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Biological Monitoring of Chlorinated Hydrocarbon Solvents

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The possibility of biological monitoring of exposure to some volatile, halogenated hydrocarbons will be discussed. Most of these agents are widely used as solvents. All agents act on the nervous system as narcotics and differ widely in toxicity. Most of the solvents undergo biotransformation to metabolites. This allows biological assessment of exposure by measurement of the solvent and/or metabolites in exhaled air, blood, and/or urine. However, the same metabolites may occur with exposure to different chlorinated hydrocarbons, eg, trichloroethanol and trichloroacetic acid from exposure to trichloroethene, tetrachloroethene, and 1,1,1-trichloroethane. On the other hand, these agents differ widely in the percentage that is metabolized. There are large gaps in our knowledge, however, and much research will have to be carried out before even tentative data can be established for most of the solvents.

This review of the possibilities for the biological monitoring of exposure to volatile halogenated hydrocarbons is mainly based on the monograph to the Commission of the European Communities, prepared by Monster and Zielhuis.[1] Considerable data concerning the biological monitoring of volatile halogenated hydrocarbons have been published internationally. Nevertheless, the difference in approach to research, the variety of analytical methods, and the frequent discordances in results usually make it difficult to make proposals for biological monitoring.

Table 1 lists the halogenated hydrocarbon solvents that will be discussed. These solvents differ widely in toxicity and in their TLVs. All solvents are more or less nonflammable and liposoluble. Table 2 lists the solvents, the formula, the metabolites, and the possibilities for biological monitoring.

Solvents

Monochloromethane (methyl chloride) is used as a blowing agent for plastic foam and as a chemical intermediate in methylation reactions. It is a gas at room temperature, colorless, and its odor is not detectable at concentrations in air that may already be injurious to health. The nervous system appears to be the critical target organ. The symptoms may occur after a latency time of several hours.

Van Doorn et al[2] identified S-methylcysteine in urine as a metabolite for almost all the retained methyl chloride in four out of six workers; the other two workers excreted less than 10%.

Stewart et al[3] and Putz-Anderson et al[4] also distinguished two groups: the majority had methyl chloride concentrations in blood and breath that were two to six times lower than in the minority. These findings strongly suggest the existence of two populations: a minority of poor converters with a high body burden of methyl chloride and a majority of "converters" with a lower methyl chloride body burden. It is not clear whether this difference in metabolism indicates a difference in susceptibility to methyl chloride.

However, how can the different types of subjects be distinguished? The probable answer is by measuring the solvent in blood or exhaled air as well as by measuring S-methylcysteine in urine.

Dichloromethane (methylene chloride) is the least toxic of the four chlorinated methanes. Dichloromethane is used as a blowing agent for foams and as solvent for many applications. Dichloromethane also has well-known narcotic effects and is slightly irritating to mucous membranes and skin.

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The increased concentration of carbon monoxide (CO) after exposure to dichloromethane was first observed by Stewart and co-workers in 1972.[5] Such symptoms of carbon monoxide poisoning as headaches, however, have not been a common feature of dichloromethane exposure. Approximately 25% of the dichloromethane absorbed is ultimately excreted as CO and the postexposure excretion of dichloromethane by exhalation is less than 5% of the amount absorbed.[6]

From the human volunteer studies of Stewart et al,[7] DiVincenzo et al,[6] and related studies, several conclusions concerning exposure to dichloromethane may be drawn. Pulmonary uptake is rapid and remains essentially unchanged after the first hour. Interruption of the exposure causes a rapid die-away curve. The retention (R) seems to decrease in relation to the increasing concentration of exposure, ie, the relative uptake decreases and the relative concentration in blood increases when the exposure concentration is increased. When the exposure concentration is increased, the concentrations in exhaled air in the postexposure period are not only absolutely higher, but also relative. The decreasing retention (R) during exposure and the relative increasing concentrations in the postexposure period with increasing exposure concentrations are possible indications that the metabolism is saturable not only in animals but also in human subjects. The half-life of dichloromethane in the postexposure period depends on the length of exposure and the time of sampling. The concentration in exhaled air more or less follows the concentration in blood. The ratio between the concentration of solvent in blood and the concentration in exhaled air depends on the solubility of the solvent in blood. Female subjects have about the same concentration in blood as male subjects during the first hours after exposure. Sixteen hours after exposure however, women tend to have higher concentrations in exhaled air.[7] This difference could be due to a higher amount of fatty tissue in women.

Engstrom and Bjurstrom[8] found that, during the first two hours after exposure, the concentration in alveolar air tended to be lower and declined more rapidly in obese subjects than in slim ones. After this, the concentration dropped more slowly in the obese group. During the later phase of elimination, the obese subjects tended to have a higher concentration in alveolar air.

