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In Vivo Conversion of Methylene Chloride to Carbon Monoxide

Ronald S. Ratney, PhD; David H. Wegman, MD; Hervey B. Elkins, PhD, Boston

A group of workers exposed to 180 to 200 ppm of methylene chloride had carboxyhemoglobin (COHb) levels of about 4.5% as measured by alveolar carbon monoxide concentrations at the beginning of their workday. This rose to about 9% after eight hours of exposure and then dropped exponentially to 4.5% by the time they started working the next day. The 24-hour time-weighted average %COHb was 7.3% compared with 2.7% for persons exposed to 35 ppm of carbon monoxide or 3.8% for persons exposed to 50 ppm of CO.

On the basis of these observations, it is proposed that the threshold limit value for methylene chloride be reduced to 75 to 100 ppm to avoid body burdens of COHb greater than those allowed persons exposed to exogenous CO.

Methylene chloride is usually considered to be the safest of the chlorinated hydrocarbons.[1] Industrially it is used primarily as a paint stripper, but also as a degreaser, aerosol propellant, and as a solvent for plastic films and cements. Production in the United States has grown rapidly from 44,000 tons in 1958 to over 235,000 tons in 1972.[2]

In order to prevent adverse health effects, the recommended threshold limit value (TLV) is now set at 500 ppm by the American Conference of Governmental Industrial Hygienists.[1] Workers exposed at this level for an eight-hour workday show no apparent narcotic effect or liver damage. Recently, however, Stewart et al[3] presented evidence that the body converts inhaled methylene chloride to carbon monoxide and that persons exposed to methylene chloride have elevated carboxyhemoglobin (COHb) levels and elevated concentrations of CO in alveolar air.

Since methylene chloride is encountered in a number of industries, it was decided to determine whether exposure to this material at the workplace resulted in an excessive body burden of CO.

We identified a plastic film plant in Massachusetts which uses large quantities of methylene chloride, along with smaller amounts of chloroform, in the production of its films. Employees in this plant have been working in an atmosphere containing the solvent eight hours per day, six days per week, for several years. Vapor concentrations in the air in the plant have fluctuated over a fairly narrow range for several years, and there is no CO in the air from combustion sources. During a continuous 42-hour period, while the plant was operating without interruption, we measured concentrations of methylene chloride in the workroom air. In addition, alveolar air samples were taken from workers at regular intervals during a 24-hour period beginning 18 hours after environmental sampling had started. These all were analyzed for CO and some were also analyzed for methylene chloride.

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Methods

Methylene Chloride in Workroom Air.—Samples were taken (1) on silica gel and analyzed by hydrolysis and titration and (2) on charcoal and analyzed by gas chromatography.

Silica Gel Sampling and Anlaysis.—Seven grams of silica gel (6×16 mesh) were placed in each arm of a glass U tube (14 mm internal diameter, each arm about 10 cm long) with a plug of glass wool between the portions. Workroom air was drawn through the U tube at about 0.5 liters/min for 90 to 120 minutes. At the conclusion of the sampling, the tubes were closed with cork stoppers.

