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# Effects of acute exposure of toluene and methyl ethyl ketone on psychomotor performance

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**Summary.** Organic solvents are used frequently in industry and workers are often exposed to various combinations of these chemicals. Several are CNS depressants, and the purpose of this experiment was to assess the behavioral effects of 4-hour inhalation exposures to two solvents, toluene and methyl ethyl ketone (MEK) alone and combined. Ethanol at 0.08% blood levels was used as a positive control. A total of 144 paid volunteers were randomly assigned to one of eight treatment combinations in a series of four two-group between subjects studies. Testing was carried out in an exposure chamber, and participants were tested before, during, and after the treatment or control condition on three performance tasks. The tasks measured alertness and psychomotor function and produced a total of 28 measures on each individual over the approximate 8 h of testing. Results indicated that toluene at 100 ppm produced a small but significant impairment on one measure of a visual-vigilance task by lowering the percentage of correct hits. MEK at 200 ppm produced no interpretable significant effects on any of these measures. Additivity was not evident when individuals were exposed to MEK (100 ppm) and toluene (50 ppm) in combination, as no significant performance differences were noted. Ethanol, at 0.08%, affected both the visual-vigilance and a choice-reaction time task at statistically significant levels on two measures, confirming the sensitivity of these two tasks to CNS depressants.

**Key words:** Human exposure - Toluene - Methyl ethyl ketone - Ethanol - Neurobehavior - Additivity

## Introduction

Throughout industry workers are routinely exposed to combinations of chemical substances in the normal work environment. Two, which are commonly found

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together in the chemical, rubber, painting, furniture, and shoemaking industries were selected for study: One an aliphatic ketone, methyl ethyl ketone (MEK), and the other an alkylbenzene, toluene. MEK production totaled 587 million pounds in 1980, and toluene 7 million pounds (U.S. International Trade Commission 1980).

Inhalation is the primary route of absorption in human industrial exposure to MEK and toluene because of the chemicals' high volatility at room temperature, but skin absorption and ingestion are also possible routes. With concentrations below 500 ppm, the primary pharmacologic action of both MEK and toluene is on the central nervous system (CNS). Both agents can be classified primarily as CNS depressants, producing fatigue, headaches, nausea, dizziness, and drowsiness. Alkylbenzenes such as toluene exhibit a special affinity for nervous tissue, with the narcotic potency being dependent to some extent on the branching or side chain length (Sandmeyer 1981). Toxicity decreases with increasing chain length except for some highly branched derivatives. Ketones generally exhibit greater narcotic properties with increasing molecular weight (NIOSH 1978).

Both solvents have been the subject of neurobehavioral research; toluene has received the most attention. One of the earliest controlled exposures involving toluene was carried out by Von Oettingen et al. (1942). They exposed subjects to concentrations of 0 to 800 ppm for 8 h. Moderate fatigue and slight headaches were reported at concentrations below 100 ppm, but as concentrations increased, confusion and impairment of coordination were evident. Stewart et al. (1975) exposed male and female volunteers for 1, 3, and 7.5 h over several days at concentrations between 0 and 100 ppm. Only females exposed for 7.5 h showed any significant performance decrement and only on one of the cognitive tests. Females had fewer correct responses on a dual task involving visual vigilance and tone detection. Performance on time estimation, addition, and coordination tests did not change. There was also the suggestion of an increase in the visual evoked potential in 1 male subject on the 5th day of 100 ppm exposure at 7.5 h. This change was interpreted as a pre-narcosis response.

Neurobehavioral studies involving MEK are limited. Nakaaki (1974) exposed two male and two female subjects to a range of concentrations (90–270 ppm), while they performed a time estimation test. Male subjects consistently underestimated the time with the effect becoming more pronounced as the exposure time increased. Geller et al. (1979) exposed baboons to 100 ppm MEK and had them perform a "match to sample" task. Discrimination ability was not affected, but response times were slowed, and spurious responses were increased.

Both MEK and toluene are considered to be relatively safe when used within their U.S. permissible exposure limit (PEL) or time weighted averages (TWA) of 200 ppm and 100 ppm respectively (29 CFR 1910). However, the assumptions of additivity inherent in the ACGIH formula for chemical mixtures (ACGIH 1982) and lack of research on organic solvents in combination (Krasavage et al. 1982), coupled with recommendations of a lower standard for toluene from ACGIH (1981) and NIOSH (1978) indicated the need for controlled studies. The ACGIH formula assumes that the combined effects of two or more chemicals are additive (unless information is available to indicate differently) and not subject solely to the individual effects of one of the chemicals. In addition to the common occur-

rence of both of these solvents in the workplace, pharmacologically they have demonstrated some interesting properties in combination with other chemicals. MEK by itself has not been found to be neurotoxic, but it has shown a potentiating effect when combined with the known neurotoxins methyl *n*-butyl ketone (MnBK) and *n*-hexane (Saida et al. 1976; Spencer et al. 1980). Further, toluene has evidenced potentiating effects with benzene and inhibitory effects with asphalt fumes, trichloroethylene and tetrachloroethene on certain biologic effects (Sandmeyer 1981).

The present study represents the third in a series of studies (Putz-Anderson et al. 1981a, b) designed to examine the behavioral effects of multiple chemical agents in the workplace. The purpose of this study was to assess the effects of acute chemical exposures singly and in combination over a period of several hours. Exposure levels of 200 ppm for MEK and 100 ppm for toluene were used, based on the NIOSH (1978) recommended levels. For the combination exposure, levels were set in accordance with the OSHA/ACGIH additivity formula; MEK was set at 100 ppm, and toluene was set at 50 ppm. Behavioral and biochemical measurements were taken to correlate the body burden levels with tests designed to assess general arousal-attentive characteristics.

## Method

### *Subjects*

A total of 144 participants were recruited over an 18-month period to participate in a series of experiments. Forty-seven were female, and the age ranges were 18–38. They were recruited from local colleges and required to pass an extensive physical exam that included neurological screening. Individuals receiving prescription medication, pregnant females, hypertensives, and persons with other serious diseases were excluded.

