toluene	14.66 (29)			1,269 (28)
Diethyl ether	15.2 (20)	50.2 (20)	50 (22)	
M-xylene	29.03 (28)			
Styrene	32 (26)	4,100 (26)		130 (26)

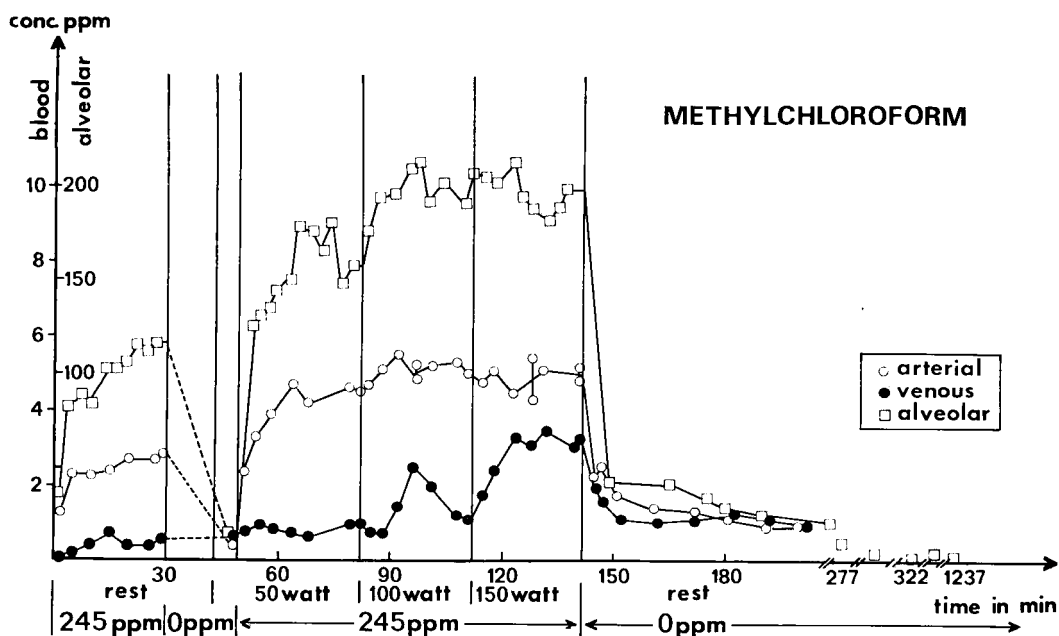
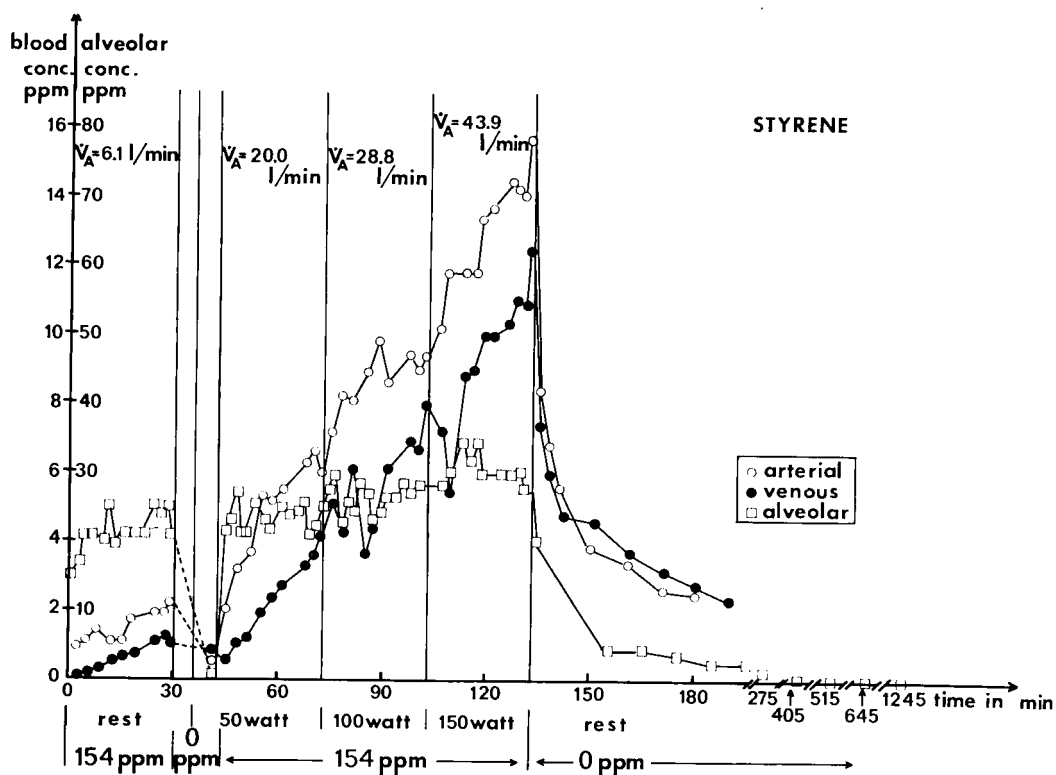


Fig. 1. Concentration of styrene and methylchloroform in alveolar air and in arterial and venous blood in one subject during and after exposure. Exposure was performed at rest and during exercise at an intensity of 50, 100, and 150 W (300, 600 and 900 kpm/min). ($\dot{V}_A$ = alveolar ventilation; 154 ppm = 0.630 mg/l of air and 245 ppm = 1.357 mg/l of air) Note that the alveolar concentration is different in relation to the arterial one for the two solvents.

occurrence presupposes no saturation of other organs. In such a case, the concentration rises in venous and arterial blood and in alveolar air. The results concur with these statements. Thus the alveolar concentration was the highest for methylchloroform (85 %) and the lowest for styrene (25 %). The partition coefficients were 1.4 and 32, respectively (table 2).

Arterial blood concentration

After 30 min of exposure at rest the relative arterial blood concentration was the greatest for methylene chloride; it was equivalent to about 290 % of the level in inspiratory air (table 1). Toluene, styrene, methylchloroform, trichloroethylene, and the aliphatic components of white spirit followed, in that order. The lowest concentration, about 120 %, was obtained during exposure to the aromatic components of white spirit.

During exercise at 50, 100, and 150 W (300, 600 and 900 kpm/min) the styrene concentration in arterial blood rose continuously. At the highest intensity it was about ten times greater than at rest and amounted to about 2,500 % of the concentration in inspiratory air (fig. 1). The corresponding value for methylchloroform, which displayed the smallest increase of the seven substances studied, was only 1.7 times more than at rest; it amounted to about 400 % of the concentration in inspiratory air (fig. 1). When the pulmonary ventilation was increased at rest, through the addition of carbon dioxide to inspiratory air, the arterial styrene level rose far more than the corresponding concentration for methylchloroform. The concentration of a highly soluble substance should increase more than that of an insoluble substance, if it is assumed that the release from the blood does not take place at widely varying rates. The partition coefficients between blood and air and between other organs and blood, respectively, should govern the concentration when exposure, pulmonary ventilation, and blood circulation remain constant.

