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Evaluation of the psychophysiological functions in humans exposed to the 'Threshold Limit Value' of 1,1,1-trichloroethane

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Salvini, M., Binaschi, S., and Riva, M. (1971). *Brit. J. Industr. Med.*, 28, 286-292. Evaluation of the psychophysiological functions in humans exposed to the 'Threshold Limit Value' of 1,1,1-trichloroethane. The effects on the psychophysiological functions in human beings of exposure to 1,1,1-trichloroethane (methylchloroform; MC) were evaluated by exposing six male university students to an average vapour concentration of 450 p.p.m. for two periods of 4 hours, separated by a 1½-hour interval.

Each subject was examined on two different days, one day undertaking a set of tests in an atmosphere containing MC vapour and on the other day in a 'control' atmosphere which did not contain MC. On each of the two days a series of tests was performed at 8.30 a.m. and repeated at 6 p.m. They comprised a perception test with tachistoscopic presentation, Wechsler Memory Scale, a complex reaction time test, and a manual dexterity test. A crossed scheme analysis was used.

After the two exposures no disturbances in motor function, coordination, equilibrium or behaviour patterns were observed in any of the subjects; there were some complaints about eye irritation at the peak exposure periods.

The following conclusion may be drawn from the results. In humans exposed to a vapour concentration of MC of 450 p.p.m. the psychophysiological functions studied were not decreased. The low percentage reduction in performance which was observed is not statistically significant. In the perception test an interaction between exposure to MC and mental fatigue was observed.

The evaluation of the concentrations of substances potentially noxious to mankind may be useful in the prevention of occupational disease only so long as reliable medical and biological reference standards are available which have been defined according to established criteria. Some specialized bodies, such as the American Conference of Governmental

Industrial Hygienists (ACGIH), have proposed special values such as Threshold Limit Values (TLVs) as guide-lines for the interpretation of the acceptable concentration of a substance in the air. 'Threshold Limit Value' refers to airborne concentrations of substances and represents conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse effects. The value indicates the time-weighted average of fluctuations in vapour concentrations in the working area for a 7- or 8-hour work-day.

TLVs are periodically revised and during the last

¹The TLV adapted in this study is the one recommended by The American Conference of Industrial Hygienists in May 1968.

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five years have steadily been lowered; not so much because the compounds have been shown to cause organic injury at the previous higher levels, but because some of these chemicals impair psychophysiological functions. Consequently, for many substances, particularly solvents, the value is not always considered as the dose capable of causing structural or metabolic lesions, but more properly as the value which will not interfere with those psychological and psychophysiological functions which are fundamental for safety at any working place. If we accept these criteria of evaluating TLVs we then have to accept the addition, to epidemiological and clinical studies of industrial diseases, of research directed toward the establishment for man of limits below those which produce measurable manifestations of early adverse effects. For effects, even though transient and reversible in nature, must be considered which may lead to poor manual manipulation and, therefore, unsafe mechanical operations.

1,1,1-Trichloroethane (methylchloroform) is among those industrially used solvents which lend themselves to this new concept justifying further study and research.

Physical and toxicological properties

1,1,1-Trichloroethane, CH_3CCl_3 , is mostly used in cold cleaning and metal degreasing but is finding increased use in other areas because of its technological properties and low toxicity. (1,1,1-trichloroethane should not be confused with its more toxic isomer 1,1,2-trichloroethane.)

1,1,1-Trichloroethane is a colourless liquid with a characteristic odour similar to that of chloroform. It is very soluble in organic solvents. It is inflammable and will not support combustion. It has a specific gravity of 1.336 at 25°C (77°F), a vapour pressure of 127 mmHg at 25°C (77°F), and a boiling point of 74.6°C (166°F).

As with other chlorinated hydrocarbons it reacts with metals and therefore must be inhibited to prevent corrosion of these metals.