### *Experimental design*

Participants were assigned to one of eight treatment combinations, which comprised a series of four independent two-group studies. The groups were as follows: (1) toluene-placebo vs. 100 ppm toluene; (2) MEK-placebo vs. 200 ppm MEK; (3) toluene/MEK-placebo vs. 50 ppm toluene and 100 ppm MEK; and (4) ethanol-placebo vs. 0.80 ml/kg absolute ethanol. The latter was run to assess the sensitivity of the neurobehavioral tests. Random assignment to a treatment combination was used to the extent possible, but equipment availability and state drinking laws compromised complete randomization.

The placebo consisted of a 2-min, 25 ppm exposure or "charge" of each chemical/combination, a procedure suggested by Stewart et al. (1977), or a "blind" cocktail in the ethanol condition. Due to equipment problems, physician unavailability and subject exclusion based on performance failure, the group sizes varied: Table 1 presents a breakdown of number of subjects used in each treatment condition by performance test.

### *General procedures*

All procedures were carried out 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 studies were conducted in single blind and the methodology for all the studies was generally the same. However, there were some minor variations in the collection of blood and breath samples because of individual schedule conflicts. Each volunteer was

**Table 1.** Number of subjects analyzed for each study and test

| Group | Test | | |
|---|---|---|---|
| | Choice R. T. | Visual-vigilance | Pattern Recog. |
| Ethanol | 16 | 9 | 10 |
| Control | 12 | 12 | 12 |
| Toluene | 30 | 26 | 18 |
| Control | 12 | 8 | 6 |
| MEK | 20 | 16 | 16 |
| Control | 22 | 14 | 18 |
| Toluene/MEK | 20 | 16 | 16 |
| Control | 22 | 14 | 18 |

requested to abstain from the use of alcohol and any medication for 24 h prior to the experiment, to eat breakfast before coming to the experimental session, and to bring two snacks for the lunch breaks. Participants, who were paid US $ 90 for their participation, were tested in pairs in a controlled-environment room with inside dimensions of approximately 2 cubic meters. Each participant sat in a chair at a desk in front of a cathode ray tube (CRT) under computer control (Digital Equipment, Corporation Model VR14).

Each participant was tested repeatedly for alertness during the approximately 8 h of testing. Three different behavioral tasks were used to obtain 28 measures on each individual. Seven measures were obtained during the 2-h-30-min pre-exposure period; 14 during the 4-h exposure period; and 7 during the 71-min post-exposure period. A 30-min break separated the exposure and post-exposure period. Subjects were required to remain at the test site for an additional 20 min for biological sampling, verification that their chemical body burden was reduced to safe levels, and for formal release by the physician in attendance at the study.

To determine the body burden of these chemicals, four alveolar breath samples were collected: (1) at the end of the pre-exposure period, (2) either 1, 1.5, or 2 h into the exposure period, (3) at the end of the exposure period, and (4) 90-min post exposure. Venous blood samples were drawn from chemically-exposed and ethanol subjects 2 h after the exposure began and 90 min post-exposure. For the MEK-exposed group, the second blood sample was drawn at the end of the four-hour exposure period. Placebo group participants routinely provided one blood sample 2 h into the exposure period, and a second blood sample was drawn as a spot check for in-house laboratory quality assurance. No blood samples were drawn from the toluene groups because the analytical laboratory was dedicated to a special study at the time. Table 2 provides a summary of the blood and breath values arranged for each condition.

Previous research (Astrand et al. 1972; Nomiyama and Nomiyama 1974; Stewart et al. 1975) on organic solvents indicated that respiratory retention should reach a constant level in about two hours. Ethanol levels would be expected to reach the desired 0.08% blood level between one and two hours after ingestion based on previous studies (Putz-Anderson et al. 1981b).

*Performance tests*

Four tests were used throughout the long testing session, but only three are reported on in this paper. The eyeblink test which measured the electromyographic activity of the right orbicularis oculi muscle, is not described as it is reported in another paper (Russo et al. in press). Two of the tests, the reaction time and visual-vigilance task were administered throughout the pre-exposure, exposure and post-exposure periods. The pattern discrimination test, however, was run only during the pre-exposure and exposure period. The pre-exposure test period provided baseline data for comparison purposes with the other periods.

**Table 2.** Sample body burden measurement

| Condition | Blood = mg% | | Breath = ppm | | | |
|---|---|---|---|---|---|---|
| | First | Second Post | First | Second | Third | Post |
| *Alkohol* = 0.80 ml/kg | | | | | | |
| Mean | 77.5 | 42.1 | 98.0 | 67.0 | 50.0 | 33.4 |
| SD | 29.0 | 29.0 | 27.0 | 25.0 | 22.0 | 15.3 |
| *N* | 16 | 12 | 18 | 17 | 6 | 11 |
| *Toluene* = 100 ppm | | | | | | |
| Mean | | | 4.8 | 7.0 | 7.6 | 2.4 |
| SD | | | 1.3 | 2.2 | 1.3 | 0.9 |
| *N* | | | 30 | 32 | 12 | 30 |
| *MEK* = 200 ppm | *Blood* = ppm | | | | | |
| Mean | 3.1 | 3.7 | 5.1 | 7.7 | 9.1 | 1.8 |
| SD | 1.2 | 1.6 | 1.2 | 2.1 | 1.3 | 0.8 |
| *N* | 20 | 18 | 10 | 21 | 18 | 19 |
| *Mix: Tol.* = 50 ppm | | *Post* | | | | |
| Mean | 1.1 | 0.7 | 2.2 | 3.0 | | 0.7 |
| SD | 0.4 | 0.4 | 1.2 | 1.1 | | 0.5 |
| *N* | 16 | 16 | 16 | 16 | | 16 |
| *Mix: MEK* = 100 ppm | | | | | | |
| Mean | 1.0 | 0.5 | 4.0 | 4.2 | | 0.4 |
| SD | 0.4 | 0.4 | 1.2 | 1.3 | | 0.4 |
| *N* | 16 | 14 | 16 | 17 | | 16 |

Note: *N* = subjects

The pre-exposure test period provided baseline data for comparison purposes with the other periods. The pre-exposure period was preceded by a 15-min training session on the tasks. Participants were not permitted to begin the testing until they had reached a training criterion of 15% or less change in two succeeding trials on the visual-vigilance and pattern discrimination test. Approximately 100 trials or 4 min practice was required to reach the criterion on the choice reaction time test.