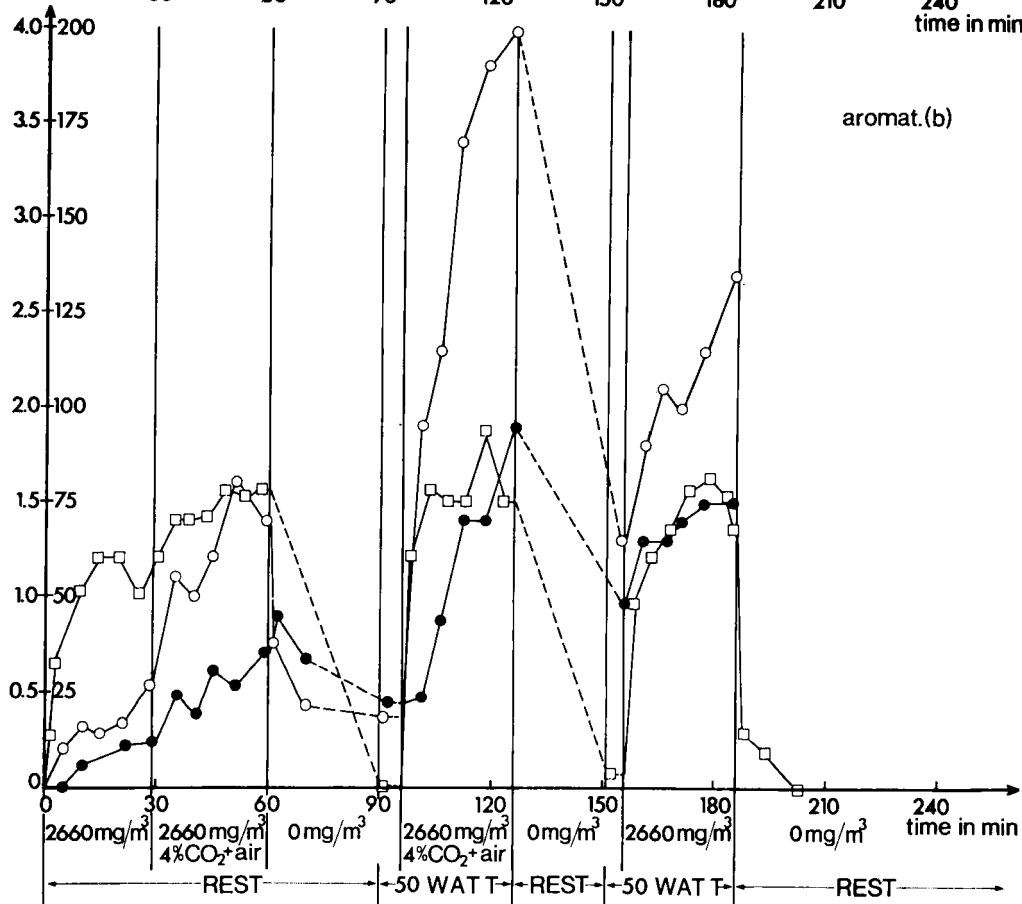
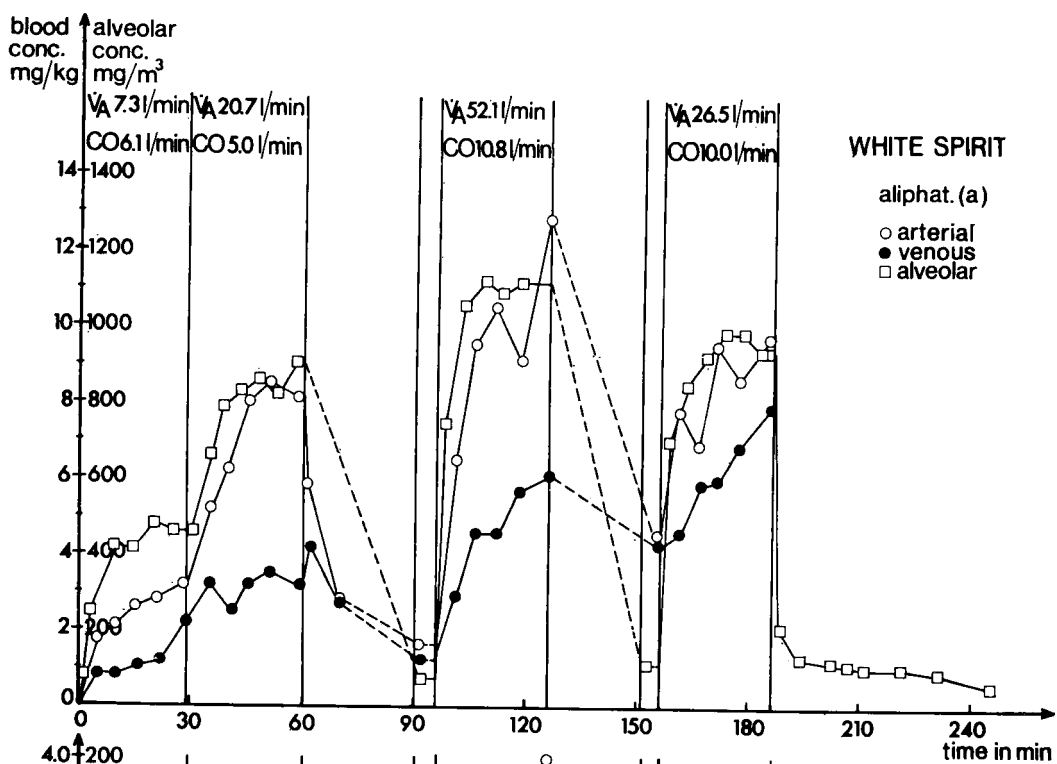
Available information on partition coefficients for different tissues and blood show that these coefficients vary considerably. For toluene Sato et al. (29) reported

a partition coefficient of 113 for fat/blood, of 1 for musculature/blood, of 17 for blood/air, and of 10 for plasma/air. The values were determined using blood, plasma, and homogenized tissues of rabbit. The fat/blood coefficient was accordingly much higher than the other coefficients. Also for styrene and methylchloroform the fat/blood coefficients are high (table 2).

At a given exposure prerequisites for a high blood concentration are a relatively high coefficient for the exchange between blood and air (A) and a relatively low coefficient for the exchange between other tissues and blood (B). The fat/blood coefficient is probably of decisive importance for the total release from the blood. In other words it extensively influences the mean tissue/blood coefficient (B). Accordingly, both A and B are high for styrene, whereas A is low and B is high in the case of methylchloroform (table 2). Thus the difference in solubility in blood (A) for the two substances explains the difference in blood concentration. In other words the refill of styrene in blood from alveolar air is greater than the delivery to the tissues. For methylchloroform the flux from blood to tissue is rapid, whereas the uptake in the lung capillaries is slow and gives a low blood concentration. In the case of toluene A is high and B is very high, i.e., about ten times more than for styrene. Therefore the concentration is relatively lower for toluene than for styrene after a period of exposure (table 1).