Astrand et al[9] reported that the amount of dichloromethane taken up increased with physical work load, whereas the retention decreased. With 50-watt work

TABLE 1
Halogenated Hydrocarbon Solvents and Their TLVs

Solvent	TLV (ppm)	1984/1985 (mg/m³)
Monochloromethane	50	105
Dichloromethane	100	350
Trichloromethane	10	50
Tetrachloromethane	5	30
1,2-Dichloroethane	10	40
Monochloroethene	5	10
Trichloroethene	50	270
Tetrachloroethene	50	335
1,1,1-Trichloroethane	350	1,900

TABLE 2
Halogenated Hydrocarbon Solvents, Formula, Metabolites, and Possibilities for Biological Monitoring

Name	Formula	Metabolite	Biological Monitoring
Monochloromethane	CH_3Cl	S-Methylcysteine	Monochloromethane (?) S-methylcysteine (?)
Dichloromethane	CH_2Cl_2	Carbon monoxide	Dichloromethane Carbon monoxide
Trichloromethane	$CHCl_3$	Trichloromethanol (?) Phosgene (?) 2-Oxothiazolidine carboxylic acid N-(2-Oxothiazolidine-4-carboxyl)-glycine	Trichloromethane 2-oxothiazoladine-4-carboxylic acid (?)
Tetrachloromethane	CCl_4	Trichloromethane (?) Hexachloroethane (?)	Tetrachloromethane (?)
1,2-Dichloroethane	$H_2ClC—CH_2Cl$	2-Chloroethanol Monochloroacetic acid	1,2-Dichloroethane (?) Monochloroacetic acid (?) Thiodiacetic acid (?)
Monochloroethene	$H_2C=CHCl$	Chloroacetaldehyde Monochloroacetic acid	Monochloroethene (?) Monochloroacetic acid Thiodiacetic acid
Trichloroethene	$Cl_2C=CHCl$	Trichloroethanol Trichloroacetic acid	Trichloroethanol Trichloroacetic acid Trichloroethene
Tetrachloroethene	$Cl_2C=CCl_2$	Trichloroacetic acid Trichloroethanol (?)	Trichloroacetic acid Tetrachloroethene Trichloroethanol (?)
1,1,1-Trichloroethane	$H_3C—CCl_3$	Trichloroethanol Trichloroacetic acid	Trichloroethanol Trichloroacetic acid 1,1,1-Trichloroethane

load, the uptake was twice as high, whereas the retention decreased from 55% to 45%. When exposure was coupled with physical work load, the concentration in alveolar air was increased during the whole postexposure period compared with exposure under rest conditions.[9] DiVincenzo and Kaplan[10] reported similar results. They showed that exercise was accompanied by increased pulmonary excretion of carbon monoxide during exposure, which undoubtedly contributed to the lower than expected carboxyhemoglobin (COHb) values encountered during heavy work loads.

Engstrom and Ejurstrom[6] measured the concentration of dichloromethane in subcutaneous adipose tissue after exposure (750 ppm, one hour, 50-watt work load). In six slim subjects, the concentration four hours after exposure was on average twice that in six obese subjects. On the other hand, the obese subjects had greater calculated amounts of dichloromethane in the total fat depots in their bodies. More studies will have to be carried out to provide data on concentrations in adipose tissue in relation to various exposure levels.

Compared with the concentration of dichloromethane in alveolar air, the concentrations of carbon monoxide and carboxyhemoglobin increase and decrease slowly; interruption of the exposure (during lunch and after exposure) cause either a slow die-away curve or none at all.[6] The maximum COHb is sometimes reached zero to two hours after exposure. The biological half-life of COHb after exposure to dichloromethane is about 12 to 16 hours, is, double the half-life of COHb levels after CO exposure. This can be explained by the continuous formation of carbon monoxide from dichloromethane after exposure. There are indications that simultaneous exposure to other solvents may increase the biological half-life of COHb. The combined effect of smoking and exposure to dichloromethane produces an additive increase in blood carboxyhemoglobin levels.[10]

Biological monitoring of dichloromethane exposure can be based on measurement of the solvent itself in exhaled air or blood. However, as production of CO with exposure for more than three to four hours per day appears to be the limiting factor in regard to health risk, biological monitoring based upon either analysis of CO in exhaled air or of COHb in blood is to be preferred. This can only be applied in nonsmoking subjects. Sampling should be done about zero to two hours after exposure or after 16 hours on the following morning.

Trichloromethane (chloroform) once was widely used as an anesthetic. Because of often-delayed liver injury, this use is now considered absolute. There is also considerable evidence that chloroform is carcinogenic in mice and rats.