The portals of entry, in order of importance, are the lungs, the gastrointestinal tract, and the skin. Absorption via the respiratory tract is the obvious risk during work in contaminated atmospheres. Gastrointestinal absorption might result from accidental ingestion. Toxic quantities may be absorbed through the skin only when 1,1,1-trichloroethane is kept in contact with the skin beneath an impermeable barrier. No matter what the route of absorption, most is eliminated through the respiratory system (Hake, Waggoner, Robertson, and Rowe, 1960).

From the toxicological standpoint 1,1,1-trichloroethane has been thoroughly investigated. After a

single vapour exposure it exerts its principal toxic action as an anaesthetic. It produces a functional depression of the central nervous system, the magnitude of which is proportional to the degree of exposure (Stewart, Gay, Erley, Hake, and Schaffer, 1961; Torkelson, Oyen, McCollister, and Rowe, 1958; Krantz, Park, and Ling, 1959; Dornette and Jones, 1960). Except for its anaesthetic properties at high concentrations, 1,1,1-trichloroethane does not exert any adverse effects on the body and is to be classified among the least toxic solvents (Plaa, Evans, and Hine, 1958).

Because of its low toxicity there is little information available from clinical data on human exposure to assess the pathological and systemic effects of 1,1,1-trichloroethane. As a result, much of our present knowledge is based on the results of experiments performed on animals (Adams, Spencer, Rowe, and Irish, 1950).

It is interesting to compare the effects produced on animals after a single exposure to 1,1,1-trichloroethane and the effects produced by repeated exposures. There is little or no likelihood that an exposure to 500 p.p.m. of 1,1,1-trichloroethane vapours in air would produce any acute physiological effects. Guinea-pigs, rabbits, and monkeys were exposed *daily* for 7 hours a day to such concentrations without any adverse effects being noted (Adams *et al.*, 1950; Torkelson *et al.*, 1958). These findings agree with those obtained when comparable studies were conducted on humans exposed 7 hours a day for five days (Stewart *et al.*, 1961).

It would appear that these favourable results are explained by the fact that 1,1,1-trichloroethane is for the most part not metabolized in the body and that after either a single or repeated exposures to 500 p.p.m. of vapour in air the substance is rapidly and totally eliminated. Using breath analysis technique with electron capture gas chromatography it is easy to identify the solvent in the expired breath many days after a 7-hour exposure to 500 p.p.m. of the vapour in air. Human subjects exposed to such concentration were found at the end of the last exposure to have a concentration of around 100 p.p.m. in the expired air, which fell to below 10 p.p.m. after 24 hours (Stewart, 1968).

As there appears to be little likelihood that an exposure to 500 p.p.m. causes any adverse effect, an exposure to the present TLV of 350 p.p.m. should guarantee a greater margin of safety.

Even though the evidence for establishing the TLV for 1,1,1-trichloroethane is precise and well documented, there is a lack of information about the transient and reversible effects related to psychophysiological efficiency produced by vapour concentrations at the present TLV of 350 p.p.m. The consideration of such criteria, which are becoming increasingly important for the establishment of

TLVs, constituted the basic reason for planning and conducting this research.

Some initial investigations on the neurological effects after an 8-hour exposure to 500 p.p.m. of 1,1,1-trichloroethane vapour have been described in the literature. However, the full evaluation of psychophysiological efficiency in a worker will be more meaningful if a complete set of tests is given which represent, within certain limits, the multiple variety of psychic activities involved in the working man. These tests should incorporate such factors as manual dexterity, psychomotor functions, perception, response to stimuli, memorization, and ability to make critical judgments.

Methods

The 1,1,1-trichloroethane used in the experiments discussed in this paper was Chlorothene[®] NU solvent, which is the trade name for inhibited 1,1,1-trichloroethane manufactured by the Dow Chemical Company.

