Psychological Reports, 1981, 48, 715-725.

EFFECTS OF ALCOHOL, CAFFEINE AND METHYL CHLORIDE ON MAN[1]

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Summary.—Industrial workers are frequently exposed to organic solvents, such as methyl chloride, and also voluntarily ingest quantities of alcohol or caffeine, all of which affect the nervous system. The purpose was to assess the behavioral effects of such substances alone and when combined. 84 paid volunteers were randomly assigned to one of six treatment groups. Each individual was then tested before and during both the treatment or control procedures on three performance tasks. The results indicated that an alcohol dose sufficient to register blood levels of 0.08% produced a significant impairment of 10% on all three tests, which included eye-hand coordination and alertness. A caffeine dose equivalent to two cups of coffee (200 mg.) produced a small, but significant impairment on only the eye-hand coordination test. However, participants who were exposed to MeCl for 3.5 hr. at levels equivalent to the current legal standard did not experience any significant impairments on the tests. Moreover, when the solvent was combined with each drug individually, the effect was essentially equivalent to the sum of the separate effects; hence, no behavioral interaction was found.

One of the largest groups of chemical agents to which workers are routinely exposed are the industrial organic solvents. They include a wide variety of compounds, such as: alcohols, ketones, ethers, aliphatic and aromatic hydrocarbons, and halogenated hydrocarbons. Of the halogenated hydrocarbons the most widely used are: methylene chloride, chloroform, carbon tetrachloride, perchloroethylene, and methyl chloride. The last agent, also called chloromethane or monocloromethane, is a widely used chlorinated hydrocarbon that is considered relatively safe. According to the Chemical Marketing Reporter (1973), over 647 million pounds of methyl chloride (MeCl) are used annually by the rubber, plastics, petroleum, and stainless steel industries. The current U. S. Standard (OSHA) specifies that levels of MeCl are not to exceed a time-weighted average (TWA) of 100 parts per million (ppm) during an 8-hr. day or a ceiling concentration of 200 ppm (Code of Federal Regulations, 1978). This recommendation was based primarily on the data available from animal studies, medical reports and surveys of symptoms of exposed workers.

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All solvents are more or less strong poisons to the nervous system. Evidence of this can be found by examining workers accidentally overdosed. Usually some level of narcosis is seen which can lead to a gradual, continuous paralysis of the central nervous system (CNS) (Irish, 1963). Further evidence of CNS effect is reflected in the symptomatology of workers who have been exposed to low levels of MeCl. A partial list of the more common complaints include: nervousness and emotional instability, insomnia, depression, fatigue, weakness and lack of limb coordination. The effects observed are similar to those resulting from alcoholic intoxication (Eckardt, 1971).

One of the first systematic investigations of MeCl on psychomotor function was undertaken by Repko, *et al.* (1976). Workers in a chemical manufacturing plant exposed to approximately 34 ppm of MeCl vapor were tested in the field and compared with a slightly younger control group. The occupationally exposed workers exhibited increased tremor and impaired performance on cognitive time-sharing tasks. By comparison, Stewart, Hake, Wu, Graff, Forster, Keeler, Lebrun, Newton, and Soto (1977) found no consistent behavioral effects on four subjects after a 7.5-hr. exposure to 100 ppm MeCl in a controlled laboratory setting.

This is the second in a series of studies designed to examine the behavioral effects from the combined action of multiple chemical agents present in the work place, including common drugs. In the initial study (Putz-Anderson, *et al.*, 1981) the effects of diazepam (Valium) and MeCl were examined singly and in combination. No interaction was found. However, the effect of a 10-mg. dose of diazepam served to reduce efficiency of performance by 10%, which was twice the effect obtained from a 3-hr. exposure to the MeCl vapor at maximum legal concentrations.