Blood/air partition coefficients

The calculated quotients between arterial blood and alveolar air concentrations for the different solvents are given in table 1. The quotients during rest and increasing exercise (rest, 50, 100, and 150 W for 30 min each) did not change for methylchloroform, but remained around 5. Consequently the partition coefficient was about 5 under the given conditions (table 1). The coefficients changed only very slightly for the aliphatic components of white spirit and methylene chloride, from 5 to 10 and from 9 to 12, respectively, and for trichloroethylene, from 10 to 15. The quotient for toluene remained relatively stable, around 15 under similar



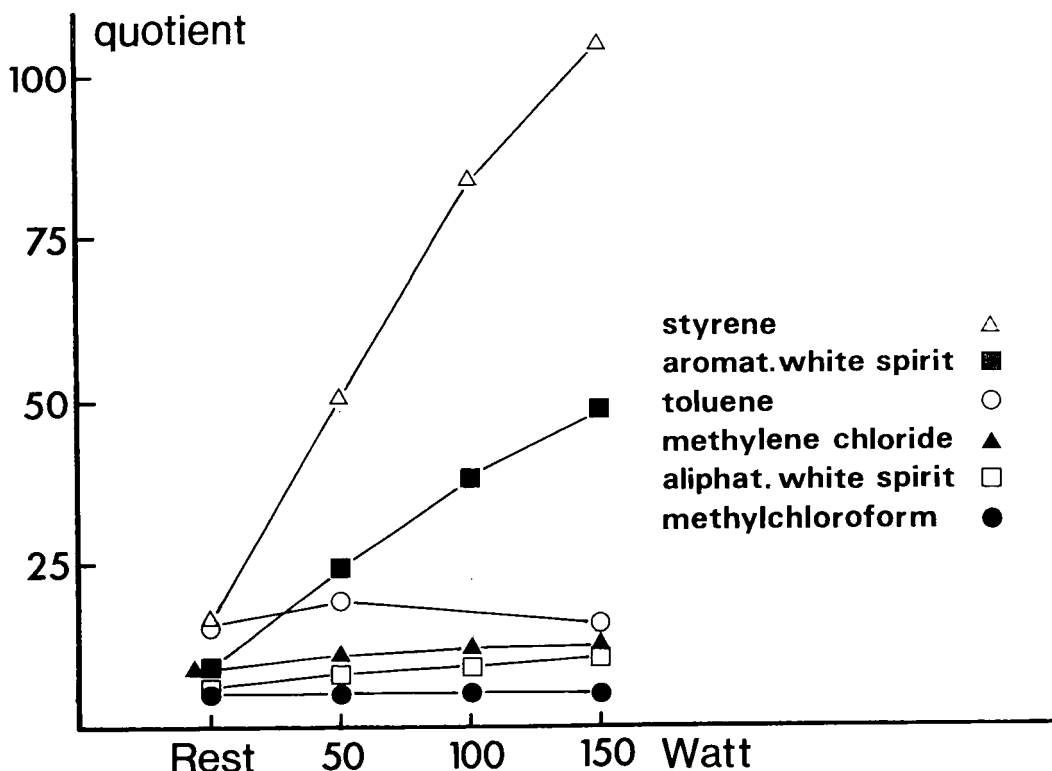


Fig. 3. Quotient between arterial blood concentration and alveolar air concentration after 30 min of exposure during rest and exercise. The exposure was made to styrene, white spirit, toluene, methylene chloride, and methylchloroform; mean values are given for 15 to 20 subjects at rest and during 50-W exercise (300 kpm/min) and for 4 to 5 subjects during 100-W and 150-W exercise (600 and 900 kpm/min).

conditions. However, the partition coefficient for the aromatic components of white spirit rose from 10 to 50 and for styrene from 15 to 105 (fig. 3). Substances with stable quotients obviously achieved some measure of equilibrium, but this was not the case for the latter solvents, i.e., the aromatic components of white spirit and styrene. Again, the greater the insolubility of a substance in blood, the less time needed for equilibrium to ensue. The greater the solubility, the longer needed. Solvents with a stable quotient were taken up in the lungs at the same rate as they were

released from the arterial blood to other tissues. The solvents with a rising factor were taken up in the blood to a greater degree than they were released. In equal blood concentrations the amount of toluene discharged is about ten times greater than the corresponding value of styrene until equilibrium sets in (table 2). As mentioned earlier this is the most probable explanation for the higher blood concentration for styrene than for toluene. The blood/air partition coefficients for both substances are high.

The sequence of the different quotients

← Fig. 2. Concentration of the aliphatic (a) and the aromatic (b) components of white spirit in alveolar air and in arterial and venous blood in one subject during and after exposure to approximately 2,660 mg/m³ of white spirit (about 2.2 mg/l of aliphatic and 0.45 mg/l of aromatic components). Exposure was performed during rest and exercise at an intensity of 50 W (300 kpm/min) with white spirit added to the air and to an air mixture consisting of 4% carbon dioxide and air. (V_A = alveolar ventilation in l/min; CO = cardiac output in l/min)

in terms of magnitude were the same in the analyzed results as in *in vitro* experiments (table 1 and 2). One explanation for the differences in absolute values might be that no equilibrium was ever achieved between tissues and organs in the experiments described. Therefore there was no equilibrium between arterial blood and alveolar air either. Another important reason for the differences is the circumstance that the figures in this material were based on the mean values of 10 to 15 people. The subjects differed with respect to blood composition and somatic constitution. However, the experiments *in vitro* were mainly based on more homogeneous animal material or on oil.

It is relatively easy to determine arterial and alveolar concentrations in man. However, animal experiments are needed to obtain concentrations in tissues. According to such experiments the amount of fat is decisive to the magnitude of uptake in the organism. The less the amount of

fat available for uptake, the faster the saturation of adipose tissue and, thus, the faster the uptake in other tissues. Therefore, thin people should attain a high blood concentration relatively quickly.

Employing a mean coefficient for the distribution of a solvent between adipose tissue and blood and a mean value for the amount of adipose tissue in man would be vastly misleading because the fat/blood coefficient is high and because the amount of body fat varies considerably from individual to individual in man. The quality of fat in different tissue cells also differs greatly. All the different models for the calculation of total uptake in different tissues of man lack practical merit for the same reasons (10, 17, 30).

Blood circulation

Blood circulation also plays a role in the uptake in various organs. Blood circulation through adipose tissue is slight at rest, and