Preliminary experiments were performed by exposing human subjects to a concentration of 350 p.p.m., the TLV proposed in 1968 by ACGIH. The duration of exposure was 8 hours with a lunch break of 1½ hours after the first 4 hours. As the findings were negative, we decided to increase the concentration of 1,1,1-trichloroethane to see if we could obtain a positive reaction. The average concentration was thus increased to 450 p.p.m., with values ranging between 500 and 400 p.p.m. On the basis of the work of Torkelson and his colleagues (1958) which indicated that a 7½-hour exposure to 506 p.p.m. of 1,1,1-trichloroethane was not followed by any objective or subjective clinical manifestations, we felt that this value allowed for a sufficient margin of safety.

The volume of the exposure room was 48 cubic metres (4 × 3 × 4). Care was taken to keep the temperature, humidity, and ventilation inside the exposure room constant (dry bulb temperature 20°C; relative humidity 45%). A small window permitted observation of the subjects and a telephone allowed continuous communication between the observers and the subjects.

The desired concentration of 1,1,1-trichloroethane was maintained by atomizing the solvent into the room every 30 minutes. The solvent (Chlorothene NU) was analysed by infrared spectroscopy. The systematic measurement of the vapour concentration in air inside the exposure room was made with a gas chromatograph equipped with a 'Carlo Erba' electron capture detector.

The test subjects, six healthy students ranging in age between 20 and 23 years, were given complete physical examinations before and after exposure. The subjects were exposed individually from 8.30 a.m. to 12.30 p.m. and from 2 to 6 p.m. During exposure the subjects alternated their activities with a one-hour study period followed by 20 minutes of physical exercise, graded to consume energy at approximately 12.56 kJ/min (3 kcal/min).

Each subject was studied on two different days, with an interval of four days, and acted as his own control, undertaking the different tests on one day in an atmo-

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sphere contaminated with 1,1,1-trichloroethane vapour and on the other day in a 'control atmosphere' which did not contain any of the solvent. In each of the two days devoted to the experiments, two sets of tests were performed by the subjects, the first immediately after entering the room at 8.30 a.m., and the other before leaving the exposure room at 6 p.m. The duration of each set of tests was about 50 minutes.

Because learning adaptation to the test during the second day of the experiment could possibly affect the 'control' or the experimental results, a crossed scheme analysis was used. Three subjects were tested first in the 1,1,1-trichloroethane atmosphere and then, 4 days later, in the 'control' atmosphere. The other three subjects were conversely tested, first in the 'control' atmosphere and then in the 1,1,1-trichloroethane atmosphere. If we indicate with A and B the two groups of three people, the complete experimental protocol may be shown as follows:

GROUP A	
ATMOSPHERE CONTAINING 1,1,1-TRI	
1st test 8.30 a.m.	2nd test 6 p.m.
BREAK	
4 DAYS	
CONTROL ATMOSPHERE	
1st test 8.30 a.m.	2nd test 6 p.m.
GROUP B	
CONTROL ATMOSPHERE	
1st test 8.30 a.m.	2nd test 6 p.m.
BREAK	
4 DAYS	
ATMOSPHERE CONTAINING 1,1,1-TRI	
1st test 8.30 a.m.	2nd test 6 p.m.

During each experiment the following tests were performed:

1. Perception test with tachistoscopic presentation—to evaluate the span of perception and the spatial organizing ability of stimuli (exposure time 1/20 second).
The tachistoscopic task consisted in the display of 13 slides, each presenting a square subdivided into nine equal parts; these inner squares included some black circles, which every time changed in number (4 or 5 or 6) and position. The subject had to draw the patterns shown.
2. Wechsler Memory Scale—to evaluate instantaneous memory and the perceptive field extension.
3. Complex reaction time—to evaluate the time lapse between different visual stimuli and the correct psychomotor response as well as the regularity of

these time lapses between stimulus and response. The task consists of 42 visual and acoustic stimuli, standardized and automatically presented; the duration of the task was 10 minutes, the duration of every stimulus was 1/50 second. The subject was placed in front of a panel containing six peripheral lamps circularly disposed and one central lamp. When the three right lamps lit, he had to press a push-button with the left hand, and when the three left lamps lit with the right hand. He had to respond to the central lights by pressing a pedal and to the sound of a klaxon by pressing another pedal. The reaction time was registered by an electronic chronoscope.