All tasks were presented and controlled by a PDP-12 computer (Digital Equipment Corporation) and user-written FORTRAN based software. The tasks were designed to assess different aspects of attention or alertness, and the performance measures obtained were fed directly into the computer. The order of test presentation was identical for each participant, but participants did not receive the same display (i.e. critical events were in a different sequence for each participant). The sequence of events was also changed for each succeeding presentation of a test to reduce anticipation.

*Visual-vigilance task*

This task was an automated version of the Mackworth Clock Test (Mackworth 1961) presented on a CRT. Centered on the screen was a figure resembling a clock with a 48 mm -diameter sweep. A central hub consisting of 8 dots (1 mm in diameter) arranged in a circle 4 mm in diameter comprised the interior of the clock. The hand was formed by a straight line pattern of

8 dots (1 mm in diameter) which were set at 3 mm intervals, with the exception of a 4 mm interval between the second and third dots where the line crossed the central hub. The dots were light green, backlighted, and set against a dark green background. The clock-hand normally moved in 21 discrete jumps, or events of 17.1 degrees around the clock, with a critical signal event being defined as a jump twice that distance (34.2 degrees). Participants responded to the critical signal by pressing a cylindrical, hand-held Switchcraft Model E-19 microswitch (1.8 cm in diameter × 5.5 cm in length). A total of 2700 events occurred divided equally among three 15-min periods. Thirty-three of the signals were critical events: 11 in each period. Speed and accuracy were equally emphasized. Participants were told that a response would be recorded as a valid "hit" within a 2-s interval following the presentation of a double jump, and that all other responses would be false alarms. Hits, false alarms, and response times to the nearest millisecond were recorded for each participant.

*Choice reaction time*

Participants were seated in front of a 16 × 25 cm response panel inclined 30 degrees at table-top level. Eight momentary push-button switches with red translucent covers (Arrow-Hart Hardware: Actuator 83501, Block 83600-30, Red Lens 83500-71, Green lens 83500-72) were arrayed in a semi-circle above a single green button. The contact area of the buttons was rectangular (1.0 × 1.8 cm). The distance between the central green button and each of the red response buttons was 9 cm, with an angle of separation of 25 degrees. The presentation of button lights was randomly generated by the software with the constraint that no button would be illuminated on 3 successive trials and that all eight buttons were equally selected. Participants were instructed to place the index finger of the preferred hand on the green button at all times except when moving the finger to depress an illuminated red button. Trial presentations were set up so that a new trial was presented to the participant as soon as the other participant with whom they were paired responded, or 1.5 s, whichever occurred first. On each trial two reaction times were recorded: response time, defined as the interval between the onset of the red button light and the release of the green button, and movement time, defined as the interval between the release of the green button and the depression of the appropriate red button. A total of 160 discrete trials were presented.

*Pattern recognition task*

The pattern recognition task required participants to detect presentations containing 7 or fewer dots, in patterns where the number ranged from 3 to 36. The dots were positioned in any of 64 locations in an 8 × 8 matrix (1.8 × 1.8 cm) in the center of a CRT screen where they were displayed for 0.5 s. The 40-min task was divided into four periods of 10 min each, 130 trials in each period. Ten of the trials contained critical signal patterns: Two each of 3, 4, 5, 6, and 7 dots. The temporal occurrence of these patterns was determined by a sequence of interstimulus-intervals (ISIs) of 3, 4, 5, 7, 8, 13, 19, 19, and 25 s, which were randomized for each period. Neutral event patterns contained between 8–12 dots for the "hard" (H) periods and 8–36 dots for the "easy" (E) periods; both types occurred in each session in an EHHE or HEEH order. The location of the dots within the 8 × 8 matrix was randomly determined for the neutral events and critical signal patterns. A hand-held microswitch was used to make detection responses, and a "hit" was registered for any response made within 1.5 s of the critical signal presentation. Other responses were recorded as false alarms. Response times for correct detections were also recorded.

*Chemical exposures/biological analysis*

Toluene and/or MEK were drawn from a reservoir through a metering pump (FMI-Model RP-G20) into a mixing flask where it was mixed with air to the desired concentration. Pressure in the mixing flask forced the air/chemical mixture into the exposure chamber at the desired concentration. Concentrations were monitored on-line continuously by Miran I infrared analyzers and were confirmed every 30 min by gas chromatography utilizing a Perkin-Elmer Model No. 3920 gas chromatograph (GC) equipped with a flame ionization detector. During

pilot studies samples of air were taken from the exposure room at known concentrations and sent to an independent lab for confirmation to check on the instrumentation before proceeding with the study. The GC and the Miran I analyzers were recalibrated each test day from bag samples prepared using a wet test meter (GCA Precision Scientific). The gas chromatographic column was 6′ × 1/8″ stainless steel, packed with 0.2% carbowax-20 m on 80/100-chromosorb W-HP. Nitrogen was used as the carrier gas at a flow rate of 20 ml/min. The chromatographic column was maintained at 100° C. A similar stainless column, containing 10% carbowax 20 m on the same solid support was utilized for separation and determination of chamber concentrations of toluene and MEK in combination. The retention time or times for toluene and MEK utilizing the 0.2% packing were 114 s and 78 s respectively; the retention times using the 10% packing were 50 s for toluene and 90 s for MEK. Table 3 provides a summary of the chamber concentrations for each exposures condition.

MEK and ethanol in blood were measured by gas-liquid chromatography using the head space technique. The determinations were performed with a Perkin-Elmer model 3920 gas chromatograph equipped with a glass column packed with 5% carbowax 20 m and a flame ionization detector. The oven was maintained at 85° C for 4 min then programmed to 220° C. The injector and detector were 150° C and 200° C, respectively. Helium was used as the carrier gas (25 ml/min). A known volume of whole blood and an internal standard (isobutanol) were treated in a sealed container at a fixed temperature to equilibrate the volatiles. An aliquot of the vapor was then injected into the GC for analysis. The method is sensitive to 0.02 ug/ml and 0.005 g/dL for MEK and ethanol in blood. Table 2 provides a summary of the body burden measurements for each study.