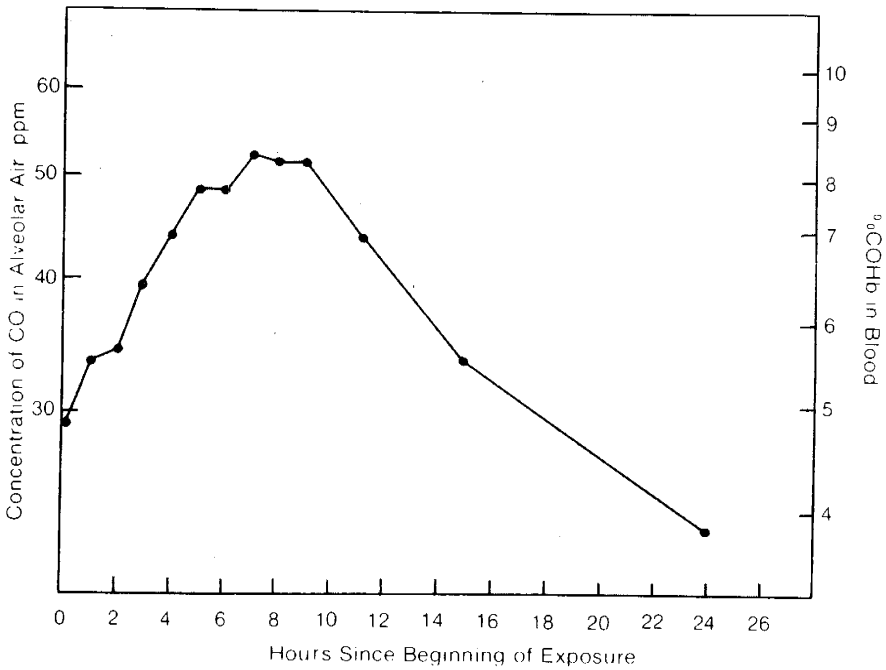
Each arm of the U tube was analyzed separately in order to provide a measure of the completeness of collection. Methylene chloride was desorbed by soaking the silica gel in 50 ml of isopropyl alcohol for two hours. A 10-ml aliquot of this solution was heated at 50 C overnight (approximately 18 hours) with 0.4 gm of solid potassium hydroxide (four pellets). Another 10-ml aliquot was heated for 95 hours with 0.6 gm of solid potassium hydroxide. At the conclusion of the hydrolysis period, excess potassium hydroxide was neutralized with 6N acetic acid and free chloride ion was titrated with 0.01M silver nitrate, using potassium chromate as the indicator.

Both methylene chloride and chloroform are hydrolyzed by base to yield free chloride ion. Methylene chloride is hydrolyzed quite slowly under these conditions. Only about 4% of the total amount of chlorine is released as chloride ion after 18 hours of hydrolysis. This rises to about 20% after 95 hours. Chloroform, on the other hand, is 80% hydrolyzed in 18 hours, and this does not increase with longer reaction times.

After 18 hours of hydrolysis, the total chloride released (q) is given by equation 1:

$$q_{18} = r_c C_c + r_{m18} C_m$$

where r_c = fractional recovery of total chlo-



Alveolar CO and blood COHb levels in men exposed continuously to methylene chloride vapor. Each point represents average of seven individuals.

ride from chloroform, r_{m18} = fractional recovery of total chloride from methylene chloride after 18 hours of hydrolysis, C_c = number of equivalents of chloroform in sample, and C_m = number of equivalents of methylene chloride in sample. After 95 hours, the total chloride released is expressed by equation 2:

$$q_{95} = r_c C_c + r_{m95} C_m$$

where r_{m95} = fractional recovery of total chloride from methylene chloride after 95 hours of hydrolysis. Equations 1 and 2 can be rearranged to give C_m (equation 3) and C_c (equation 4):

$$C_m = (q_{95} - q_{18})/(r_{m95} - r_{m18})$$

$$C_c = (q_{18} - r_{m18} C_m)/r_c = (q_{95} - r_{m95} C_m)/r_c.$$

Charcoal Tube Sampling and Analysis.—This is a modification of the charcoal tube method developed by the National Institute for Occupational Safety and Health.[4] One gram of activated charcoal (6×16 mesh) is placed in a glass tube (6 mm internal diameter) and held in place with glass wool. Before and after sampling, the ends are covered with masking tape. Air was drawn through the charcoal tubes at 1 liter/min for ten minutes.

Vapors adsorbed onto the charcoal were eluted with 5 ml of carbon disulfide by shaking on a mechanical shaker for 30 minutes. Aliquots of the resulting solution were injected into the gas chromatographic column. The column stationary phase was the free fatty acid phase on dimethylchlorosilane-treated Chromosorb, and peaks were detected with a flame ionization detector.

The peak heights corresponding to methylene chloride from three to five successive injections were averaged, and the amount injected was calculated by comparison with peak heights obtained from a standard solution studied at the same time.

Measurement of CO and Methylene Chloride Concentrations in Alveolar Air.—Alveolar air samples were collected by the expired air technique. Each subject was requested to inhale deeply and hold his breath for 20 seconds. He was then instructed to exhale through a Rudolph low-dead-space pulmonary valve, Model 1400, fitted with a 1-liter low resistance bag and a 1.3-liter alveolar air high resistance collection bag. The first liter of expired air flowed into the low resistance bag and was discarded. The 1.3 liters of expired air collected in the high resistance bag was analyzed for CO and, in selected instances, a 500-ml aliquot was passed through a charcoal collection tube and analyzed for methylene chloride as described above.

