CHAPTER 9

WORK LOAD AND UPTAKE OF SOLVENTS IN TISSUES OF MAN

Irma Åstrand
Unit for Work Physiology, Department of Occupational Health, National Board of Occupational Safety and Health. S-171 84 Solna, Sweden

ABSTRACT

Subjects were exposed to different solvents in inspiratory air through a breathing valve both at rest and during physical exercise on a bicycle ergometer. The uprake in the organism was increased during physical work compared to ai rest. The uptake was 5-6 times higher during heavy physical work compared to at rest for in blood easy soluble solvents whereas it was only doubled for more insoluble solvenrs. Tho uptake can be estimated from the quotient between the concentration in alveolar and inspiratory air and the pulmonary ventilation The concentration in subcutaneous adipose tissue was higher in lean than in obese subjects. The half-life of methylene chloride in adipose tissue was about 8 hr and for styrene and xylene about 2-4 days.

INTRODUCTION

The uptake of solvents in the organism of man was measured in a series of experiments, This article summarizes some of the results which were obtained in exposure *to* toluene, industrial xylene. styrene, methylene chloride, methylchloroform, trichloroethylene. butanol and white spirit. In 1975 a review was written of results available at that time.' The present paper was presented in Stockholm to the International Symposium on Occupational Health Hazards Encountered in Surface Coating and Handling of Paints in the Construction Industry in October of 1979.

EXPERIMENTAL DESIGN, SUBJECTS AND METHODS

The same design of the uptake studies was used for all solvents. Young, healthy malts were used as subjects. Each subject was exposed during both rest and exercise on a bicycle ergometer. Each period of exposure usually lasted 2 hr, 30 min at rest, 30 min at a work load of 50 W. 30 min at 100 W and another 30 min at 150 W. The solvent was given *to* the subject in the inspiratory air through a breathing valve. The concentration m the air was constant and it was usually kept around the Swedish threshold limit value of the solvent By using the same work loads and exposure time for all solvents

both pulmonary ventilation and blood circulation could be kept fairly constant during the 30 minute periods of exposure, meaning *that* the influence of the solubility in blood and tissues of different solvents could be studied.

The total uptake of the solvent was continuously measured with *the* Douglas' bag technique. The concentrations of solvents in air, in arterial and venous blood and in some instances in subcutaneous adipose tissue were measured by different gas chromatographic methods. Further details on the experimental design, analytical methods and error of the methods *are* given in the different part reports.[2,4-6,8-10]

RESULTS AND DISCUSSION

Uptake measurement. Examples of uptakes of methylene chloride, trichloroethylene, industrial xylene and styrene will be presented.

In Figure 1. the uptake of a subject exposed to methylene chloride is illustrated.[5] With increasing work loads, the pulmonary ventilation increased and thereby the given amount of the solvent. The pulmonary ventilation was about 6 times higher at 150 W than at rest. The amount taken up was about doubled during work compared to at rest, and of about the same size during the three cycling periods. During the whole period of exposure the percentage uptake declined from about 55% at rest, down to 25% at 150 W. The uptake in two hr in a group of 5 subjects was in mean 2.0 g, constituting about 31% of the inhaled amount of 6.5 g

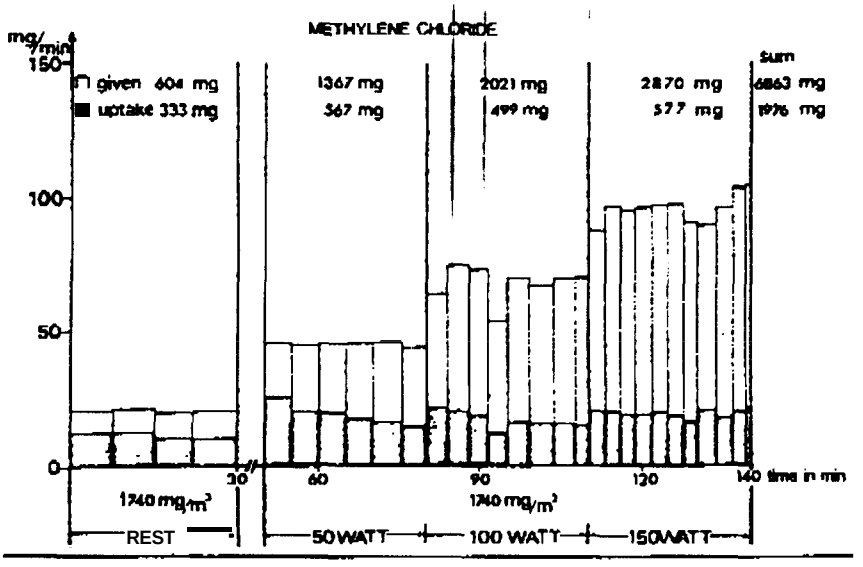


FIGURE 1 The *amount* of methylene chloride supplied and taken up in one subject during exposure. Exposure was performed with 1.740 mg/m³ of methylene chloride during rest and exercise at an intensity of 50, 100 and 150 W.[5] (Reprinted by Permission from CRC Press, Inc.)