Few data exist on chloroform metabolism in healthy workers; most data refer to studies in anesthetized patients. At least a part of the chloroform is metabolized to carbon dioxide, and another part is exhaled unchanged; the formation of trichloromethanol phosgene, 2-oxothiazolidine-4-carboxylic acid (OTZ) and N-(2-oxothiazolidine-4-carboxyl)-glycine (OTZG) is also assumed.[11] The reaction of phosgene with tissue molecules is believed to produce liver and kidney damage.

Up to now, no metabolite has been identified in the blood or urine that could be considered useful in evaluating occupational exposure to chloroform.

Tetrachloromethane (carbon tetrachloride) is being used less because of awareness of the hepatotoxicity and the availability of less hazardous solvents. The evidence is sufficient to show that carbon tetrachloride is carcinogenic in experimental animals.

Liver and renal function tests are regarded as the most sensitive and practical methods of detecting early health impairment.[12] In acute exposure, both liver and kidney function may be most critical; in chronic exposure, liver effects are predominant.

Only a few studies on metabolism exist. The formation of CCl_3-radicals is assumed to be the initial step in biotransformation. The radicals subsequently bind irreversibly to celiular macromolecules and initiate lipid peroxidation. Part is excreted unchanged and another part as CO_2. The formation of the radicals is supported indirectly by the appearance of small amounts of chloroform and hexachloroethane in tissue of rabbits after administration of tetrachloromethane.[13]

It is very probable that measurement of carbon tetrachloride in exhaled air or blood will be the method of choice for biological monitoring. However, few data exist.

1,2-Dichloroethane (ethylene dichloride) is used as a starting material for vinyl chloride; it is also used as an antiknock agent in gasoline and as a solvent. At very high concentrations, 1,2-dichloroethane is irritating to the eyes, nose, and throat. Exposure may also affect the CNS, liver, kidneys, and skin. A specific critical target organ has not been identified. There is sufficient evidence that 1,2-dichloroethane is carcinogenic in mice and rats. The nature of the metabolism of 1,2-dichloroethane has not been established, but some appears to go through 2-chloroethanol to monochloroacetic acid and further to oxalic acid: however, S-carboxymethylcysteine and thiodiacetic acid have also been detected.[14] However vinylchloride gives the same metabolites.

No references have been found that would indicate satisfactory biological monitoring for industrial hygiene control. Among the possible methods are measurement of dichloroethane in blood and exhaled air or measurement of its metabolites in blood and urine.

Monochloroethene (vinyl chloride) is used as a monomer in polyvinylchloride (PVC) production. Many studies in workers have shown that vinyl chloride is a human carcinogen.

Up to about 15 years ago, vinyl chloride was regarded as rather harmless, so little effort was devoted to studying its metabolism.

Currently, it is thought that vinyl chloride is metabolized by epoxidation with subsequent production of chloroacetaldehyde. Further oxidation and conjugation with glutathion are responsible for the metabolites found in the urine, such as s-arboxymethylcysteine and thiodiacetic acid.[15,16] No valid routine biological monitoring method exists to evaluate vinyl chloride exposure at present-day accepted levels. Increased urinary excretion of metabolites such as thiodiacetic acid promises

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distribution, metabolism, and excretion of perchloroethylene. PER is almost totally excreted by exhalation. Only a small amount of the PER that is absorbed in the body is metabolized to trichloroacetic acid (2%) and excreted in urine.[23-25]

PER has a long half-life when measured in expired air or blood, probably because of deposition in fat and similar tissue. It has a half-life of approximately four to six days in short-term experiments and approximately six to eight days in long-term exposure (workers in dry cleaning shops). The blood/air and fat/air partition coefficients of PER at 37°C are about 15 and 2,000, respectively.[26, 27]

In cases of exposure to PER, the concentration of TCA in blood and urine is much lower than after exposure to TRI, but the kinetic behavior of TCA is more or less the same. Work load during exposure increases the blood and exhaled air concentrations not only during exposure, but also in the postexposure period. Alcohol consumption during exposure has no effect on the concentration of PER either during or after exposure.

Repeated exposure experiments indicate that PER accumulates in the body; therefore, PER in alveolar air and in blood in the first hour after exposure is probably more indicative of a TWA concentration than of a recent concentration; the concentration on the following morning and after the weekend probably indicates the TWA exposure during the preceding days or weeks. For TCA in blood and urine, the time of sampling is not important; it indicates the TWA exposure during the preceding week(s).

In contrast to the experiments, small amounts of trichloroethanol (TCE) were found in the urine of workers in industrial studies.[28, 29] Japanese studies indicate that the capacity of humans to metabolize PER above 100 ppm is limited.[30, 31] In addition, they find much higher values for TCE and TCA in urine. This difference may be at least partly explained by the difference in analysis. They used a nonspecific spectrophotometric method: a modified Fujiwara reaction.