Carbon monoxide concentrations were measured using an Ecolyzer carbon monoxide monitor, Model 2400, employing the 0- to 100-ppm scale. Samples were analyzed immediately after collection.

Direct measurements of COHb levels in blood samples would have been desirable, but it was felt that this was not feasible since the projected number of samples was large and refusals were anticipated. In place of direct measurements, levels of %COHb were calculated from alveolar CO concentrations according to equation 5[5]:

$$\%COHb = 230 P_{CO_2} \times (\%O_2Hb/P_{O_2})$$

where P_{O_2} is assumed to be 98 mm Hg and $\%O_2Hb$ is assumed to be (99−%COHb).

Exposure Routine

The workers participating in this study were engaged in their normal workday routine in their normal workplaces. They were not subject to any special experimental exposures. In addition, two of the authors and a staff member of the Massachusetts Division of Industrial Safety (DIS) were present in the plant during the study and were exposed to the same atmospheric concentrations as the workers.

Those workers studied were the four production men who were working on the 7 AM to 3 PM day shift. They were aged 20, 21, 26, and 33, were in good health, and had been working in this job for at least one year. Two of them were nonsmokers and the other two agreed to stop smoking beginning 12 hours before the first alveolar air samples were taken and continuing until the final sample was collected. The two authors and DIS staff member were nonsmokers, were in good health, and were aged 33, 33, and 41. The three had been exposed to the work environment for eight hours on the day prior to the 24-hour period of alveolar air sampling.

Alveolar breath samples were taken from all seven subjects as they arrived at work on the second day of workroom air sampling. The breath samples were taken once every hour for the next eight hours, ie, to the end of the work shift. After the subjects left the workplace, alveolar air samples were collected at 1, 3, 7, and 16 hours (the last, as they returned to work the next day).

Results

Environmental.—Samples of air in the workroom were taken on silica gel and charcoal on the day preceding the studies on subjects. The concentration of methylene chloride varied from 245 ppm to 471 ppm, with a mean of 286 ppm. The concentration of chloroform during the same period varied from 25 to 53 ppm, with a mean of 46 ppm. During the day on which alveolar air samples were taken, the methylene chloride environmental concentration (measured by the charcoal technique) varied from 159 to 219 ppm, with a mean of

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183 ppm. The chloroform concentration varied from 25 to 36 ppm, with a mean of 31 ppm. The process is such that exposure depends on machine operation (breakdowns result in higher concentrations) and thickness of film being produced (thicker film causes higher concentrations). These variables probably account for the differences on the two days.

These measurements represent the general plant air to which workers are exposed during about 90% of their working day. There were other areas where the methylene chloride concentrations were much higher, but workers were in these areas for only short periods (minutes at a time). The methylene chloride concentrations in these contaminated areas ranged from 300 ppm near a film stretcher to 845 ppm in a room where solvents and resin were loaded into a closed mixer and also where the resin solutions were filtered. In general, employees entered this room only once every 16 hours, and those whose alveolar air was studied did not enter it at all during the day samples were obtained.

Methylene chloride in alveolar air samples was detected in qualitatively significant amounts during and after exposure in every specimen. Only selected samples of alveolar air from the four employees were studied during and after exposure.

Alveolar Air.—The results for CO in alveolar air and the calculated values for %COHb are shown in Table 1. Mean values are shown plotted on semilog scale in the Figure. The mean CO concentration in alveolar air is seen to be 29 ppm and 23 ppm at the start of two successive working days. These levels are not uncommon for smokers, but the study group consisted of nonsmoking individuals. The increase in alveolar CO is linear during the working day and appears to reach a plateau at seven to eight hours at this exposure. Following removal from exposure, loss of CO is exponential and at a slower rate than for those experimentally exposed directly to CO.[6]

These data suggest that nonsmoking workers exposed chronically to methylene chloride constantly produce CO endogenously, which results in an increased COHb load. In this population, the base level appears to be at least 4.5% COHb. During exposure, the rate of increase of CO in alveolar air is about 3 ppm/hr or 0.5% COHb/hr.