*Ethanol administration*

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 of the participant's choice of orange juice, tomato juice, or pina colada mix, two drops of tabasco sauce, and crushed ice. The drink was weight-adjusted, and designed to produce blood alcohol levels of 0.08%. Additional quinine water replaced the alcohol in the placebo cocktail.

## Results

The results section only includes information on three of the performance tasks and the biochemical measurements. As mentioned previously, the eye-blink tests have been analyzed and published separately (Russo et al. in press). Multivariate analysis of covariance was used to evaluate the results. The pre-exposure period scores served as baseline values and were used as the covariate in adjusting for differences in the pretreatment scores. To adjust for loss of participants and its affect on the data structure, a type III sums of squares analysis was used in computing mean squares (Freund and Littell 1981). As a general rule, measurements were considered to be statistically significant when demonstrated on both the multivariate and the univariate statistic, at $P = 0.05$.

*Ethanol ingestion study*

*Biochemical data.* Within 1 h after each of the 18 participants consumed a beverage containing 0.8 ml per kg of 100% ethanol, the concentration of ethanol in the breath averaged 98 ppm, S.D. = 27 ppm. Approximately 3 h later, the average breath level dropped to 67 ppm, S.D. = 25 ppm. The last breath sample was taken 30 min prior to the participant's departure, which was almost 5.5 h after

**Table 3.** Chamber exposure concentrations for each study

| Measure (PPM) | Exposure times | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | h 1 | | h 2 | | h 3 | | h 4 | |
| *MEK 200 ppm condition* | | | | | | | | |
| Mean | 177.2 | | 195.9 | | 186.2 | | 196.2 | |
| SD | 10.8 | | 2.8 | | 12.6 | | 4.6 | |
| *N* | 10 | | 10 | | 10 | | 10 | |
| *Tol 100 ppm condition* | | | | | | | | |
| Mean | 96.4 | | 101.0 | | 100.8 | | 102.1 | |
| SD | 7.9 | | 2.0 | | 2.2 | | 0.9 | |
| *N* | 16 | | 16 | | 15 | | 15 | |
| *Tol 50 ppm/MEK 100 ppm mixed condition* | | | | | | | | |
| | TOL | MEK | TOL | MEK | TOL | MEK | TOL | MEK |
| Mean | 49.0 | 98.3 | 51.4 | 97.5 | 50.8 | 98.5 | 50.9 | 98.8 |
| SD | 3.6 | 4.0 | 2.3 | 2.3 | 2.4 | 3.8 | 1.3 | 3.2 |
| *N* | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

*N* = Number of sessions

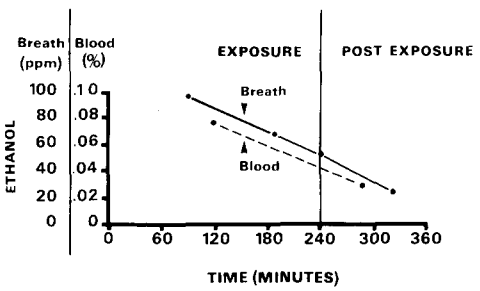


**Fig. 1.** Average concentration of ethanol in blood and breath for the treatment group obtained at each designated sample-period. Time is expressed in elapsed minutes from onset of treatment

the original ethanol dose; it yielded an average breath concentration of 36 ppm, S.D. = 11 ppm. Figure 1 displays a plot of the breath and blood-alcohol values for each sample period.

The first blood sample was drawn approximately 2 h after the ethanol beverage was consumed. An average blood-alcohol level of 77.5 mg% was detected, S.D. = 29 mg%. Variation in individual blood-alcohol values exceeded expectations. The scores ranged from a high of 140 mg% to a low of 28 mg%. The low value was the result of one subject not finishing the cocktail because of nausea. A second sample of blood was drawn about 3 h later, i.e., 5 h after ingestion, and about 1 h before the participants left the study. For this sample an average blood-alcohol concentration of 42.1 mg% was computed. The standard deviation remained at 29 mg%. Moreover, data from 6 participants were incomplete due to illness associated with drinking the ethanol beverage, which precluded their completing all of the tests.

*Performance changes.* Table 4 Panel A provides a summary of mean data and the corresponding probability values (*P*) from the statistical analysis. The probability levels shown in the last column of Table 4 were obtained from the results of a multivariate analysis of covariance (Manacova); the pre-test scores were used as the covariate in adjusting for pretreatment group differences. The degrees of freedom for the Manacova test were 3 and 16 for the numerator and denominator of the *F* ratio, respectively.

The results for both the control/placebo and treatment group are shown for each of the three tests administered during the four measurement periods. For the visual-vigilance test the participants in the control/placebo group, labeled "C" in the heading of Table 4, correctly detected 77% of the signals presented during the pre-test session while the treatment group detected 74%. During the pre-test session the control group also produced a false alarm rate of 21% [i.e., the percentage of positive responses that were scored as incorrect]. By comparison the treatment group, labeled "E" in Panel A had a false alarm rate of 33%. Response time data for the vigilance test are shown in row 3 or Panel A. The control group's response time averaged 680 ms, whereas the treatment group averaged 754 ms.

As indicated in Panel A only the false alarm measure of vigilance was statistically significant, $P = 0.03$. Subsequent univariate analyses verified that the significance occurred during both the first and second exposure time periods, $P = 0.05$ and 0.03 (df 1.18) respectively. During the second period the treatment group averaged a false alarm rate of 20%, whereas the control/placebo group produced an average of 5% false alarms. By the end of the test period, labeled "Post" in Panel A, the false alarm rate for both groups converged to about 12%, which was not significant, $P = 0.79$.