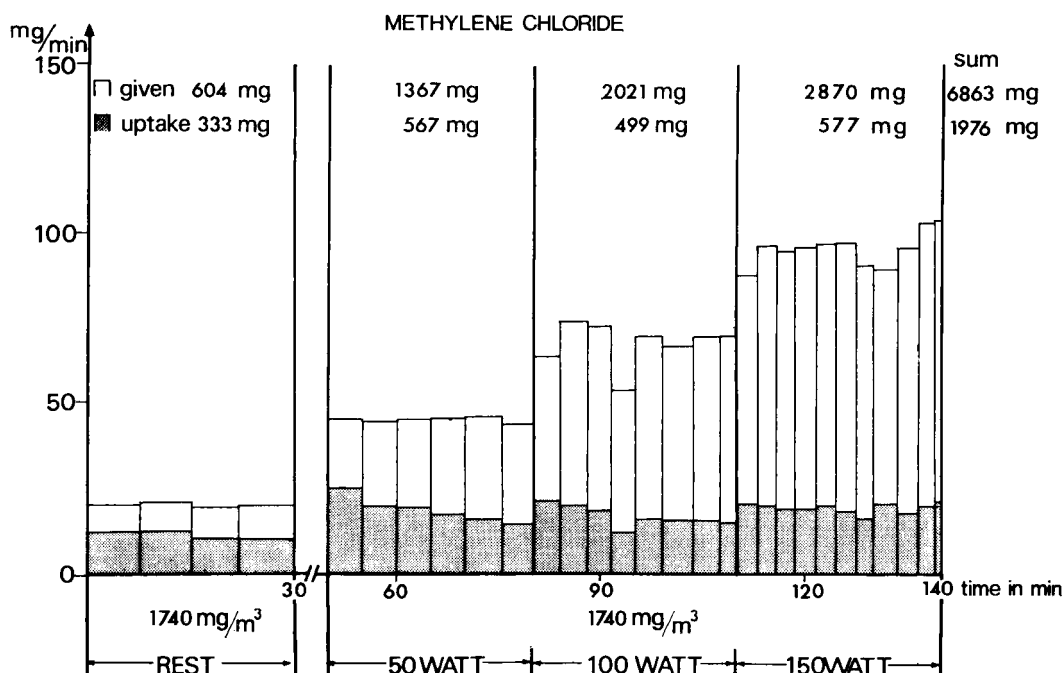


Fig. 4. The amount of methylene chloride supplied and taken up in one subject exposed to 1.740 mg/l during rest and 50-, 100-, and 150-W exercise (300, 600 and 900 kpm/min). The amounts supplied and taken up during each 30-min period and during the whole exposure of 2 h are given. Note that the amount taken up is about the same irrespective of the amount supplied; the percentage uptake decreased during the 2 h.

Table 3. The amount of uptake in milligrams and as the percentage of the solvent supplied during four exposure periods of 30 min each. The percentage figure is noted below the uptake in milligrams. The exposure was performed both during rest and exercise. The amount in blood was estimated from the arterial concentration and an estimated blood mass of 5 kg. The exposure was performed with several different concentrations.

Solvent	Rest	Rest	Rest	Rest	Total	Milligrams in blood after 2 h
Styrene (2 subjects)	65 65	140 65	235 65	310 65	750	30
Aliphatic white spirit (2 subjects)	145 60	160 55	145 45	200 45	650	20
Aromatic white spirit (2 subjects)	40 75	45 70	60 65	75 65	220	3
	Rest	Rest	50 W	50 W		
Aliphatic white spirit (2 subjects)	145 65	260 60	200 25	500 35	1,110	40
Aromatic white spirit (2 subjects)	35 75	65 70	90 60	195 65	390	8
Methylene chloride (5 subjects)	125 55	240 50	235 40	450 35	1,050	45
Trichloroethylene (5 subjects)	80 55	155 50	160 40	310 40	700	30
	Rest	50 W	50 W	50 W		
Methylene chloride (4 subjects)	130 55	300 45	245 35	220 30	900	25
Trichloroethylene (5 subjects)	80 50	180 45	160 40	150 35	565	17
	Rest	50 W	100 W	150 W		
Methylene chloride (5 subjects)	275 55	565 45	575 30	635 25	2,050	70
Trichloroethylene (5 subjects)	185 60	380 50	420 35	420 25	1,400	45

it is probably even less during physical exercise. Blood circulation through the kidneys, the liver, and the gastrointestinal tract may be reduced during physical exertion as compared to rest (6). However, it is important to keep in mind that blood circulation through the lungs and the nervous system, including the brain, increases along with coronary blood circulation. Thus physical exertion produces conditions favoring large uptakes in the lungs, slight delivery to certain organs, and great delivery to others. This effect of physical exercise, entailing some restriction in

blood circulation to other organs, probably contributed to the high relative blood concentrations listed in table 1.

Arteriovenous difference

Arteriovenous difference declined for all solvents during the heaviest exercise. This occurrence should mean that each liter of arterial blood released less solvent during heavy exercise than under other conditions. However the total amount released per unit of time was greater. Since the venous blood was sampled from a periph-

eral vein, it did not represent central venous blood. It is important to note that peripheral blood does not supply the same information as central venous blood. This is even more apparent when the difference in blood distribution during rest and during exercise is considered. Measuring arteriovenous difference (arterial and central venous blood) and cardiac output would otherwise make it possible to determine the amount of solvent discharge.

In the studies of methylchloroform, styrene, and white spirit cardiac output was measured in addition to arterial and peripheral venous blood concentrations. The discharge calculated was in all cases greater than the amount supplied to the alveoli, evidently because the peripheral venous blood contained less of the substance than the central venous blood. Cardiac output amounted to about 5.0 l/min at rest and to 9.0, 13.0, and 17.0 l/min at exercise intensities of 50, 100, and 150 W, respectively.

Measurement of uptake via respiration

The simplest and most exact method yet devised for measuring uptake involves determining pulmonary ventilation and the concentrations in inspiratory and expiratory air. Measurements of this type were performed in the studies concerning styrene, white spirit, methylene chloride, and trichloroethylene (fig. 4).

During the first period of exposure at rest there was a comparatively small variation in the relative uptake between the different solvents (table 3). The relative uptake was calculated as the percentage of the inspired amount. It varied between 55 and 75 %. During extended exposure at rest it decreased for the aliphatic components of white spirit, whereas it remained high for styrene and the aromatic components of white spirit.

During 50-W exercise the percentage uptake declined further for the aliphatic components of white spirit. However for

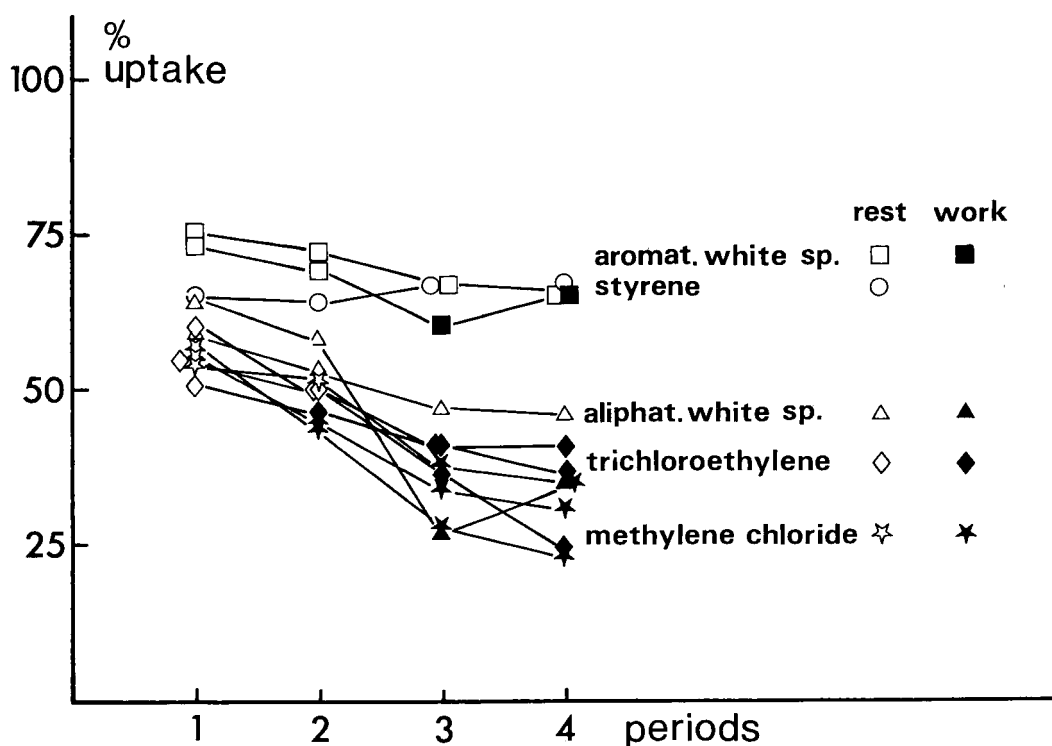


Fig. 5. The uptake in the percentage of supplied solvent during four consecutive periods of exposure during rest and exercise. Subjects were exposed to styrene, white spirit, trichloroethylene and methylene chloride. Number of subjects and amount of exposure can be found in table 3.