In Figure 2, the uptake of a subject exposed to trichloroethylene is illustrated.[4] The uptake decreased during the whole period of exposure. It was about 55% during the first 30 minute period at rest and it succesively declined to about 6% during the last period at 150 W. It was almost zero at the end of exposure. After two hr, the concentration in the arterial blood of the subject was nearly in equilibrium with the concentration in the alveolar air. The subject was in good physical condition and fairly thin. The supplied amount in two hr to a group of 5 subjects was in mean 3.9 g. The uptake wa 1.4 g, constituting about 36% of the inhaled amount.

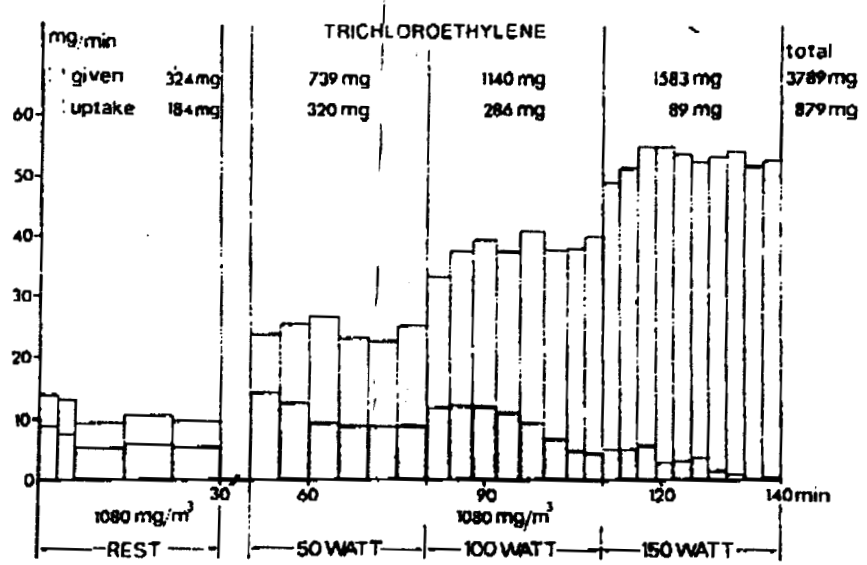


FIGURE 2. The amount of trichloroethylene supplied and taken up in one subject during exposure. Exposure was performed with 1,080 mg/m³ of trichloroethylene during rest and exercise at an intensity of 50, 100 and 150 W.[4] (Reprinted by Permission from CRC Press, Inc.)

In Figure 3. the mean uptake of a group of 6 subjects exposed to industrial xylene, a mixture of xylene isomers and ethylbenzene, is illustrated.[5] The uptake rose from about 80 mg during the rest period to about 390 mg durio gthe last period of exercise. The percentage uptake was about 65% at rest and about 50% during 150 W. During the two hr exposure an average of 1.0 g or 59% was taken up of a supplied amount of about 1.7 g.