Comment

The excretion of CO by persons exposed to methylene chloride as reported here is consistent with the findings of Stewart et al.[3] It is hypothesized that a person exposed to methylene chloride converts the solvent to CO, which is then excreted through the lungs. During exposure, production of CO is at a rate greater than the rate of excretion, and thus accounts for the gradual increase in %COHb.

In their study subjects, Stewart et al noted that %COHb continued to increase after exposure ceased in those exposed to short-term high exposures (986 ppm).[3] In the population studied here, the alveolar CO levels apparently reached a plateau after an exposure period four times as long, at a concentration only one fifth as great.

In both Stewart et al's subjects and ours, excretion of CO in the post-exposure period was prolonged as compared with normal excretion rates for CO. Peterson and Stewart showed that alveolar CO concentrations decrease exponentially.[6] Nonsmoking men who have been removed from a CO-containing atmosphere excrete CO such that the half-life of COHb is 320 minutes (5.33 hr). In the present study population, COHb levels dropped from 9% to 4% in 16 hours. The half-life of 13 hours is approximately 2.5 times that which would be observed in an individual excreting CO that had been inhaled from the atmosphere.

This prolonged excretion of CO most likely results from storage of methylene chloride in body tissues, with conversion to CO continuing subsequent to removal from exposure to methylene chloride. Although reported studies have not demonstrated accumulation of methylene chloride, Stewart et al[7] have shown that repeated eight-hour exposures to another chlorinated hydrocarbon (1,1,1-trichloroethane) results in accumulation of the solvent.

The excretion pattern of CO in those exposed to methylene chloride then derives from the combination of the conversion of methylene chloride to CO and the storage of the solvent in body tissues. Endogenous CO production exceeds excretion during exposure, and this results in a gradually increasing level of COHb. After exposure is terminated, CO excretion proceeds at its normal rate; however, the methylene chloride stores continue to be converted to CO and, in effect, produce a continuous exposure to CO from endogenous sources.

The TLV for methylene chloride has been set at a level which will avoid narcotic effects or liver injury.[1] The results of the observations reported here indicate that the endogenous conversion to CO of inhaled methylene chloride should be the controlling factor. Although the data presented in this article refer to a small number of people, the finding of significant levels of COHb in persons chronically exposed to methylene chloride at levels well below the current TLV (500 ppm) suggests that some estimate of a safe exposure level based on these data is necessary.

The current TLV for CO is 50 ppm, which is based on a desire to prevent borderline acute effects.[1] However, in 1972 the National Institute for Occupational Safety and Health recommended lowering the TLV to 35 ppm.[8] This value was chosen so that a sedentary worker exposed to this concentration would have a COHb level of 5% or less at the end of eight hours.[6,9] The limit of 5% COHb was based on studies of persons with insidious and overt coronary artery disease who showed evidence of compromised cardiac function at COHb levels in excess of 5%. The recommendation does not protect cigarette smokers, since chronic smokers without exogenous exposure to CO have COHb levels of 4.5%.

In order to estimate a safe exposure level for methylene chloride, we calculated the 24-hour time weighted average (TWA) %COHb for persons exposed to CO and to methylene chloride. This was done by using a combination of integral calculus and simple

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Table 1.—Alveolar CO and Calculated COHb Levels*