WHITE SPIRIT

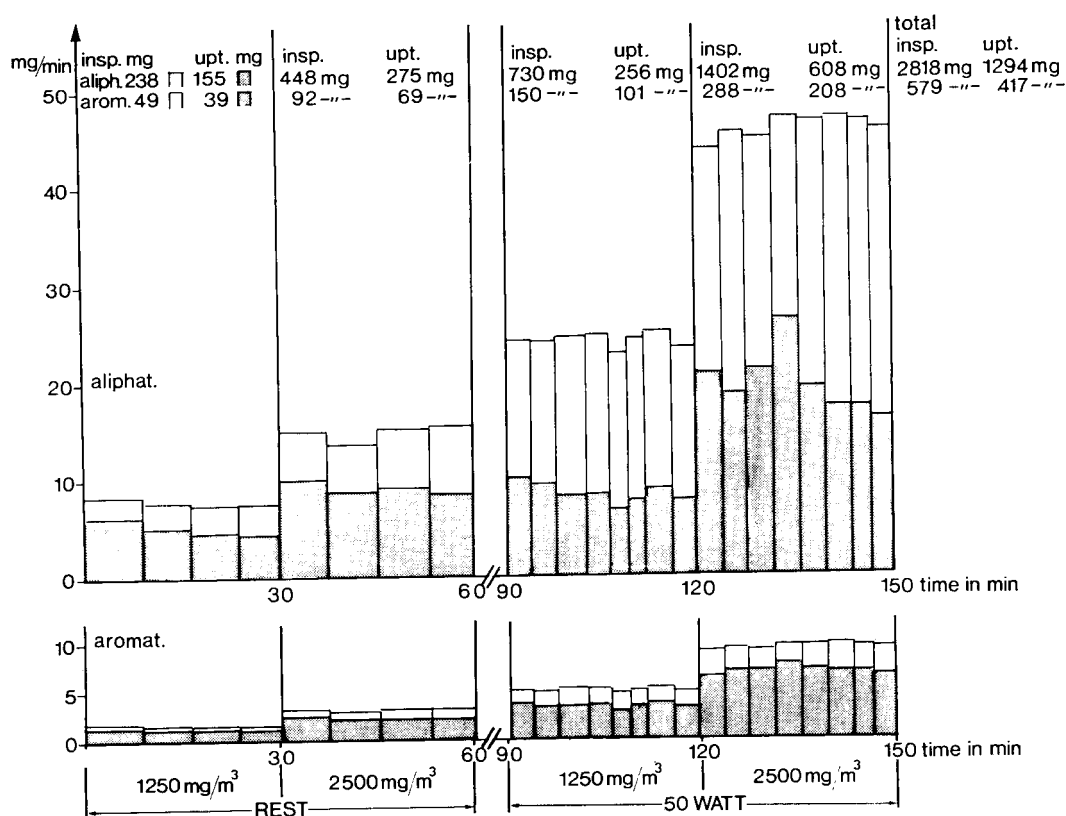


Fig. 6. The amount of aliphatic and aromatic components in white spirit supplied and taken up in one subject. The exposure was performed at rest and during 50-W (300 kpm/min) exercise to approximately 1.038 and 0.212 mg/l of aliphatic and aromatic components and to 2.075 and 0.425 mg/l, respectively. The amounts supplied and taken up during each 30-min period and during the whole exposure of 2 h are given. Note the difference in uptake between aliphatic and aromatic components: the percentage uptake of aliphatic components decreases, while it is fairly stable and high for aromatic components.

the aromatic components the relative uptake was practically unchanged. For methylene chloride and trichloroethylene it decreased from about 55 % at rest to 35 % during 50-W exercise. With higher work intensities it declined to 25 %.

The substances with the highest resting uptake percentage (aromatic components of white spirit) also had the highest value during exercise. The substances with the lowest values during rest (methylene chloride and trichloroethylene) showed a sharp drop during exercise (fig. 5). This diversity was probably due to differences in solubility in blood and fat for the solvents, rather than to differences between the subjects. According to table 2 the fat/

blood partition coefficient is low for methylene chloride and high for styrene. For white spirit no coefficients of the same kind are available. However the aromatic components of white spirit followed a concentration pattern in alveolar air and in arterial and venous blood which resembled the pattern for styrene. The aliphatic components of white spirit followed the pattern of methylene chloride. It seems reasonable to assume that aromatic components are highly soluble in blood and fat, whereas aliphatic components are less soluble (fig. 6).

The blood contained about 30 mg of a total uptake of 750 mg of styrene after 2 h of exposure (table 3). It contained about