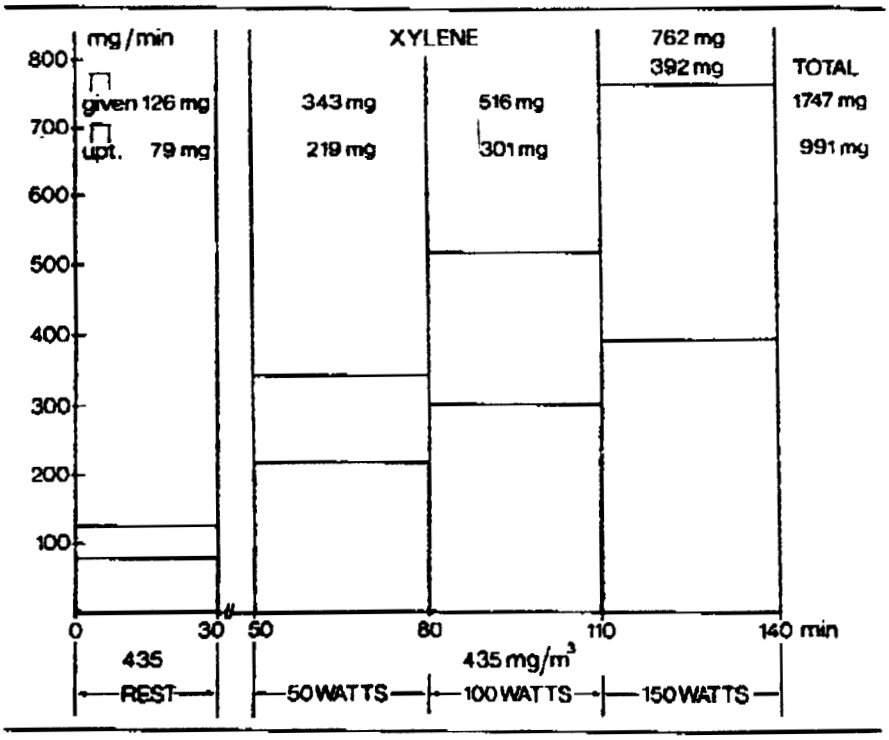


FIGURE 3 The mean amount of xylene supplied and taken up in six subjects during exposure. Exposure was performed with 435 mg/m³ of xylene during rest *and* exercise at an intensity of 50, 100 and 150 W.[1] (Reprinted *by* Permission from CRC Press. Inc.)

In Figure 4, the mean uptake of 7 subjects exposed to styrene is illustrated.[10] The uptake was high during the whole exposure. About 63% or 0.5 g of the supplied amount of 0.8 g was taken up. The percentage uptake stayed high all the time. The uptake increased up to 5-6 fold during heavy physical work.

For all solvents. the uptake was at least doubled during physical work compared *to* at rest. For styrene and and xylene the uptake increased 5-6 fold during 150 W as compared to at rest, whereas the uptake for methylene chloride and trichloroethylene was only doubled. The explanation of these findings is that both styrene and xylene are easily soluble, whereas methylene chloride and trichloroethylene are comparatively insoluble in blood and probably also in the *tissues.* The more soluble *the* substance is the slower the equilibrium is reached between the concentration in blood and alveolar air and between tissues and blood. Especially, in the later part of the exposure *the* degree of metabolism also plays a role for the uptake.

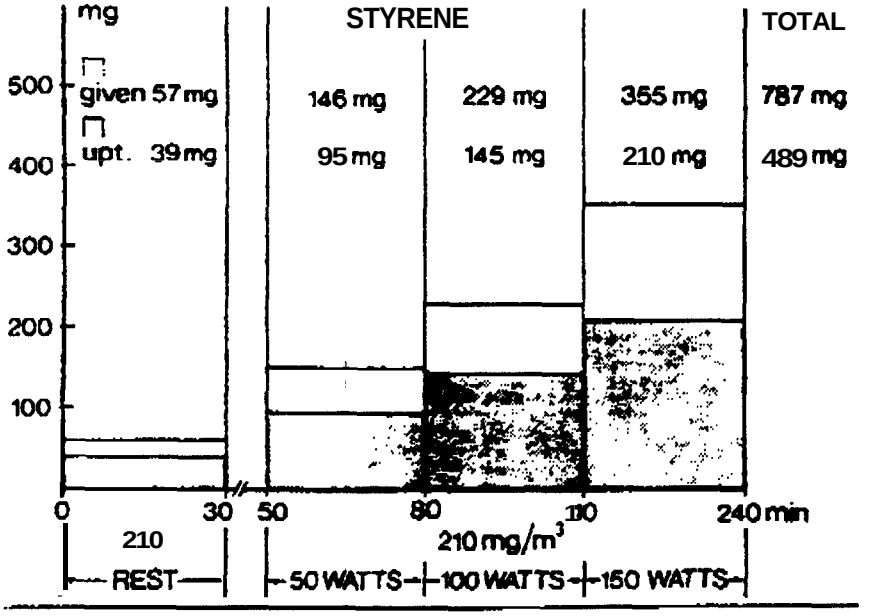


FIGURE 4 The mean amount of styrene supplied a d taken up in seven subjects during exposure. Exposure was performed with 210 mg/m³ of styrene during rest and exercise at an intensity of 50, 100 and 150 W.[10] (Reprinted by Permission from CRC Press, Inc.)

Alveolar concentration. When the percentage uptake of the different solvents were related to the alveolar concentration over the inspiratory concentration, a linear correlation was observed.[11] (Fig. 5). The correlation between the two measures indicates that the uptake of a gas in the lungs approaches zero at the same time as the alveolar concentration approaches the concentration in inspiratory air. and that the percentage uptake increased when the concentration in alveolar air decreases.

The relationship between the *two* variables is natural. The fact that the uptake never reached 100% is due to the dead space ventilation. Accordingly. *the amount taken* up of a solvent may be estimated from the concentrations in the alveolar and inspiratory air and the pulmonary ventilation. This method of estimation was tried in the field with success.[7,13] It should be noted, however, *that the correlation* only exists for solvent uptake in the lung capillaries.

The uptake in the lungs is distributed by the blood to the different tissues and organs. The higher the uptake per unit of time, *the* higher the concentration in *the* blood and *the* higher *the* concentration in different organs. This means that the concentration in vital organs varies despite a constant concentration in the ambient air. Therefore, what one would like to have is some sort of biological limit values *as complements to the* ordinary threshold limit values. Francesco Gamberale has worked together with our group. He made an extensive study of these problems.[12] He was able to show at which uptake a significant increase

in simple reaction time can be demonstrated for the solvents discussed here. Such values can be used as biological limit values when discussing acute effects.'