The last two rows in Panel A show the results for the choice reaction time test. During the pre-test session, both groups were relatively similar in their test scores. There was a statistically significant difference in response time but not movement time during the first hour after the participants ingested the ethanol beverage, which coincided with the highest ethanol breath concentration (Fig. 1). Specifically, the treatment group took an average of 45 ms longer to respond to the onset of the signal stimulus than the control group. The overall Manacova probability level was 0.01. The effect was not evident during the second or post-exposure session. The pattern recognition test indicated no significant differences. Moreover, data were not collected in the post-exposure period.

### *Toluene exposure study*

*Exposure and biochemical data.* The average concentration of toluene in the chamber throughout the 4-h exposure period was 100.1 ppm, (S.D. = 2.5 ppm). Breath levels for the 30 participants averaged 6.5 ppm (S.D. = 1.5 ppm). From the second through the fourth hours of exposure, breath levels increased by an average of 1.8 ppm/h. Moreover, the breath levels continued to increase through the fourth and final hour of exposure. Approximately 90 min (see Fig. 2) after the exposure was terminated, the average breath level had dropped to 2.4 ppm (S.D. = 0.9 ppm). Data providing information on toluene blood levels were not

**Table 4.** Performance on visual-vigilance, pattern recognition, and choice reaction time for toluene (T), methyl ethyl ketone (MEK), and ethanol (E) and their relevant placebo controls

Panel *A*: Ethanol

| Measure | Exposure time periods | | | | | | | | | | | Manacova |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PRE: 1 h | | During: 1–2 h | | | During: 3–4 h | | | Post: 1 h | | | |
| | C | E | C | E | *P* | C | E | *P* | C | E | *P* | *P* |
| Visual-vigilance: | | | | | | | | | | | | |
| % Hits | 77 | 74 | 72 | 63 | 0.43 | 65 | 66 | 0.62 | 61 | 65 | 0.45 | 0.90 |
| % F. A. | 21 | 33 | 11 | 26 | 0.05 | 5 | 20 | 0.03 | 12 | 13 | 0.79 | 0.03 |
| Resp time | 680 | 754 | 713 | 858 | 0.26 | 744 | 912 | 0.17 | 769 | 892 | 0.18 | 0.56 |
| Pattern recognition: | | | | | | | | | | | | |
| % Hits | 88 | 90 | 83 | 80 | 0.35 | 83 | 79 | 0.23 | – | – | – | 0.30 |
| % F. A. | 41 | 42 | 39 | 41 | 0.70 | 35 | 34 | 0.72 | – | – | – | 0.74 |
| Choice reaction: | | | | | | | | | | | | |
| Resp time | 345 | 350 | 323 | 368 | 0.01 | 323 | 349 | 0.13 | 329 | 336 | 0.84 | 0.01 |
| Move time | 199 | 188 | 192 | 189 | 0.77 | 191 | 186 | 0.98 | 182 | 177 | 0.93 | 0.96 |

Panel *B*: Toluene

| Measure | Exposure time periods | | | | | | | | | | | Manacova |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PRE: 1 h | | During: 1–2 h | | | During: 3–4 h | | | Post: 1 h | | | |
| | C | T | C | T | *P* | C | T | *P* | C | T | *P* | *P* |
| Visual vigilance: | | | | | | | | | | | | |
| % Hits | 66 | 59 | 73 | 51 | 0.01 | 65 | 49 | 0.15 | 58 | 55 | 0.76 | 0.01 |
| % F. A. | 19 | 15 | 10 | 10 | 0.85 | 9 | 16 | 0.26 | 14 | 13 | 0.96 | 0.70 |
| Res time | 753 | 854 | 923 | 940 | 0.49 | 872 | 899 | 0.50 | 958 | 945 | 0.60 | 0.90 |
| Pattern recognition: | | | | | | | | | | | | |
| % Hits | 86 | 88 | 94 | 86 | 0.01 | 86 | 83 | 0.29 | 79 | 79 | 0.92 | 0.07 |
| % F. A. | 30 | 33 | 17 | 28 | 0.22 | 19 | 23 | 0.77 | 23 | 23 | 0.65 | 0.51 |
| Choice reaction: | | | | | | | | | | | | |
| Resp time | 353 | 331 | 330 | 328 | 0.44 | 323 | 319 | 0.50 | 332 | 314 | 0.32 | 0.21 |
| Move time | 177 | 174 | 175 | 173 | 0.96 | 175 | 172 | 0.93 | 178 | 165 | 0.12 | 0.30 |

Panel *C*: MEK

| Measure | Exposure time periods | | | | | | | | | | | Manacova |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PRE: 1 h | During: 1-2 h | | During: 3-4 h | | | Post: 1 h | | | | | | |
| | C | MEK | C | MEK | *P* | C | MEK | *P* | C | MEK | *P* | *P* |
| Visual vigilance: | | | | | | | | | | | | |
| % Hits | 77 | 78 | 60 | 75 | 0.02 | 54 | 70 | 0.06 | – | – | – | 0.49 |
| % F. A. | 11 | 13 | 12 | 6 | 0.07 | 20 | 10 | 0.06 | – | – | – | 0.12 |
| Resp time | 799 | 711 | 859 | 724 | 0.06 | 807 | 734 | 0.83 | – | – | – | 0.13 |
| Pattern recognition: | | | | | | | | | | | | |
| % Hits | 93 | 84 | 86 | 88 | 0.07 | – | – | – | – | – | – | 0.07 |
| % F. A. | 34 | 37 | 33 | 31 | 0.23 | – | – | – | – | – | – | 0.23 |
| Choice reaction: | | | | | | | | | | | | |
| Resp time | 340 | 324 | 338 | 319 | 0.34 | 327 | 323 | 0.81 | – | – | – | 0.59 |
| Move time | 185 | 171 | 183 | 170 | 0.67 | 177 | 174 | 0.30 | – | – | – | 0.41 |

Panel *D*: T/MEK Mix.