4. Test of aspiration level—to evaluate possible modifications of those cognitive processes which allow us to perform a certain job satisfactorily.

During the second test, both in the 1,1,1-trichloroethane atmosphere and in the 'control', manual dexterity was evaluated also by the O'Connor test method.

The task consisted in threading three fine needles in a round hole, for 3 minutes with the right hand, for 3 more with the left hand, and lastly for 3 minutes with both hands.

The results were statistically analysed by analysis of variance, to determine not only the effects of 1,1,1-trichloroethane on performance and learning but also the onset and degree of mental fatigue and any interaction between them.

Two important phenomena may occur in psychophysiological tests—learning and mental fatigue, which may cause variation in the results so that the evaluation of the effects of a particular condition may lead to invalid conclusions. For example, learning could have masked a hypnotic effect of 1,1,1-trichloroethane; on the other hand, we may have been led to believe that 1,1,1-trichloroethane produced a deterioration of performance which in fact was due to the qualitative and quantitative reduction of effort normally observed in similar tests performed under conditions of mental stress. By analysing the 'cross-over' variance for the results obtained during the 8.30 a.m. tests and the 6 p.m. tests, and also analysing the variance for the results pooled, then combining the results, a comparative variance of the above factors was determined.

No allowance was made for mental fatigue in the manual dexterity tests or resultant interactions.

Results

After two 4-hour exposures, separated by a 1½-hour interval, no disturbances in motor function, co-ordination, equilibrium, or behaviour patterns were observed in any of the subjects. Subjectively, there were transient complaints of dizziness together with slight excitation but these were limited to the first 30 minutes of exposure. At the periods of peak exposure there were some complaints about eye irritation, hyperaemia, and photophobia.

Perceptive test (Table 1)

1,1,1-Trichloroethane caused a 20% drop which is statistically insignificant. However, there was a positive relationship with mental strain. Under

stress conditions, exposure to the solvent decreased perceptive capabilities. Learning ability significantly improved the test performance.

TABLE 1
PERCEPTIVE TEST—ANALYSIS OF VARIANCE

	SSQ	D.F.	S ²	F
Methylchloroform (MC)	2.11	1	2.11	3.98
Mental fatigue (MF) ..	4.17	1	4.17	7.87 ¹
MC × MF	3.02	1	3.02	5.70 ¹
Learning (L)	33.33	1	33.33	62.89 ²
L × MF	13.29	1	13.29	25.08 ²
Subjects (S)	82.37	5	16.47	31.08 ²
S × MF	37.93	5	7.59	14.32 ²
Error	4.27	8	0.53	

¹P < 0.05 ²P < 0.01 ³P < 0.001

SSQ = sum of squares about the mean; D.F. = degrees of freedom; S² = estimate of variance; F = Snedecor's variance ratio.

Immediate memory test (Table 2)

1,1,1-Trichloroethane lowered instantaneous memory performance by 6%, which is not statistically significant. Equally non-significant was the interaction between 1,1,1-trichloroethane and mental strain. Learning improved the performance of each subject but, under conditions of mental fatigue, learning itself declined. The statistical individual variance for this test was insignificant.

TABLE 2
IMMEDIATE MEMORY TEST—ANALYSIS OF VARIANCE

	SSQ	D.F.	S ²	F
Methylchloroform (MC)	343	1	343	4.14
Mental fatigue (MF) ..	400	1	400	4.83
MC × MF	27.34	1	27.34	0.33
Learning (L)	1365.33	1	1365.33	16.49 ¹
L × MF	682	1	682	8.24 ¹
Subjects (S)	625.20	5	125.04	1.51
S × MF	93	5	18.60	0.22
Error	662.34	8	82.79	

¹P < 0.05 ²P < 0.01

Complex reaction times (Tables 3 and 4)

Tests were conducted to determine the variation of both the speed and regularity of response to certain stimuli. 1,1,1-Trichloroethane caused a decreased reaction time of 2.5%. Neither this decrease nor the interaction between 1,1,1-trichloroethane and mental stress is statistically significant. On the other hand,

learning lowered the reaction time significantly; such learning was more affected by mental stress. Variations in subjective responses were also important in assessing reaction times.