In the present study two common drugs were studied, caffeine and alcohol (ethanol), in combination with the same exposure to MeCl vapor. The major expectation rested on the view that an individual's general level of alertness or arousal would be changed as a consequence of ingesting either alcohol or caffeine with a concurrent MeCl exposure. Specifically, the combined treatment of MeCl and alcohol would impair performance on tests of alertness by an amount at least equal to their separate effects. Alternatively, caffeine, acting as a stimulant, would increase the individual's arousal and performance level to partially offset the effect of MeCl.

METHOD

Subjects and Experimental Design

Eighty-four participants, of whom 32 were female, were recruited from neighboring universities over a 6-mo. period and given physical examinations. The ages ranged from 18 to 32 yr., with a mean age of 24 yr. Participants were assigned randomly to one of six groups comprising a 2×3 factorial design. The first factor (MeCl) consisted of two levels or concentrations: 0 ppm-control, 200 ppm. The second factor consisted of the drug-treatments: ethanol (0.8 ml./kg. of absolute ethanol), caffeine (3 mg./kg.), and placebo. Each group had 12 participants, except the group who received the combination of 0 ppm MeCl and placebo, which had 24 participants. In this group 12 participants received the alcohol-placebo, and 12 received the caffeine-placebo.

Procedure

Each participant's level of alertness was tested repeatedly throughout the 5.5-hr. session. Ten measures were accumulated during the 2-hr. pretreatment period and a second set of 12 measures were obtained during the 3.5-hr. treatment period. From three tasks a total of 22 measures were obtained for each individual. These tests were visual-vigilance, dual-task and time-discrimination. The pretreatment testing began with the time-discrimination task followed by the dual-task. Due to the length of the visual-vigilance task (50 min.), the test was not administered during the pretreatment phase. During the subsequent treatment or control period, the test order was as follows: dual-task, time-discrimination, visual-vigilance, dual-task and time-discrimination.

All procedures were in accordance with the American Psychological Association's ethical principles in the conduct of research and the guidelines of the NIOSH Human Subject Review Board. The study was conducted as a single-blind. Each volunteer was requested to abstain from the use of caffeine, alcohol, and any medication for 24 hr. prior to the experiment. Participant-pairs were tested in a controlled-environment room with inside dimensions of approximately 2 cubic m. Each participant sat in a chair at a desk in front of a remote, computer-controlled cathode ray tube (CRT). Pure MeCl was administered from a pressurized cylinder through an inlet port of the environmental room and recirculated in a semi-open system. Room concentrations were measured by infrared spectrophotometer and a gas chromatograph with an integrator. The method followed that of Stewart, Hake, Wu, Graff, Forster, Keeler, Lebrun, Newton, and Soto (1977).

Alcohol (ethanol) was administered as a beverage in the form of a cocktail. Absolute ethanol (0.8 ml./kg.) was combined with 100 ml. of quinine water, 75 cc. pina coloda mix, two drops of Tabasco sauce, and three ice cubes. The drink was designed to produce blood alcohol levels of approximately 80 mg.%. The placebo cocktail was identical, except quinine water was substituted for the ethanol and two drops of Tabasco sauce were added. Caffeine was administered in capsule form to produce a dose of 3 mg./kg. The caffeine placebo contained lactose.

Alveolar breath samples for both MeCl and alcohol were collected every hour to verify the treatments. Venous blood samples were obtained prior to exposure and approximately 90 min. after exposure commenced. Procedures dealing with the analyses of the breath and blood samples were also patterned after the methods developed by Stewart, Hake, Wu, Forster, Keeler, Lebrun, Newton, and Soto (1977). To achieve simultaneous peak body-burdens for MeCl and since both alcohol and caffeine are pharmacologically active within minutes after ingestion, each drug was administered at the beginning of the treatment or exposure period.