| Measure | Exposure time periods | | | | | | | | | | | Manacova |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PRE: 1 h | | During: 1-2 h | | | During: 3-4 h | | | Post: 1 h | | | |
| | C | T/MEK | C | T/MEK | *P* | C | T/MEK | *P* | C | T/MEK | *P* | *P* |
| Visual vagilance: | | | | | | | | | | | | |
| % Hits | 77 | 72 | 62 | 71 | 0.03 | 66 | 67 | 0.23 | 61 | 63 | 0.35 | 0.19 |
| % F. A. | 26 | 26 | 25 | 21 | 0.53 | 18 | 16 | 0.78 | 15 | 26 | 0.13 | 0.20 |
| Resp time | 658 | 756 | 736 | 723 | 0.03 | 707 | 766 | 0.63 | 721 | 820 | 0.52 | 0.02 |
| Pattern recognition: | | | | | | | | | | | | |
| % Hits | 86 | 88 | 87 | 85 | 0.53 | 79 | 82 | 0.82 | – | – | – | 0.43 |
| % F. A. | 40 | 41 | 34 | 35 | 0.97 | 31 | 32 | 0.91 | – | – | – | 0.98 |
| Choice reaction: | | | | | | | | | | | | |
| Resp time | 334 | 357 | 319 | 341 | 0.85 | 318 | 332 | 0.49 | 333 | 330 | 0.15 | 0.44 |
| Move time | 185 | 205 | 164 | 194 | 0.15 | 167 | 186 | 0.60 | 157 | 191 | 0.02 | 0.11 |

$P$ = probability level of $F$ test value

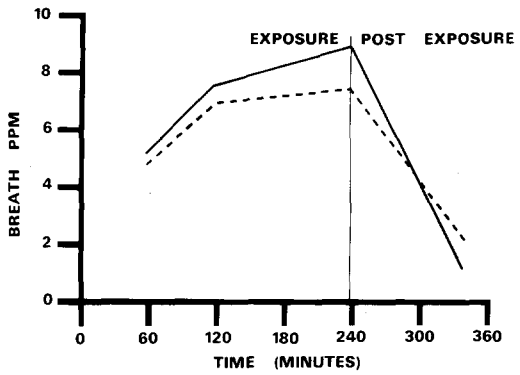


**Fig. 2.** Average concentration of toluene (- - -) and MEK (——) in breath for the exposed group obtained at each designated sample-period. Time is expressed in elapsed minutes from onset of exposure

available as a result of a concurrent and unexpected demand placed on the chemical analytical facilities. However, for comparison purposes blood level values were available from a previous study with similar exposure duration and concentration values (Stewart et al. 1975).

*Performance changes.* A complete set of summary data are presented in Table 4, Panel B along with the statistically-derived probability values obtained from the Manacova test. Only the measure of hits, shown in the last column in Panel B, for the visual-vigilance test was statistically significant, $P = 0.01$. The effect was most pronounced during the first two hours of the exposure (row 1, Panel B). The control group averaged 73% correct detections, whereas the treatment group averaged only 51% correct detections. The results of the subsequent univariate test confirmed that the reduction in correct detections occurred primarily during the first exposure period ($P = 0.01$). During the second exposure period, hours 3 and 4, the same trend was also observed in the data, but failed to reach statistical significant ($P = 0.15$). An interesting parallel is found in the pattern recognition test. Although, the measure of hits in this test failed to reach statistical significance in the overall Manacova analysis ($P = 0.07$), the treatment group had fewer correct detections on the average than the control group, 86% and 94% respectively. Again, by the second exposure period this trend disappeared, as it had in the visual-vigilance test. None of the choice reaction time measures were significantly affected by the exposure to toluene.

### *Methyl ethyl ketone exposure study*

*Exposure and biochemical data.* The average MEK concentration in the test chamber over the course of the 4-h exposure was 188.9 ppm (S.D. = 9.1 ppm), which was about 10 ppm less than the desired level of 200 ppm. Most of the variation occurred during the first and third hours of exposure, which averaged 177.2 ppm, (S.D. = 10.8 ppm), and 186.2 ppm, (S.D. = 12.6 ppm), respectively. By contrast the average exposure level in the chamber for the second and third hours was within 5 ppm of the 200 ppm level (S.D. = 2.8 for hour two and 4.6 for hour four).

For the 20 individuals exposed to MEK, breath levels during the 4-h exposure averaged 7.3 ppm, S.D. = 1.2 ppm. Ninety minutes after the exposure terminated,

the average breath levels had fallen to 1.8 ppm, S.D. = 0.8 ppm (see Fig. 2). Results from the analysis of two blood samples, taken about 2 h and 4 h after the exposure began, showed concentrations of 3.1 ppm (S.D. = 1.2 ppm) and 3.7 ppm (S.D. = 1.6 ppm), respectively (see Fig. 4).

*Performance changes.* There were no statistically significant effects from exposure to MEK as shown in the summary data in Table 4, Panel C. In the last column under the heading Manacova, all probabilities exceeded the 5% criterion. Because of the exceptional amount of initial training time required in this phase of the study, no data were collected during the post-exposure session.

### *Toluene/MEK combination study*

*Exposure and biochemical data.* The concentration of each solvent in the chamber was independently monitored throughout the 4-h test period. For toluene the average concentration was 50.5 ppm (S.D. = 1.1 ppm), whereas for the same period MEK was maintained at 98.3 ppm (S.D. = 0.6). The levels were consistent with the current ACGIH recommendation for multiple solvent exposures (ACGIH 1982). Since the chamber was charged rapidly with the vapors from each solvent, the desired concentrations were achieved within the first 30 min following the beginning of the exposure. The results for breath samples of each solvent are plotted in Fig. 3; blood sample results are reflected in Fig. 4.

Approximately 2 h after the exposure began, the average breath concentration of MEK for the 16 exposed participants was 4.0 ppm (S.D. = 1.2 ppm). A second MEK breath sample was taken about 2 h later, immediately prior to the end of the exposure. The average MEK-breath concentration had increased by only 0.2 ppm, and the individual variability was unchanged (S.D. = 1.3 ppm). The last breath sample collected for MEK analysis occurred about 75 min after the exposure had terminated. The breath level by this time had dropped to an average concentration of 0.4 ppm (S.D. = 0.4 ppm). By comparison toluene breath levels increased from an average of 2.2 ppm (S.D. = 1.2 ppm) at the 2-h sample to 3.0 ppm (S.D. = 1.1 ppm) at the 4-h sample period. The toluene breath level for the post exposure sample averaged only 0.7 ppm (S.D. = 0.5 ppm).