TABLE 3
COMPLEX REACTION TIMES (SPEED OF RESPONSES)—
ANALYSIS OF VARIANCE

	SSQ	D.F.	S ²	F
Methylchloroform (MC)	24.08	1	24.08	1.86
Mental fatigue (MF)	126.08	1	126.08	9.71 ¹
MC × MF	7	1	7	0.54
Learning (L)	234.08	1	234.08	18.03 ²
L × MF	117.08	1	117.08	9.02 ¹
Subjects (S)	399.42	5	79.88	6.15 ¹
S × MF	152.50	5	30.50	2.35
Error	103.84	8	12.98	

¹p < 0.05 ²p < 0.01

TABLE 4
COMPLEX REACTION TIMES (REGULARITY OF
RESPONSES)—ANALYSIS OF VARIANCE

	SSQ	D.F.	S ²	F
Methylchloroform (MC)	37.96	1	37.96	3.16
Mental fatigue (MF)	10.08	1	10.08	0.84
MC × MF	0.33	1	0.33	0.03
Learning (L)	0.75	1	0.75	0.06
L × MF	7.33	1	7.33	0.61
Subjects (S)	23.42	5	4.68	0.39
S × MF	120	5	24	2
Error	96.01	8	12	

Analyses of the results on variability of the regularity of response (Table 4) did not disclose any statistically interesting findings.

There was no significant relationship of inhaled air to 'critical judgment'. The effects observed could not be attributable to the 1,1,1-trichloroethane exposure. These effects can hardly be explained by individual variability; the significance of these effects may be a matter for future research.

Manual ability and dexterity (Table 5)

The dexterity of the left and right hands separately and of the two together was analysed. 1,1,1-trichloroethane did not interfere with any of the three tests. Learning significantly improved test performance, particularly when using both hands simultaneously. Individual variation was very high in this test. This was understandable because some subjects were able to use the left hand effectively.

TABLE 5
MANUAL ABILITY AND DEXTERITY—ANALYSIS OF
VARIANCE

	SSQ	D.F.	S ²	F
<i>Right hand</i>				
MC v. MC	24.08	1	24.08	1.09
A v. A	184.08	1	184.08	8.34 ¹
Between subjects	282.42	5	56.48	2.56
Error	88.34	4	22.08	
Total	578.92	11		
<i>Left hand</i>				
MC v. MC	14.08	1	14.08	4.44
A v. A	36.75	1	36.75	11.59 ¹
Between subjects	349.42	5	69.88	22.04
Error	12.67	4	3.17	
Total	578.92	11		
<i>Left and right hands</i>				
MC v. MC	10.08	1	10.08	4.17
A v. A	60.75	1	60.75	25.10 ¹
Between subjects	315.50	5	63.10	26.07
Error	9.67	4	2.42	
Total	396	11		

¹p < 0.05 ²p < 0.01

Discussion and conclusion

The purpose of this research was to evaluate the effect on the psychophysiological performance in humans exposed to 350 p.p.m. of 1,1,1-trichloroethane vapour in air.

The preliminary experiments had shown that an 8-hour exposure to 350 p.p.m. of 1,1,1-trichloroethane did not affect psychophysiological performance. No effects have been demonstrated in later experiments after an 8-hour exposure (consisting of two 4-hour periods separated by a 1½-hour lunch break) to 450 p.p.m. of 1,1,1-trichloroethane, i.e., 100 p.p.m. higher than the 1968 TLV recommended by the ACGIH.