Subject	Hours Since Beginning of Exposure During Exposure 0	1	2	3	4	5	6	7	8	After Exposure 9	11	15	24
1	26	29	29	31	31	36	34	36	36	38	33	38	17
	4.4	4.9	4.9	5.2	5.2	6.0	5.7	6.0	5.7	6.3	5.5	4.7	3.6
2	32	32	32	34	41	49	43	42	41	50	33	27	21
	3.3	5.3	5.3	5.7	6.8	8.0	7.0	6.9	6.8	8.1	5.5	4.6	3.6
3	30	32	39	39	44	45	47	55	58	56	46	29	23
	5.0	5.3	6.4	6.4	7.2	7.4	7.7	8.8	9.3	9.0	7.5	4.9	3.9
4	32	33	32	38	45	49	43	49	51	50	41	24	25
	5.3	5.5	5.3	6.3	7.4	8.0	7.0	8.0	8.3	8.1	6.8	4.1	4.2
5	24	41	41	54	60	65	74	85	77	68	61	44	29
	4.1	6.8	6.8	8.7	9.6	10.3	11.5	13.0	12.0	10.7	9.7	7.2	4.9
6	30	35	36	42	41	48	51	56	50	50	46	42	26
	5.0	5.8	6.0	6.9	6.8	7.8	8.3	9.0	8.1	8.1	7.5	6.9	4.4
7	27	28	31	34	40	42	45	41	44	44	39	38	23
	4.6	4.7	5.2	5.7	6.6	6.9	7.4	6.8	7.2	7.2	6.4	6.3	3.9
Mean	29	33	34	39	43	48	48	52	51	51	43	33	23
	4.9	5.5	5.7	6.4	7.1	7.8	7.8	8.4	8.3	8.3	7.1	5.5	3.9

* First value: CO in alveolar air (expressed in parts per million); second value: calculated % COHb.

mensuration, assuming a linear increase in %COHb during exposure and an exponential decline afterward.

Peterson and Stewart[6] have shown that nonsmokers who are not exposed to CO have a COHb level of 0.75%. As noted above, a nonsmoker exposed to an average CO concentration of 35 ppm will have a COHb level of 5% after eight hours. Peterson and Stewart showed that this will drop exponentially after exposure has ceased, and it can be calculated from their data that it will have returned to normal (0.75%) by the end of the 16th hour postexposure.

The workers who participated in this study had an average %COHb level of about 4.5% on reporting to work. This rose to 9% after eight hours of exposure to methylene chloride at 180 ppm and then dropped back to 4.5% after 16 hours off the job. The 24-hour TWA COHb in these circumstances is 7.3%. Calculations establish that this corresponds to a 24-hour TWA COHb level of 2.7%. The results of similar calculations for exposure to 50 ppm of CO and to 180 ppm of methylene chloride are summarized in Table 2 along with the basic data used in these calculations.

Table 2.—Eight-Hour Exposure to Carbon Monoxide or Methylene Chloride

	35 ppm CO	50 ppm CO	180 ppm CH_2Cl_2
Preexposure % COHb	0.75	0.75	4.5
Maximum % COHb	5.0	6.4	9.0
Half-life for elimination of COHb, hr	5.3	5.3	13
24-hr TWA % COHb	2.7	3.8	7.3

If the increase in %COHb is directly proportional to average methylene chloride concentration, it would be necessary to keep levels well below 100 ppm to maintain the resulting %COHb below that produced by 35 ppm of CO. A methylene chloride exposure of about 100 ppm would produce the same TWA %COHb as 50 ppm of CO.

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References

1. *Documentation of the Threshold Limit Values*, ed 3. Cincinnati, American Conference of Governmental Industrial Hygienists, 1971.

2. *Summaries of Trade and Tariff Information: Schedule 4*, publication 284. US Tariff Commission, 1969, vol 6.

3. Stewart RD, et al: Experimental human exposure to methylene chloride. *Arch Environ Health* 25:342-348, 1972.

4. White LD, et al: A convenient optimized method for the analysis of selected solvent vapors in the industrial atmosphere. *Am Ind Hyg Assoc J* 31:225-232, 1970.

5. McFarland RA, et al: *A Study of the Effects of Low Levels of Carbon Monoxide Upon Humans Performing Driving Tasks: Final Report on CRC-APRAC Contract CAPM-9-69(2-70)*. Boston, Harvard School of Public Health, 1971.

6. Peterson JE, Stewart RD: Absorption and elimination of carbon monoxide by inactive young men. *Arch Environ Health* 21:165-171, 1970.

7. Stewart RD, et al: Experimental human exposure to methyl chloroform vapor. *Arch Environ Health* 19:467-472, 1969.

8. *Criteria for a Recommended Standard for Occupational Exposure to Carbon Monoxide*, HSM 73-11000. National Institute for Occupational Safety and Health, 1972.

9. Coburn RF, Forster RE, Kane PB: Considerations of the physiological variables that determine the blood carboxyhemoglobin concentrations in man. *J Clin Invest* 44:1899-1910, 1965.

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