Blood samples, which were collected from each participant, provided both a mid-exposure measure and a post-exposure measure of body burden (see Fig. 4). For the mid-exposure sample, the average blood concentration of MEK was 1.0 ppm (S.D. = 0.4). The analysis for the post sample showed a 55% decrease in the average concentration of MEK in the blood. The blood samples were also analyzed to determine the concentration of toluene. Between the first and second samples of blood, the concentration of toluene dropped by an average of 33%, or about 22% less than that for MEK. Specifically, for the mid-exposure sample the average blood concentration was 1.1 ppm (S.D. = 0.4 ppm), and for the post-exposure sample the average concentration in the blood was 0.7 ppm (S.D. = 0.4 ppm).

*Performance changes.* Table 4 (Panel D) shows the summary data for the three performance tests, as well as the Manacova probability values for each measure

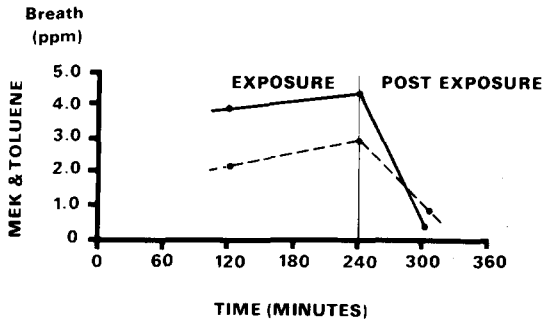


**Fig. 3.** Average concentration of toluene (- - -) and MEK (——) in breath for the combined exposure group obtained at each designated sample-period. Time is expressed in elapsed minutes from onset of exposure

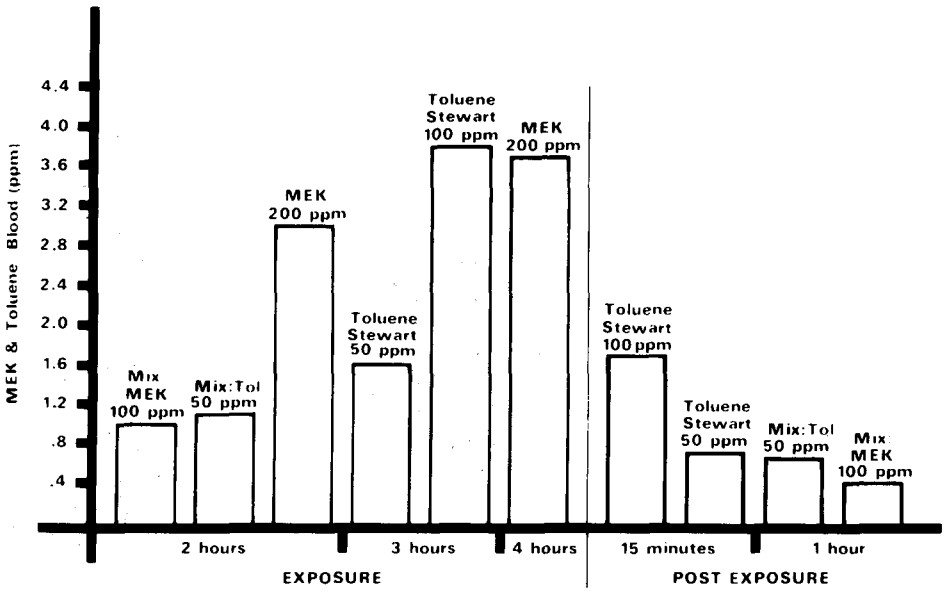


**Fig. 4.** Average concentration of toluene and MEK in blood for the combined exposure group compared with single exposure groups. Toluene levels are from Stewart et al. (1975) study. Samples were taken after a 2, 3, or 4 h exposure at 15 min or 1 h post-exposure

(right-hand column). The only statistically significant effect occurred with the response time measure in the visual-vigilance test ($P = 0.02$). Unfortunately, the meaning of this measure is almost totally obscured by the large differences between the groups in their initial performance levels, i.e., during the pre-test session. The group designated for the combined exposure, labeled T/MEK in Panel D of Table 4, was nearly a tenth of a second (13%) slower in their average response time than the control/placebo group.

Although the Manacova adjusts for a portion of this initial difference, the data collected for the two groups during the exposure periods fail to pass the test of reasonability. For example, during the first exposure session, the treatment group averaged 723 ms response time, which was also statistically significant ($P = 0.03$), and therefore different from the control group. However, the control group was actually slower than the treatment group in their average response

rate. By contrast, during both the second test session, and the post-exposure test period, the group data follow the trend that would be expected, if in fact, there was an adverse effect from exposure to the combined solvents of MEK and toluene. However, the corresponding *P* values are 0.63 and 0.52, respectively, which are not significant. Furthermore, the response time on the choice reaction failed to meet statistical significance, nor even to follow the trend established in the visual-vigilance test. In summary, the response-time data collected from the visual-vigilance test only demonstrate the difficulty in interpreting trends when the groups are not sufficiently equivalent in terms of their pre-treatment of baseline measures.

## Discussion

The biochemical measurements which were used primarily for confirmation of body burden levels showed that the desired levels were reached in the ethanol condition. The blood-alcohol levels in subjects at the time of measurement produced a mean of 77.5 mg% vs the desired 80 mg%. However, the sample was taken 2 h after ingestion, and peak blood concentration levels generally occur within 1 h after ingestion. Further, the average fall in blood ethanol is approximately 15 mg% per hour according to Forney and Harger (1969). Therefore, the average mg% level probably exceeded the desired maximum concentration level for the ethanol subjects.