Monster et al[28] investigated exposure to PER in dry-cleaning shops during the entire work week. Blood, alveolar air, and urine were sampled on several days of the work week. Table 4 shows the estimated concentrations in the biological specimens in a daily TWA exposure to 50 ppm.[1] The results also indicate that PER in blood after work on Friday seemed to be the best parameter for estimating the TWA-week exposure. For PER in alveolar air and TCA in urine and blood, the spread was somewhat larger. TCE was more related to the TWA exposure during two preceding days than to the TWA exposure during the week or during one day.

TABLE 4
Mean Concentrations of Tetrachloroethene (PER), Trichloroethanol (TCE), and Trichloroacetic acid (TCA) in Blood, Alveolar Air, and/or Urine in Subjects Exposed to a TWA Exposure of 50 ppm (345 mg/m³) PER 8 h/d, 5 d/wk[1]

Medium	Time of Sampling After Exposure		
	End of Exposure	5–15 min	64 h
Blood (mg/L)			
PER		2.3	0.82
TCE		—	—
TCA		5.8	3.8
Alveolar air (PER)			
mg/m³		160	53
ppm		23	8
Urine (mg/g creatinine)			
TCA	9.7		4.9
TCE	0.5		—

TABLE 5
Mean Concentrations of 1,1,1-Trichloroethane (MC), Trichloroethanol, (TCE) and Trichloroacetic Acid (TCA) in Blood, Alveolar Air, and Urine in Subjects Exposed to a TWA Concentration of 50 ppm (275 mg/m³) of MC 8 h/d, 5 d/wk[1]

Test	Time of Sampling After Exposure			
	End of Exposure	5–15 min	16 h	64 h
Blood (mg/L)				
MC		0.9		0.07
TCE		0.16		—
TCA		2.3		1.6
Alveolar air				
MC, mg/m³ (ppm)		210 (39)	13 (2.4)	8 (1.5)
TCE mg/m³		0.014	0.007	—
Urine (mg/g creatinine)				
TCA	4.9		2.5	0.9
TCE	2.5		1.8	1.5

The data published for biological monitoring of PER are limited in scope and not yet sufficiently validated, but they are very promising. Because PER (and TCA) appear to accumulate in the body, adequately controlled observations in industry in workers exposed for at least a few weeks are needed to establish valid biological monitoring parameters.

1,1,1-Trichloroethane (methylchloroform [MC]) is widely used as a solvent. The principal and first response is depression of the CNS. The low toxicity appears to be related to the low solubility in blood and adipose tissue (λ blood/air: 3 to 6, λ fat/air: 360)[26, 27] and the small amount of metabolism that occurs. MC is almost totally excreted by exhalation, whereas only small amounts of TCE (2–5%) and TCA (1% to 2%) are excreted in urine.[32, 33] The kinetic behavior of TCE and TCA is more or less the same as after exposure to TRI or PER. Work load during exposure to MC increases its concentration in alveolar air during the whole postexposure period.[33]

Monster[34] investigated exposure to MC in four workshops. During an entirely normal work week, exposure to MC was measured with personal air samplers. Blood, alveolar air, and urine were sampled on several days of the work week. Table 5 shows the estimated concentration at the end of the work week after daily exposure to 50 ppm MC. The concentrations of TCE and TCA in urine are somewhat lower than those found by Seki et al[35] and Tada.[36] This can partly be explained by differences in analysis: Seki et al and Tada used the nonspecific spectrophotometric Fujiwara reaction. The results also indicated that TCA in blood after work on Friday seemed to be the best parameter for estimation of the TWA-week exposure. TCA was followed by MC in exhaled air the next Monday. The combination of two parameters measured at the same time resulted in a somewhat smaller SD than for single parameters. The best combinations were MC and TCA in blood on Friday

evening and the following Monday, but the combination of TCE and TCA in urine on Friday was also reasonably satisfactory.

For one-day exposure, the smallest SD was obtained for TCE in blood and urine. The reliability of the estimation increased, however, when estimation of the TWA exposure was calculated for the previous two days instead of one day. The best method to use for estimation of exposure to MC depends on the nature of the investigation: long-term exposure: TCA and MC; short-term exposure: MC (directly after exposure); one (two) day(s) exposure: TCE.

Also in the case of MC, more data, particularly from repeated exposure studies and from studies in industry, should be available before an adequate proposal for biological monitoring can be presented.

Conclusion

There are still large gaps in our knowledge, and much research will have to be carried out before even tentative data can be established for most of the solvents. Only for the solvents trichloroethene, tetrachloroethene, 1,1,1-trichloroethane, and to a lesser extent, dichloromethane are the relations between environmental monitoring more or less available, and they are available only as group average values.

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