The following material conclusions may be drawn from these results:

(1) In humans exposed to concentrations of 450 p.p.m. of 1,1,1-trichloroethane those psychophysiological functions which we examined were not depressed to an extent which is statistically significant. In the perception test an interaction between exposure to 1,1,1-trichloroethane and mental stress was observed. This suggests that a decrease in performance may occur when persons under mental stress are exposed to 1,1,1-trichloroethane.

(2) An increase in learning was demonstrated by comparison of the performance during the first day of testing with that of the second day.

(3) Mental fatigue was determined by comparing test performance results from the 8.30 a.m. with those from the 6 p.m. test. There was a quantitative and qualitative performance drop in the perception test. On the other hand, in the complex reaction times there is a paradoxical rise which had been noticed previously in other similar experiments.

(4) In the more complex tests, learning is significantly decreased because of increased mental stress.

(5) Variance between test subjects is higher in the more complex tests. Under mental stress one notices that in the perceptive test individual variation is not as pronounced and tends to level out.

It is stressed that the controlled exposure periods of 4 hours with a 1½-hour lunch break followed by another 4 hours were comparable to exposures which could be expected in a typical industry. If test subjects were exposed to a gas or vapour which in a short period of time reached a relative equilibrium in the blood, the concentration in the arterial blood would remain at a steady state of equilibrium with the exposure concentration; this could very well be the case with nitrogen or ethylene. On the other hand, 1,1,1-trichloroethane vapours do not reach equilibrium (steady state) in the arterial blood of exposed subjects even after 3 or 4 hours, because this material has a relatively high coefficient of solubility in blood.

1,1,1-Trichloroethane is eliminated via the lungs for a long period of time, and exponentially for 24 hours after a given exposure [7 hours at 500 p.p.m. (Stewart, 1968), 3 hours at 600 p.p.m. (Gazzaniga, Binaschi, Sportelli, and Riva, 1969)], (Figure).

It cannot be assumed that exposure to 1,1,1-trichloroethane vapour for 8 consecutive hours is equivalent to two exposures of 4 hours' duration with a 1 to 2 hours' non-exposure period in between. The validity of comparisons of experiments performed on animals exposed for 7 or 8 consecutive hours to industrial situations where exposures may occur at intermittent intervals may likewise be questioned.

Therefore, the exposure cycle in the controlled experiment was chosen to reproduce conditions which were comparable to those of workers, and the experiment was statistically designed to bracket the area of practical significance. As previously mentioned, none of the measured changes in performance was statistically significant. In essence, this means that any worker may be exposed to either 350 p.p.m. or 450 p.p.m. of 1,1,1-trichloroethane vapour daily during two 4-hour periods without any loss in psychophysiological functions.

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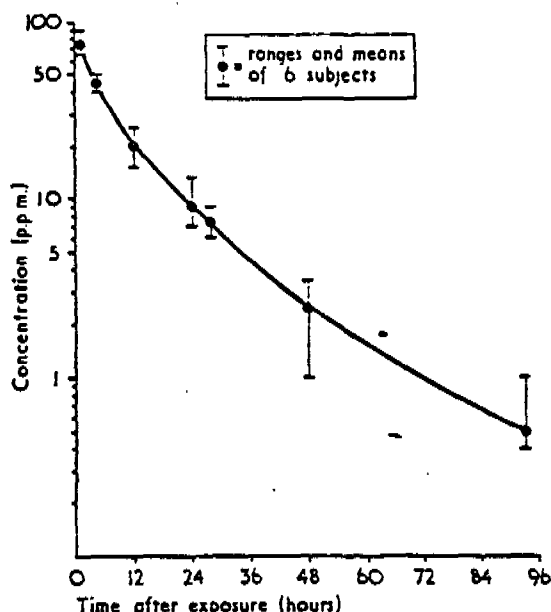


FIGURE Expired 1,1,1-trichloroethane in alveolar air. Concentration (p.p.m.) after 3 hours' exposure at 600 p.p.m.

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