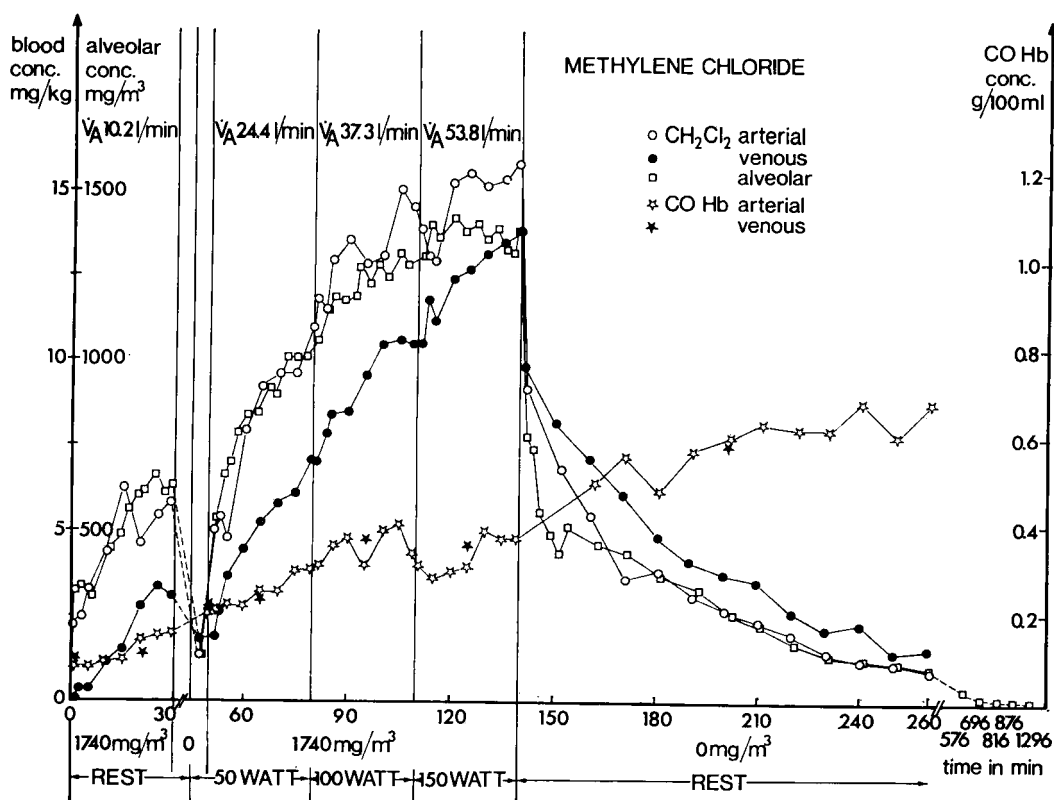


Fig. 7. Concentration of methylene chloride in alveolar air and in arterial and venous blood, as well as the carboxyhemoglobin concentration in the arterial and venous blood, of one subject during and after exposure to methylene chloride in the inspiratory air. The exposure was performed at rest and during exercise with an intensity of 50, 100, and 150 W (300, 600 and 900 kpm/min). ($\dot{V}_A$ = alveolar ventilation l/min) Note the gradual increase in carboxyhemoglobin concentration which continued for hours after the end of exposure.

40 mg of aliphatic white spirit components out of an uptake of about 1,110 mg after 2 h of rest and exercise. The value was 8 mg out of an uptake of 390 mg for aromatic components and about 45, 25, and 70 mg out of 1,050, 900 and 2,050 mg, respectively, for methylene chloride. The relative amount of trichloroethylene in blood was of the same magnitude as for methylene chloride. A blood volume of about 5 l was assumed in these calculations, i.e., a blood weight of 5 kg. Furthermore, it was assumed that all the blood was arterial. This latter assumption leads to an overestimation of the content in blood. Thus the quantity found in blood only made up 3 to 4 %, at the most, of the total uptake of every solvent. The remainder had been released from the blood to other organs and tissues. The solvents which remained on a rela-

tively high uptake level during the fourth period may accordingly accumulate in large quantities during, e.g., exposure throughout an 8-h work day. Biotransformation may be another factor to consider.

When solubility is greater in fat than in blood (e.g., styrene), the solvent remains in the organism for a relatively long period of time. The substance is transported with venous blood from the inner organs to the liver and hence to the lungs. Thus the liver remains exposed for a long time.

At a given toxicity substances which are soluble in fat represent greater risks than those which are insoluble in fat, provided their metabolites are not toxic. One example of a comparatively insoluble substance with a highly toxic metabolite is methylene chloride, which is metabolized into carbon monoxide (8) (fig. 7). However

there is some evidence that the solubility in fat is in some cases directly related to toxicity (21). Furthermore, another toxic effect, i.e., the antihemolytic effect of different solvents, can be correlated to their partition coefficients in an iso-octane/water system (19).

Values obtained from previously cited measurements (2, 3, 5) were entered into equations used for the estimation of uptake (10, 17, 30). Measured uptake failed to coincide with the estimated uptake in all cases. As mentioned earlier, this situation occurred because in the equations it was assumed that the individual was constructed along the lines of the envisioned model, which is not usually the case.

Checks at the work site

It is obviously important to be able to determine or calculate the uptake of solvents in workers. Often the concentration in

ambient air is monitored at different work sites. If the concentrations are kept well below the threshold limit values, further measurements are usually not necessary. However supplementary biological values may be needed in individual cases. Then a method with a reasonable accuracy must be used for the estimation of uptake. Continuous measurements of respiratory volumes and of concentrations in inspiratory and expiratory air are not possible as routine measures. Arterial blood samples are precluded for practical reasons. However, alveolar air samples, venous blood samples, arterialized capillary blood samples from a fingertip, and urine samples can be taken.

Arterial blood concentration closely correlated with the alveolar air concentration in the cases of methylchloroform, toluene, the aliphatic components of white spirit, methylene chloride, and trichloroethylene (table 2) (fig. 8). Correlation was poor for styrene and the aromatic components of

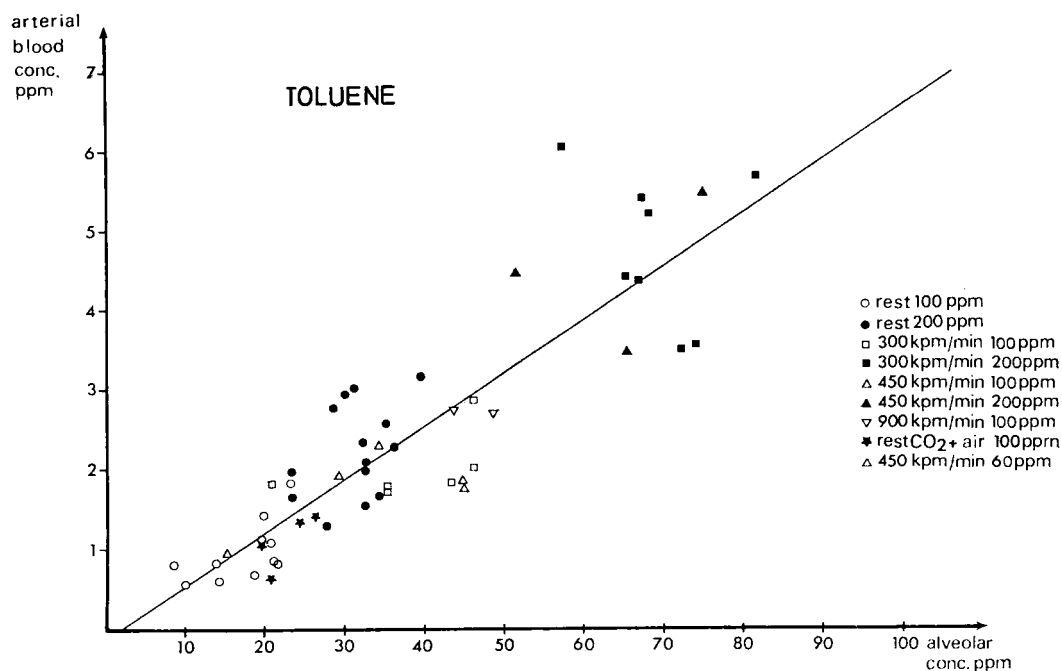


Fig. 8. Relation between the concentration of toluene in arterial blood and alveolar air after 30 min of exposure at rest and during work. Each symbol stands for one exposure period, i.e., a subject is represented by more than one symbol. (Regression line $y = -0.12 + 0.067 x$) Symbols: $\circ$ rest, 100 ppm; $\bullet$ rest, 200 ppm; $\square$ 50 W, 100 ppm; $\blacksquare$ 50 W, 200 ppm; $\triangle$ 75 W, 60–100 ppm; $\blacktriangle$ 75 W, 200 ppm; ∇ 150 W, 100 ppm; $\star$ rest, CO_2 + air 100 ppm. (100 ppm = 0.375 mg/l; 200 ppm = 0.750 mg/l) For this solvent the alveolar concentration reflects well the arterial concentration even if the standard deviation is great.