Performance Tests

The three tests used in the present study were identical to those used in a previous study (Putz-Anderson, *et al.*, 1981). Each test consisted of an independent, performance-based task, presented and controlled by a PDP-12 computer (Digital Equipment Corp.[4]). The tasks were designed to assess different aspects of attention or alertness and were adaptive in that signal conspicuity was performance adjusted to maintain a stable criterion. Stability was achieved by automatically increasing or decreasing the level of task-load (input) to correspond to the operator's performance (Wiener, 1973). Hence, 80 to 90% of the measured variance on a given trial was in response to the optimal level of task-load introduced during a given condition. The label "Threshold Performance Level" (TPL) was given to the quantitative measure of that point on the continuum of task-loads where performance levels approached 70% accuracy. The remaining 10 to 20% of the measured variance was assessed by response time (RT). Participants were trained for 70 min. until performance levels stabilized.

Visual-vigilance Task

The task resembled an automated version of Mackworth's Clock Test (Mackworth, 1961) with a CRT display. Once every second a light dot (0.2 cm. d.) "jumped" a standard distance of 5 cm. away from the center of the display, paused for 0.35 sec., and then returned to the center for 0.35 sec. At random times the length of the "jump" was increased or decreased by a value established during training for each participant. As with the original Clock Test the signal was a jump longer in length than the standard, and required a button push as a response. Threshold performance level (TPL) scores were computed for each participant. The score indicated the level of task difficulty as determined by the size of the signal jump. The optimum signal value was established by the adaptive process to maintain a 70% performance accuracy.

[4]Mention of company names or products does not constitute endorsement by the National Institute for Occupational Safety and Health.

Dual Task

Tone-detection and eye-hand, compensatory tracking were combined to form the two components of the dual task. A low-intensity tone (65 db, 750 Hz) was presented briefly (250 msec.) through a light-weight headphone set. A silent interval of 750 msec. followed the tone. The sequence was repeated every second for the duration of the 25-min. test period. At random times a tone slightly higher in frequency was presented. This occurred once every 25 sec. and served as the signal. The computer used the same algorithm as in the previous test for determining the magnitude of the signal. The required response to a signal was a button push. The mean values of the threshold performance level and RT scores were obtained for each participant.

The compensatory tracking task required the participant to view two arrows in the middle of the CRT: one stationary, pointed down (target), and the other pointed up (cursor). The latter oscillated horizontally in response to a semi-random, sinusoidal forcing-function of 5 c./min. By applying light horizontal pressure to a control lever, mounted in front of a CRT, the participant attempted to align the cursor with the stationary arrow. The tracking activity scores (TA) represented the average amount of error or deviation between the target and cursor.

Time-discrimination Task

Each participant listened through headphones to a sequence of 1-sec. tone bursts interspersed with 2-sec. off-times. The task was to push a button in response to a signal which was defined as a tone burst longer in duration than the standard 1-sec. burst. On the average of once every 48 sec., throughout the 25-min. test duration, a signal was randomly presented. The same algorithm of adaptation was used in this test as was used in the other two tests. A threshold performance score was computed to measure the smallest temporal increment separating the signal and the standard tone of 1 sec. which was detected with a 70% accuracy by each participant. In addition to the threshold score, a RT was obtained.

RESULTS

Exposure and Biochemical Data

Within 30 min. after the exposure started, the time-weighted average concentration of MeCl in the chamber for each session was 199 ppm, with a standard deviation of 4.1 ppm. Since MeCl at low levels is odorless, participants were no more successful than chance in assessing whether they had inhaled MeCl. Those individuals who received either ethanol or caffeine or their respective placebos were considerably more successful in judging what they had received. For the ethanol and placebo groups, 87% of the participants correctly assessed whether they had received the real substance, while 62% of those participants who received caffeine or the placebo guessed correctly. Since two of the subjects who were exposed to MeCl and also had drunk the alcohol beverage became nauseated immediately after consuming these, their data were not included in the statistical analyses.