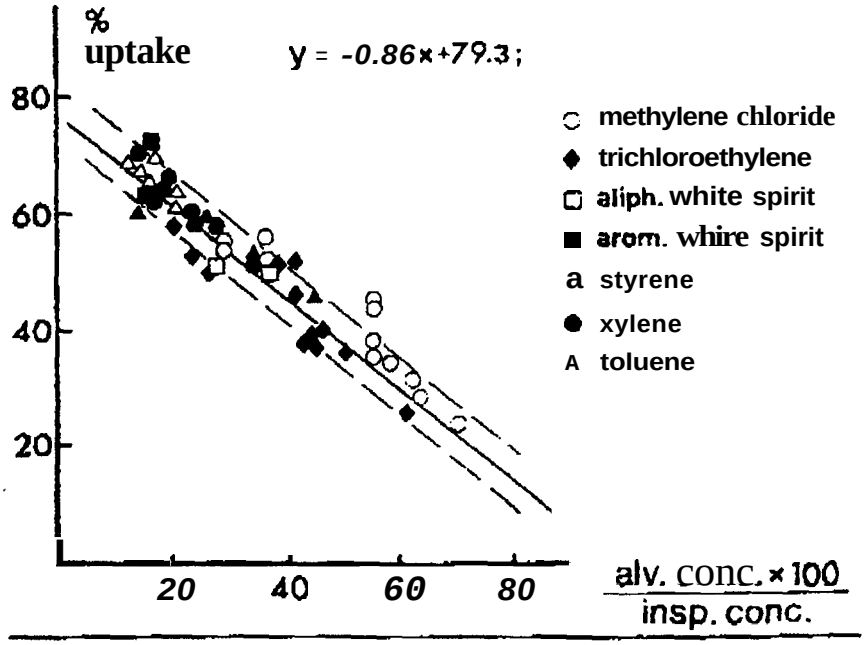


FIGURE 5 Uptake of solvents in the lungs as the percentage of the amount supplied in relation to the quotient between the concentrations of alveolar and inspired air. The uptake was measured during a 30 min period, and the corresponding alveolar concentration was based on three measurements during the last 10 min of the same period. In most cases each symbol represents a mean value of four to six subjects. The equation of the regression line was calculated on the basis of 46 such mean values. The number of subjects was: 14 for methylene chloride, 15—trichloroethylene, 4—white spirit, 7—styrene, 12—xylene and 7 for toluene (altogether about 60 subjects). The deviation from the line (SD) = ±5; = 0.949. (Reprinted by Permission from CRC Press, Inc.)

Content in subcutaneous adipose tissue. Jörgen Engström wrote his thesis *on* concentration of solvents in subcutaneous adipose tissue.[6] In Figure 6. the concentration of methylene chloride in subcutaneous adipose tissue after 1 hr exposure is given.' The concentration was, as a rule, higher *in* lean than in obese subjects. The concentration did not change significantly during the first 4 hr after exposure. The concentration was measured in 2 subjects the morning after the *exposure* and the estimated mean half-life of the concentrations m adipose tissue was 8 hr. The estimated mean amount of solvent retained in the total fat deposits of the body was greater in the obese subjects. The estimated total *amount* of methylene chloride in far stores 4 hr after exposure was actually related to the estimated amount of the body fat expressed in per cent of body weight (Fig. 7).