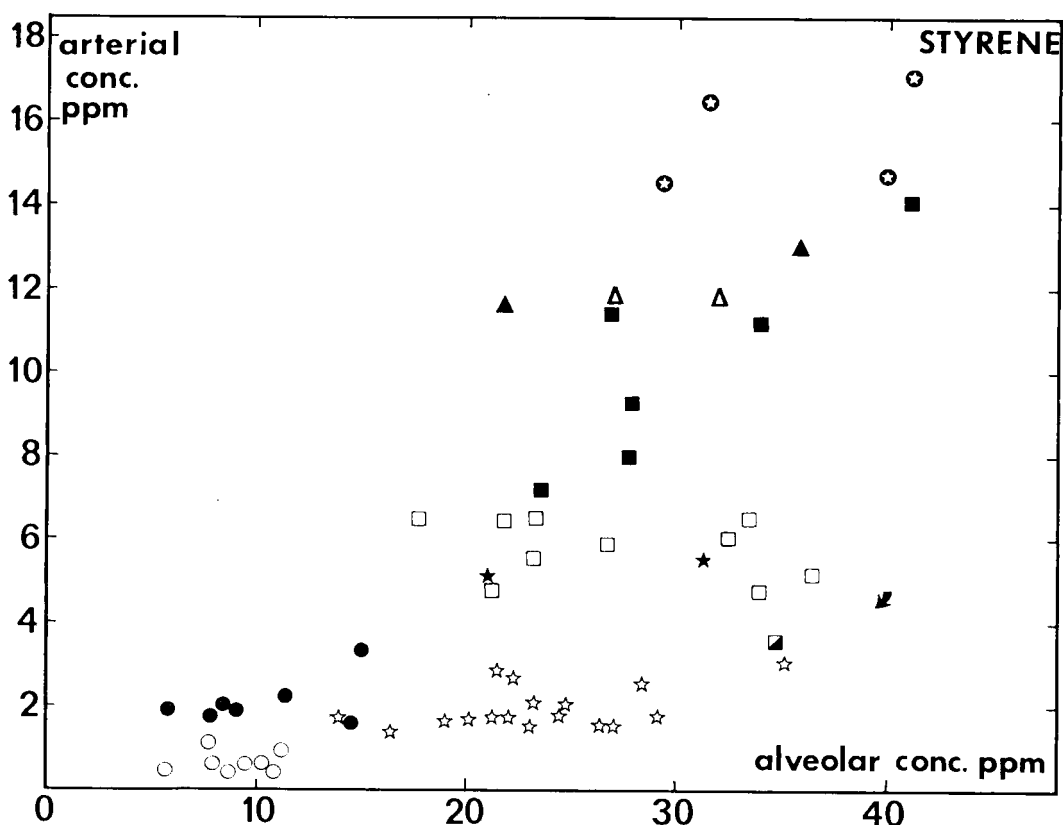


Fig. 9. Relation between the concentration of styrene in arterial blood and alveolar air after 30 min of exposure at rest and during work. Each symbol stands for one exposure period, i.e., a subject is represented by more than one symbol. Symbols: ○ rest, 50 ppm; ● 50 W, 50 ppm; ☆ rest, 150 ppm; □ 50 W, 150 ppm; ■ 100 W, 150 ppm; △ 100 W, 150 ppm, 90 min; ⊕ 150 W, 150 ppm; ★ rest, 150 ppm + CO₂; ▲ 50 W, 150 ppm + CO₂; ◻ rest, 250 ppm; ◼ rest, 350 ppm. (50 = 0.210 mg/l; 150 ppm = 0.630 mg/l; 250 ppm = 1.050 mg/l; 350 ppm = 1.470 mg/l) Note the wide scatter, e.g., an alveolar concentration from 5 up to 30 ppm can correspond to the same arterial concentration of 2 ppm.

white spirit (fig. 9). Thus alveolar air samples only give a good estimate of the arterial blood concentration when solvents with poor solubility in blood are dealt with. However the arterial concentrations of highly soluble substances are probably of more interest. In order to obtain this information, analyses of arterialized capillary blood should be preferable to analyses of venous blood for the following two reasons: (a) a capillary sample will display the same concentration as an arterial sample and (b) a capillary sample is easier to take (3).

A high level in venous blood reflects a high level in organs and tissues. However the partition coefficients for different or-

gans/blood differ considerably. Hence the venous concentration only provides a rough estimate of uptake.

Both alveolar air samples and arterial, venous and capillary blood samples must be taken during exposure in order to give acceptable information about exposure. Stewart et al. (31, 32) considered that the degree of exposure could be calculated on the basis of alveolar samples taken after the termination of exposure. The procedure was tested in the present investigations for all seven substances in a total of at least 60 exposure trials. However this calculation method is apparently misleading, at least when exposure is intermittent and lasts only 2 h. It was not possible

to calculate the exposure of any subject with acceptable accuracy (fig. 10). The same negative results were obtained for arterial and venous blood samples taken after the termination of exposure (3). One reason for the negative results might be that concentrations are lower at rest than during exercise, irrespective of constant exposure. Furthermore, a concentration is an indication of a certain uptake rather than an indication of a certain level of exposure. Consequently, high values after the termination of exposure indicate a large residual amount of the substance in the organism, and vice versa.

In order to measure metabolites, urine

samples can be taken (3). The intention is to establish the degree of uptake of a substance. However for such a calculation the amount of the total uptake metabolized must be known. This is often not the case. Controlled exposure experiments are necessary for the interpretation of such results. Another disadvantage of this technique is the fact that acute exposure can never be traced.

Metabolites can preferably be analyzed in blood samples in certain cases. Such a measurement is relevant when the metabolite is more toxic and/or accumulates to a greater extent than the substance itself, as in the case of trichloroethanol, which