For the individuals exposed to MeCl the average value of the recorded alveolar breath levels was 74 ppm or 37% of the chamber concentration. The standard deviation amounted to 43% of the mean value. The correlation between MeCl breath and blood levels was 0.91 ($N = 34$, $p = .01$). The average MeCl blood level was 14.5 ppm, whereas, the standard deviation amounted to 100% of the mean value. The average blood alcohol level was 83.9 mg.%, $SD = 17.15$ mg.%. Caffeine blood levels averaged 2.4 μg./ml., $SD = 1.1$ μg./ml.

Behavioral Data[5]

Two sets of difference or "change" scores were calculated for the dual task and time-discrimination test. The first set involved the difference between the pretreatment scores and the scores obtained during the initial 70 min. of the treatment phase (early) scores. The second set (late scores) involved the differences between the pretreatment scores and the scores obtained during the last 70 min. of the treatment phase. Specifically, the raw scores (amount impairment), obtained during the pretreatment period, were subtracted from the scores obtained during the treatment period; the results were divided by the scores obtained during the pretreatment period. Since preexposure data from the visual-vigilance task were not available, the obtained data represented an absolute or actual value of the indice for the particular experimental condition. Analyses were performed using multivariate techniques. A 5% significance criterion was chosen; the average test power was 0.70.

Table 1 shows the percent of change that occurred between the pretreatment sessions and the treatment sessions for two of the three tests. Data were averaged across the five test indices for both early and late treatment assessment phases. During the control condition (zero concentration of MeCl and drug placebo) the average change in the performance was less than 1% (−0.24). During the MeCl-treatment session impairments of less than 1% were registered on three of the indices. However, a few positive values were also recorded during the time-discrimination test. The net result was a positive change of 0.25%.

The data obtained during the drug treatments are shown in Table 1 (Rows 3 and 5). After the alcohol dose was administered performance on the subsequent behavioral tests declined by an average of 11.9%. During the

[5]Data are available from the Clearinghouse, NIOSH, Robert A. Taft Laboratories, Cincinnati, Ohio 45226.

TABLE 1

DEGREE OF IMPAIRMENT OR IMPROVEMENT ON BEHAVIORAL MEASURES EXPRESSED AS PERCENT CHANGE (%C) BETWEEN PRE-TREATMENT AND SUBSEQUENT TREATMENT PERIODS: EARLY (E) AND LATE (L) DURING METHYL CHLORIDE/ALCOHOL OR CAFFEINE STUDY

Condition		Methyl Chloride/Alcohol or Caffeine Study												M %C
MeCl	Drug	Dual-task						Time Discrimination						
		Threshold		RT		Tracking		Threshold		RT				
		Early	Late	Early	Late	Early	Late	Early	Late	Early	Late			
0	Placebo	+1.1	−2.1	−4.1	−1.2	+0.8	+0.1	−1.2	+1.3	−0.4	+3.3			−0.24
200	Placebo	−0.1	−0.1	−1.0	−1.2	−0.9	−1.2	+3.6	−1.4	+0.7	+4.1			+0.25
0	Alcohol	−8.8	−4.9	−14.2	−16.1	−12.8	−24.1	−7.3	−1.1	−11.8	−18.0			−11.91
200	Alcohol	−4.2	−3.7	−11.6	−9.4	−11.2	−41.2	−8.1	−2.8	−12.7	−9.6			−11.45
0	Caffeine	0.0	−1.4	+0.1	−7.3	+12.1	+11.5	−1.0	+2.6	+2.8	+8.5			+2.86
200	Caffeine	0.0	0.0	−0.8	−2.7	+20.7	+13.0	+5.8	+6.8	−0.6	+4.2			+4.64

Note.—A − indicates impairment; + improvement.

treatment period when caffeine was administered (Table 1, Row 5), tracking activity (TA) was improved markedly (12.1%). An average performance improvement of 2.86% was computed from the 10 measures obtained during the caffeine treatment. When MeCl and caffeine were combined, the data indicated an average increase in performance accuracy of only 4.64%.