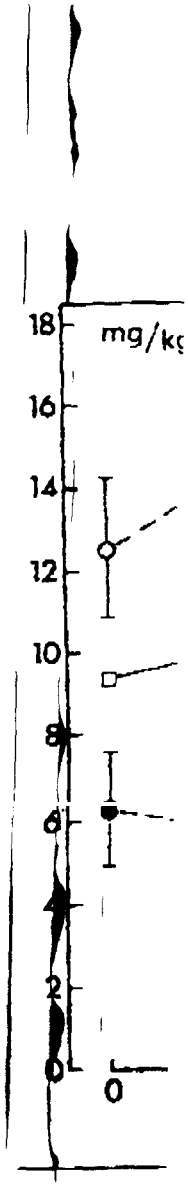


FIGURE 6 Co
subjects (group I
12 subjects are a
during exercise
(SE) of the mea

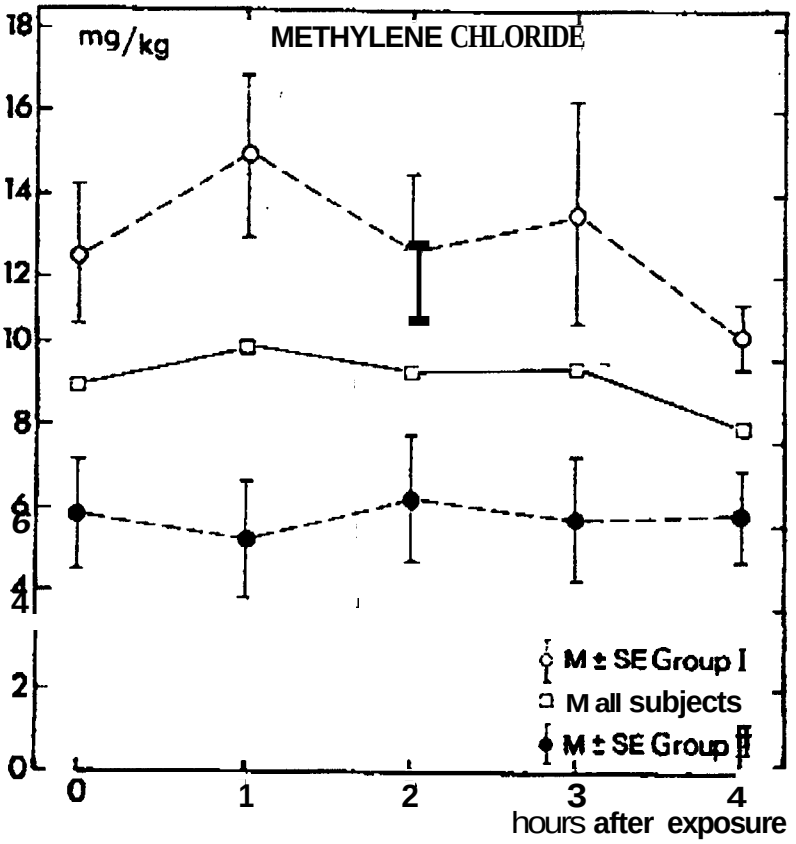


FIGURE 6 Concentration of methylene chloride in the subcutaneous adipose tissue of six slim subjects (group I) and of six obese subjects (group II) during 4 hr after exposure. Mean values of all 12 subjects are also given. Exposure was performed in 1 h with 2.600 mg/m³ of methylene chloride during exercise at an intensity of 50 W. The figure shows the mean values (M) and standard errors (SE) of the means.[8] (Reprinted by Permission from CRC Press, Inc.)

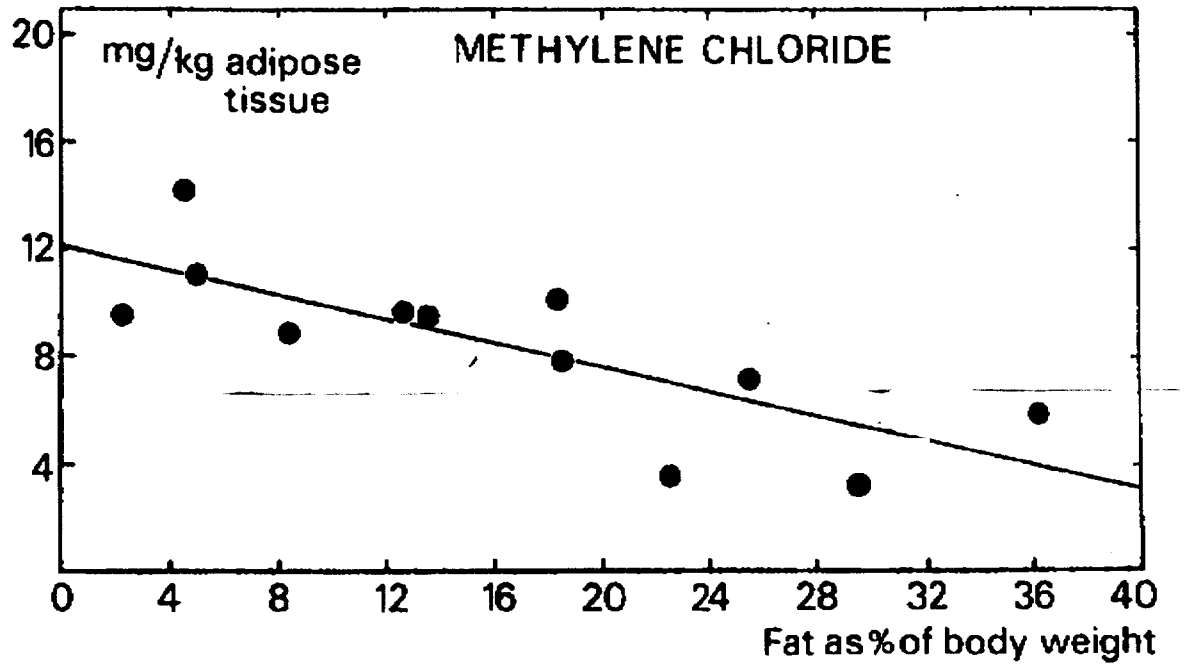
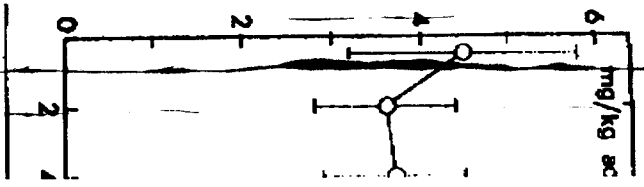