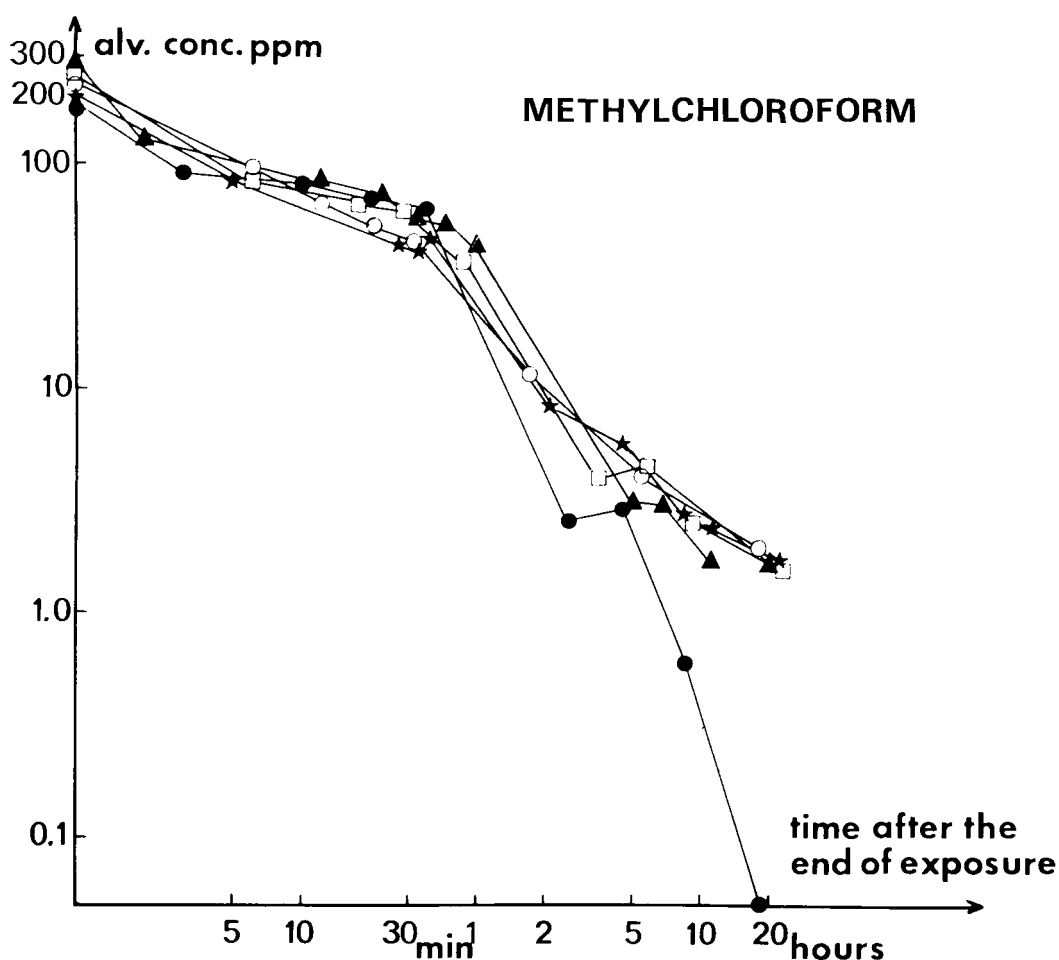


Fig. 10. Concentration of methylchloroform in alveolar air at the end of and at different times after exposure to approximately 250 and 350 ppm (1.357 and 1.900 mg/l) of methylchloroform in the inspiratory air. The exposure was performed at rest and during work with an intensity of 50 W (300 kpm/min) for five subjects.

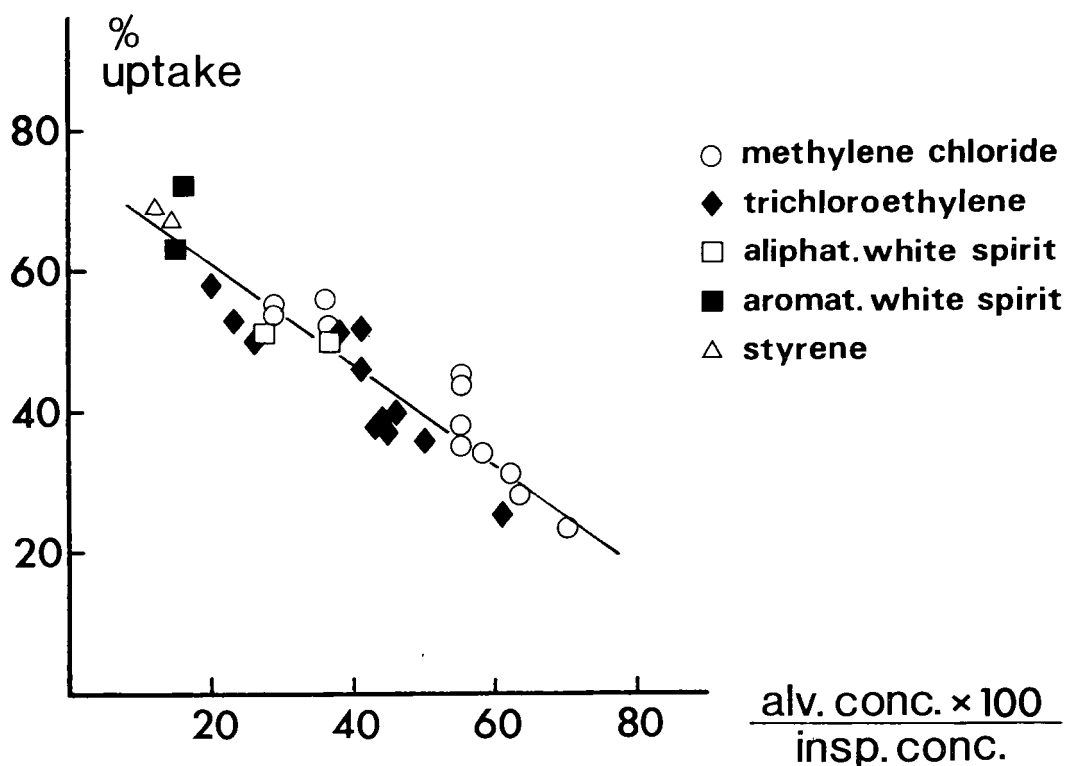


Fig. 11. Uptake (percentage of amount supplied) in relation to alveolar concentration (percentage of concentration in inspiratory air) after 30 min of exposure at rest and during exercise. Each symbol gives the mean value of two subjects for styrene and the aliphatic and aromatic components of white spirit, the mean value of four or five subjects for methylene chloride, and the mean value of five subjects for trichloroethylene. Note the rather high correlation ($r = -0.930$) irrespective of the solvent. (Regression line: $y = -0.72x + 74.91$)

is formed during exposure to trichloroethylene.

The best correlation seems to prevail between the measured percentage uptake and the alveolar air concentration as the percentage of the concentration in inspiratory air (fig. 11). This correlation should obviously exist. Thus simple measurements of the concentrations in alveolar air and inspiratory air during exposure and estimations of pulmonary ventilation make it possible to estimate the magnitude of total uptake.

CONCLUSIONS

The various effects of a solvent, present in the inspiratory air, on man depend on a number of more or less mutually dependent factors. The following factors are the

most important: (a) pulmonary ventilation and blood circulation and therefore the intensity of physical work, (b) solubility in blood, (c) solubility in tissues, and (d) toxicity of the substance or its metabolites. Thus it is important to measure and evaluate the following: (a) uptake in the lungs. (This can be estimated from the pulmonary ventilation and the ratio between the concentration in alveolar air and inspiratory air.); (b) solubility in blood and tissues (The amount of fat and the quality of the fat in the respective tissues are of decisive importance to uptake, but there is a great lack of reliable data on this subject.); and (c) the effect of a given dose/concentration on, e.g., the nervous system (The effect can be assessed by measuring psychomotor and cognitive functions.).

The preceding conclusions were derived

from experiments with seven different substances. The solvents can be ranked with regard to the percentage of uptake and therefore to the solubility in blood and tissues accordingly (largest uptake first and smallest uptake last): styrene, the aromatic components of white spirit, toluene, trichloroethylene, the aliphatic components of white spirit, methylene chloride, and methylchloroform.

ACKNOWLEDGMENT

The studies were financed in part by grants from the National Safety Fund and the National Council for Building Research.

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Received for publication: 1975-05-09.