Table 1 (Row 4) shows the performance changes that occurred with the treatment combination of 200 ppm MeCl and alcohol. Performance data recorded during the combined treatment showed an overall decline of 11.45%, which was essentially equivalent to the change found when just alcohol was given. Finally, the average change in performance registered during the control condition was small (less than 1%). This value represents the change due to nonexperimental factors, such as fatigue. As such, it can be used to adjust the scores for each treatment group to obtain an actual or net percent change due to the treatment. For example, the average impairment found during the alcohol treatment was 11.9%. Since the control value was 0.24%, the data for the alcohol treatment were adjusted to obtain a net decline of 11.5%.

In addition to the data on percent change, Table 1 also shows the relative consistency of the different measures in assessing the experimental effects across the two time periods. For example, the treatment which showed the greatest effect—alcohol (Table 1, Row 3)—produced relatively uniform impairments across all 10 measures. In a similar manner MeCl (Table 1, Row 2) also showed relatively uniform, but low levels for all 10 measures. This trend was also observed with data from the visual-vigilance test. Since only treatment scores were available from the test, group means were compared, rather than percent of change. Specifically, the group who received the alcohol dose had an average threshold performance level score that represented an 8% impairment in vigilance, compared with the control group (placebo). Those individuals who received the caffeine dose showed a 4% improvement over the control group on the vigilance task. The vigilance data obtained during the MeCl exposures also paralleled the data from the other two tests. The MeCl threshold and RT scores were within 5% and 9%, respectively, of their control values.

The results of the analysis support the observations evident from Table 1, i.e., the MeCl treatment had no significant behavioral effect ($F_{12,65} = 1.39$, Wilk's $\psi = 0.79$, $p = 0.19$). The effects of the drug treatments on the tests were significant ($F_{24,130} = 5.14$, Wilk's $\psi = 0.26$, $p = 0.01$). In addition, the combined treatment of MeCl exposure and drug ingestion was not significant ($F_{24,130} = 1.29$, Wilk's $\psi = 0.65$, $p = 0.18$). An analysis of the time of treatment assessment (early vs late) indicated that only the drug treatment produced data which differed significantly between the two test periods ($F_{14,140} = 4.43$, $p < 0.01$).

Further analysis of the drug treatment was undertaken using the Newman-Keuls test for mean differences (Keuls, 1952). The critical difference required for significance of the means varied between 6% and 11% of the base or placebo values. The results indicated that for 22 of the 24 mean comparisons the behavioral effects of alcohol were significantly different from that of the caffeine treatment and also from that of the placebo ($p < 0.05$). The two exceptions included the visual-vigilance RT from the early test phase and the RT on the time-discrimination test during the later test phase. The six threshold scores accumulated during the alcohol treatment yielded significant differences in the mean comparison tests. However, only the tracking activities index from the dual-task test was sensitive to the effects of the caffeine treatment. When tracking activities during the caffeine treatment were compared with the pretreatment scores for the same individuals, tracking error decreased by an average of 10% ($p < 0.05$).

Discussion

Each of the drug treatments, alcohol and caffeine, when administered independently produced significant changes in performance on tests designed to assess the level of alertness. The expected improvement due to caffeine, however, was weak in comparison to the effect of alcohol, which produced predictable and systematic impairments on almost all of the test indices. In contrast, an acute exposure to low levels of the solvent MeCl for 3.5 hr. was not significant on the same tests. When each drug was administered in conjunction with the solvent exposure, the combined result was essentially equivalent to the effect of the drug alone. No interactive or potentiating changes were found.