FIGURE 7 Concentration of methylene chloride in the subcutaneous adipose tissue of 12 subject 4 hr after exposure termination as related to the estimated fat % of body weight. Exposure was performed in 1 h with 2,600 mg/m^3 of methylene chloride during exercise at an intensity of 50 W.[8] (Reprinted by Permission from CRC Press, Inc.)



In Figure 8, the mean concentration in adipose tissue after 2 hr exposure to styrene is given.[10] The concentration did not change significantly during the first 24 hr. Four subjects were followed during a longer period of time after the exposure. In all 4 subjects, styrene was detectable for up to 13 days after exposure (Fig. 9). The half-life of the concentrations varied between 2 and 4 days.

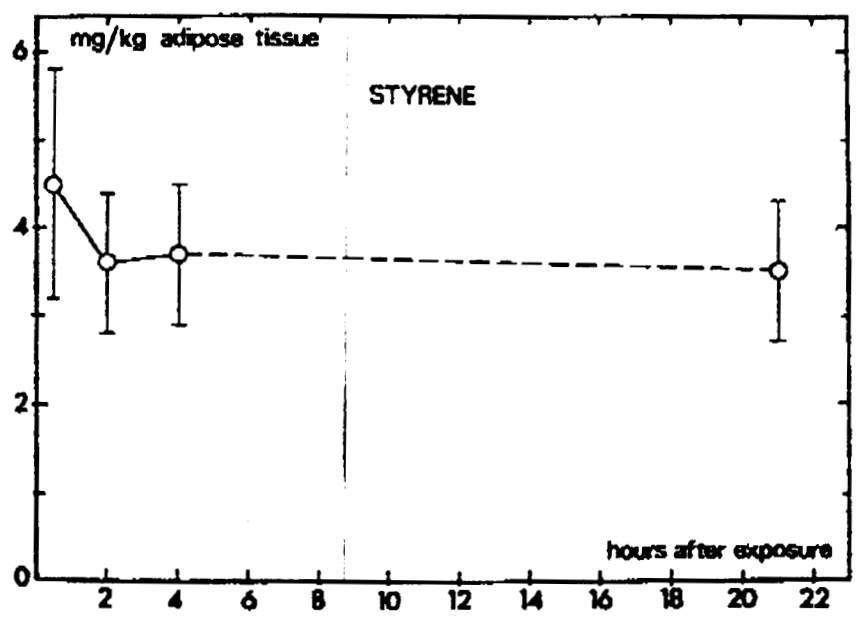


FIGURE 8 Concentration of styrene in the subcutaneous adipose tissue of 7 subjects in the first 24 hr after 2 hr exposure to about 210 mg/m³ in inspiratory air. Exposure was performed during rest and exercise at an intensity of 50, 100 and 150 W. Mean values and standard errors are given.[10] (Reprinted by Permission from CRC Press, Inc.)

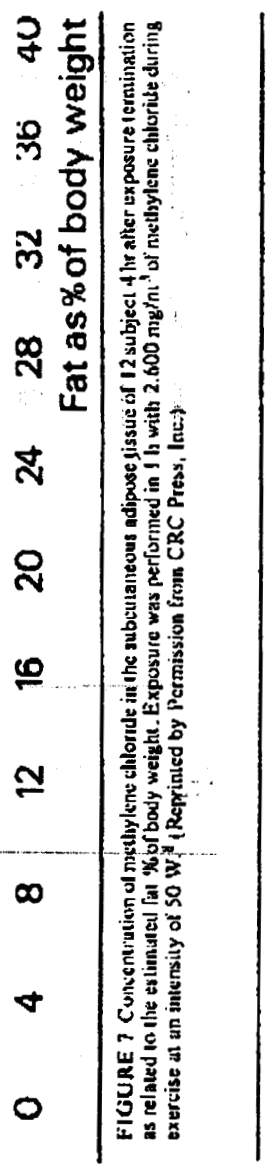


FIGURE 7 Concentration of methylene chloride in the subcutaneous adipose tissue of 12 subject 4 hr after exposure termination as related to the estimated fat % of body weight. Exposure was performed in 11 h with 2,600 mg/m³ of methylene chloride during exercise at an intensity of 50 W.[9] (Reprinted by Permission from CRC Press, Inc.)

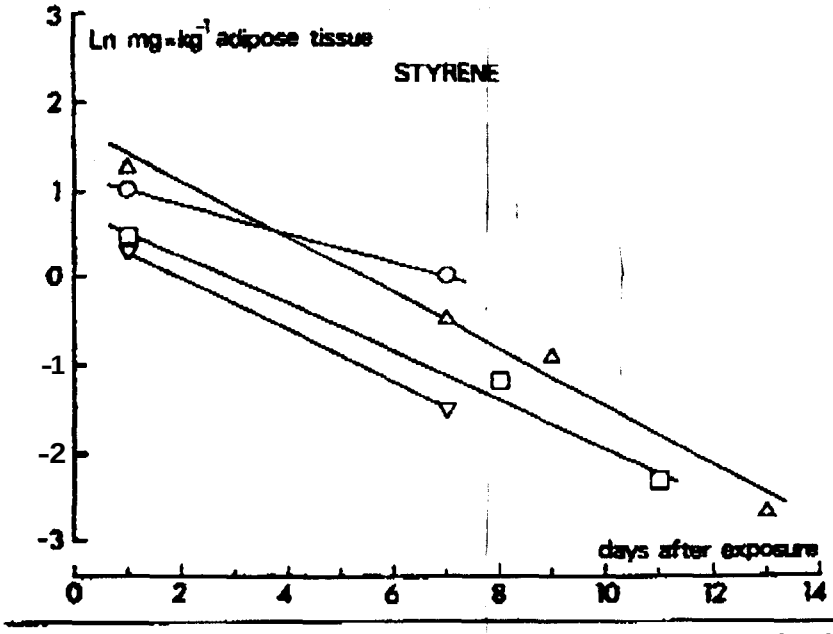
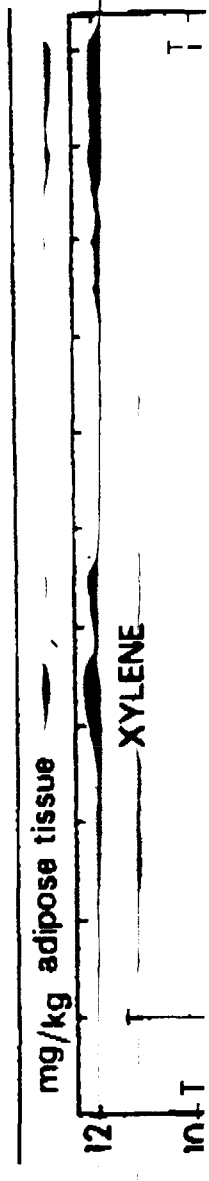


FIGURE 9 Concentration of styrene in the subcutaneous adipose tissue of 4 subjects from 1 to 13 d after 2 hr exposure to 210 mg/m³ in inspiratory air. Exposure was performed during rest and at an intensity of 50, 100 and 150 W.[10] (Reprinted by Permission from CRC Press, Inc.)

Figure 10 illustrates the concentrations in adipose tissue after exposure to industrial xylene.[9] There was no change in concentration during the first 24 hr. In a subsequent study the half-life of xylene in subcutaneous adipose tissue varied between 1 and 5 days."

Because of poor blood perfusion of adipose tissue, only small amounts or around 10% of the total uptake were retained in adipose tissue. It is probably no risk of accumulation of methylene chloride in adipose tissue *if* the threshold limit values are not exceeded. However, because of the long half-life in adipose tissue of styrene and xylene, accumulation can be expected in occupational exposure. In three persons occupationally exposed to styrene, the mean concentration in adipose tissue was about *80* times higher than in ambient air.[7] There *is* reason to suspect that the elimination after industrial exposure takes much longer than two weeks.

What is the implication *of* an accumulation of a solvent in the adipose tissue? It means that as long as the solvent stays in the adipose tissue, it probably also stays in other fat-riche tissues. It also means that indirect exposure of internal organs such as the nervous system and the liver continues as long as the release from the adipose tissue continues. If the solvent and/or its metabolites are toxic the effect will *of* course be carried *on* during a longer *time,* and that is probably associated with a greater risk of development of diseases.