Unlike the present study, both the studies by Repko, *et al.* (1976) and Putz-Anderson, *et al.* (1981) showed small behavioral impairments on a time sharing task after an exposure to MeCl. In the former study, workers exposed to MeCl were tested at the worksite, whereas in the latter the exposures were in a controlled laboratory. The same time sharing task (dual task) and exposure concentration, which were used in the earlier study (Putz-Anderson, *et al.*, 1981), were also used in the present study, yet in contrast to the earlier study, the behavioral data from the MeCl exposure were statistically nonsignificant.

Although the results of the two studies are contradictory in terms of the statistically derived decision, ultimately, the belief in (i.e., acceptance of or rejection of) a proposition is not an all-or-none affair; rather it is a matter of degree. Moreover, in the present analysis the confidence in the findings of either study must be modulated in view of the large individual differences in the uptake or body burden of MeCl. In the earlier study the variability of the breath level (*SD*) amounted to 35% of the mean value. An examination of the data showed that three of the 24 individuals exposed to MeCl had breath levels almost twice those of their peers. In the present study the *SD* of the MeCl breath levels was even larger, amounting to 43% of the mean value. Ten of the 34 exposed participants in the present study registered high breath levels.

The finding of large interindividual differences in the two studies served to collaborate similar observations reported by Stewart, Hake, Wu, Graff, Forster, Keeler, Lebrun, Newton, and Soto (1977). They found that four out of approximately 20 subjects had much higher concentrations of MeCl in their alveolar breath samples after identical exposures with their peers. As in the present study, the breath concentrations of their high-responders were elevated from 60 to 110% over the predominant low-responders. No direct explanation for the effect was presented. It is evident that a uniform exposure limit or environmental-concentration standard may result in radically different biological-concentrations in a sizeable sample of exposed individuals.

The significant effects of alcohol and caffeine on the behavioral tests of alertness were expected. Numerous investigators have found similar effects on humans in behavioral experiments, even with relatively small doses of alcohol or caffeine (Goldberg, 1943; Moskowitz & Sharma, 1974; Hollingsworth, 1912). Carpenter (1959) investigated the combined effects of alcohol and caffeine, and reported that caffeine lowered RT significantly, but only for those individuals who worked under adverse conditions, such as low light intensity or after the ingestion of alcohol.

As in the present study, the divided-attention or dual-task has been found by a number of investigators to be particularly sensitive to the effects of ingested alcohol. Chiles and Jennings (1970) required subjects to perform multiple tasks which included compensatory tracking, mental arithmetic, monitoring and choice reaction time after ingesting alcohol. When tasks were combined, or work load was increased, subjects were less able to compensate, and the impairing effects of alcohol were found. By comparison, the time-sharing task in the present study, which was also successful in differentiating between the control and drug treatments, consisted of a dual arrangement with a continuous tracking task and a single tone-monitoring activity. The results from the above studies, also using dual-tasks, are consistent with the findings of Hauty and Payne (1955). They reported that 200 mg. of caffeine, administered to subjects before performing a long-term dual-task involving compensatory tracking and gauge monitoring, prevented the usual performance decrement. In general, the data support the notion advanced by Putz (1979) that multiple tasks with high demand characteristics are sensitive indicators of stress conditions.

The behavioral results from the present study also correspond to the findings obtained by Stewart, Hake, Wu, Kalbfleisch, Newton, Marlow, and Vucicevic-Salama (1977) in a laboratory investigation of perchloroethylene (PCE), alcohol and diazepam. Both alcohol and diazepam produced significant impairments on a battery of behavioral tests, which included eye-hand coordination, rotary pursuit and dual-task. However, neither a significant nor consistent solvent effect on perchloroethylene or an interaction was found. As a result, Stewart, *et al.*'s conclusion with respect to perchloroethylene was similar to the conclusion in the present study for MeCl; that is, MeCl at the concentration studied (200 ppm) did not have a significant effect on tests of alertness and coordination. Furthermore, the addition of alcohol or caffeine at relatively low levels added no significant decrement or compensatory effect over and above that imposed by the presence of the drug alone.

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Accepted April 20, 1981.