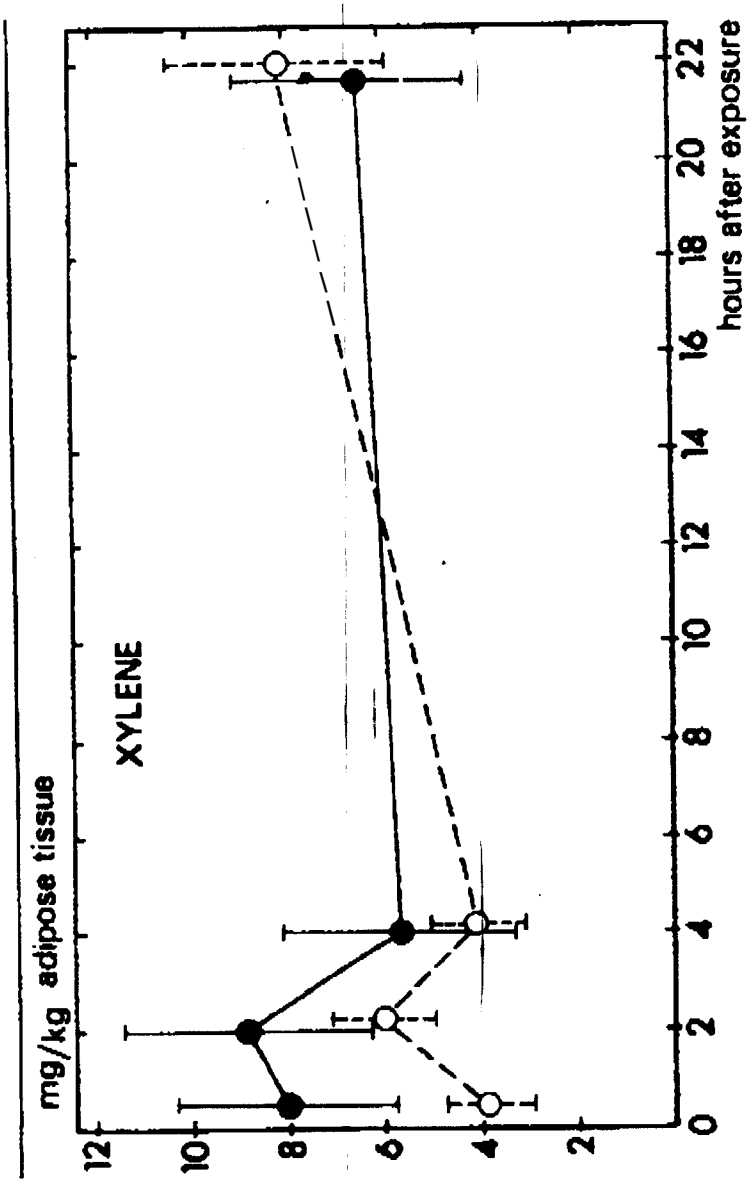


FIGURE 10 Concentration of xylene in the subcutaneous adipose tissue of subjects after exposure. • = mean and standard errors of 6 subjects exposed to 870 mg/m^3 in 2 hr during rest and exercise; o = mean and standard errors of 6 subjects exposed to 435 mg/m^3 in 2 hr during rest and exercise. [Reprinted by Permission from CRC Press, Inc.]

REFERENCES

1. Åstrand I: Uptake of solvents in the blood and tissues of man. A review. *Scand J Work Environ & Health* 1:199, 1975.
2. Åstrand I, Engström J, Ovrum P: Exposure to xylene and ethylbenzene. I. Uptake. distribution and elimination in man. *Scand J Work Environ & Health* 4:185, 1978.
3. Åstrand I and Gamberale F: Effects on humans of solvents in the inspiratory air; A method for estimation of uptake. *Environmental Res* 15:1, 1978.
4. Åstrand I and Övrum P Exposure to trichloroethylene: I. Uptake and distribution in man. *Scand J Work Environ & Health* 4:199, 1976.
5. Åstrand I, Övrum P and Carlsson A.: Exposure to methylene chloride: I. Its concentrations in alveolar air and blood during rest and exercise and its metabolism. *Scand J Work Environ & Health* 1:78, 1975.
6. Engström J: Organic solvents in human adipose tissue. *Arbete och Hälsa* 1978:22. Arbetarskyddsverket. Stockholm.
7. Engström J T, Åstrand I and Wigaeus E: Exposure to styrene in a polymerization plant. Uptake in the organism and concentration in subcutaneous adipose tissue. *Scand J Work Environ & Healrh* 4:324, 1978.
8. Engström J and Bjurström R: Exposure to methylene chloride. Content in subcutaneous adipose tissue. *Scand J Work Environ & Health* 3:215, 1977.
9. Engström J and Bjurström R: Exposure to xylene and ethylbenzene. II. Concentration in subcutaneous adipose tissue. *Scand J Work Environ & Healrh* 4:195, 1978.
10. Engström J, Bjurström R, Åstrand I. and Övrum P: Uptake, distribution and elimination of styrene in man, Concentration in subcutaneous tissue. *Scand J Work Environ & Healrh* 4:315, 1978.
11. Engström J and Riihimäki V: Distribution of m-xylene to subcutaneous adipose tissue in short-term experimental human exposure. *Scand J Work Environ & Health* 5:126, 1979.
12. Gamberale F: Behavioral effects of exposure to solvent vapors. Experimental and field studies. *Arbete och Hälsa* 1975:14. Arbetarskyddsverket, Stockholm.
13. Övrum P, Hultengren M and Lindqvist T: Exposure to toluene in a photogravure printing plant. Concentration in ambient air and uptake in the body. *Scand J Work Environ & Health* 4:327, 1978.