The blood and breath concentration samples obtained during the solvent exposure periods were not consistent with expectations despite the fact that the chamber concentrations were at the targeted levels. However, the post-exposure blood and breath samples were generally at the desired levels. During the 4 h exposure period for toluene, breath samples were generally taken once near the 2 h mark, at the end of the exposure period, and 90 min post-exposure. Blood samples were not taken. In the MEK exposures, both blood and breath were taken at the 2 h mark and at the end of exposure. In approximately one-half the Toluene and MEK exposures, an extra breath sample was taken at between 1 and 1.5 h after exposure began. Breath was again taken at 90 min post-exposure. In the combined exposure, the procedures were the same as in the MEK condition, except that the second blood sample was taken 90 min post-exposure.

Previous research with toluene on expired breath concentrations under constant exposure reveals that a steady state is reached within two hours, so that the expired air percentages are a relatively fixed percentage of the chamber atmosphere. According to Stewart et al. (1975) it ranges from 10–20% and is not affected much by exposure duration. Nomiyama and Nomiyama (1974) also reported values within this range, reporting an average of 16.6% for their exposures. In the present study the expired air percentage was only around 7% on exit from the chamber after 4 h of exposure. During exposure the increase in alevolar breath percentage rose from 4.86% at the 2 h mark to 7.6% at the end of exposure.

In the MEK study a similar pattern emerged. Previous research (Tada et al. 1972) found expired air concentrations of approximately 9% with a 200 ppm

exposure for 1–3 h. In the present study the expired air concentrations averaged about 5%. Tada's et al. (1972) work also revealed that MEK was much like toluene in that duration of exposure did not affect expired air percentages greatly. In the present study, as with toluene, the MEK breath levels rose during the course of the exposure. The two blood samples taken averaged 3.1 ppm on the first draw and 3.7 at the end of the exposure. Comparable levels from other studies are not available in the literature.

The differences between the expired breath levels obtained in previous studies from those obtained in this study are probably due to procedural factors. The decay curve on the cessation of exposure is quite rapid, and samples in the present study were not always obtained immediately on exit from the chamber. Stewart's (1975) work with toluene shows a very rapid decay curve in the first 30 min, and they recommend that the most stable period for obtaining breath measurements is 1–3 h post-exposure. In their study at one-hour post exposure the average expired air percentage was 2.3 ppm for a three-hour exposure at 100 ppm for five subjects. In this study at 90 min post-exposure the average levels were 2.4 ppm. Comparable post-exposure levels for MEK were not available. Based on the more stable post exposure levels it was felt that the desired body burden levels were reached for the toluene exposures, and while there is no similar comparative data for the MEK study, desired body burden levels were also considered to be obtained.

In the combination study, the MEK and toluene expired breath levels were roughly within 4 and 5% of the chamber concentration respectively. The increase noted in the single exposure studies between the first and second samples was not as apparent. Combined peak blood-levels were 1.1 ppm for toluene and 1.0 ppm for MEK when the exposure levels were 50 and 100 ppm, respectively. In a previous single exposure study at 50 ppm for 3 h the blood concentration averaged 1.6 ppm, and at 100 ppm it rose to 3.9 ppm just before exiting the chamber (Stewart et al. 1975).

Using Stewart's values for blood toluene, and the body burden level values from the present study, there is some evidence that when these two organic solvents are used in combination at these low dose levels, the body burden level concentrations do not equal a corresponding 50% decrease in chamber concentration, especially the blood level concentrations. Reducing the chamber concentrations of toluene and MEK by 50% produced corresponding peak blood level concentration reductions of 77% for toluene (using Stewart's single exposure data) and 73% for MEK. These comparisons are graphically represented in Fig. 3 and 4. Expired breath percentages dropped 60% for toluene and 54% for MEK. The breath results seem to more closely approximate the 50% reduction in chamber concentrations. Examining the total body-burden levels of the two organic solvents under the combined exposure condition, neither of the combined breath measurements (peak and post) exceeded either the toluene or MEK single exposure levels. Combined peak blood concentrations levels were also lower than either the MEK single exposure levels, or the toluene levels reported in Stewart's (1975) work. These results indicate that the body burden levels for these two solvents in combination at these dose levels were not additive. This suggests that the ACGIH/OSHA mixtures formula, which

assumes additivity, is conservative for these two solvents at this exposure level during a 4 h exposure duration.

Interpretation of the behavioral data will begin with a brief discussion of the ethanol ingestion condition as a reference point for the sensitivity of the tests. Only two behavioral performance tests, the visual-vigilance task and the choice reaction time task showed any significant differences between the treatment group and the control group. On the visual-vigilance task the difference was manifested in a statistically significant higher false-alarm rate for the ethanol subjects during both the first and second exposure periods. Both groups showed improvement in false-alarm rates over the course of the experimental session when compared with the pre-exposure scores, so the difference between the groups was apparently in the rate of improvement in making correct responses to noncritical events. Effects of ethanol on the choice reaction time task were evident with longer response times being generated in the first exposure period when the blood ethanol concentrations were the highest; movement time was not affected. These results are consistent with those reported by Chiles and Jennings (1970) where a slightly higher ethanol dose (2.5 ml 100 proof vodka/kg) produced an increase in a similar response time measurement in the choice reaction time task, but not movement time.

In terms of the tests used in this study, the visual-vigilance task seemed to produce the most sensitive measurements of general arousal or attention. Every treatment condition produced at least one significant result on the visual-vigilance task. However, as this series of studies showed, there was a lack of consistency with the task. Ethanol affected the false alarm rate, toluene the correct response rate, and the directional differences with MEK appeared to be due to the performance of the control group. The choice reaction time test seemed to show much better consistency as it was affected only by the ethanol condition, and not by the low levels of toluene and MEK. Toluene has shown effects on a choice reaction time task, but only at the 500 ppm level (Gamberale and Hultengren 1972).

In the single exposure studies, significant effects were noted in the toluene exposure condition but not in the MEK condition. The MEK study lacked any post-exposure date collection, and there may have been some procedural problems because the MEK control group's performance was considerably worse than the performance of the other control groups used in the study. Under the toluene single-exposure condition, only one measurement, the correct detection of critical events (percentage hits) showed any significant differences. It occurred only in exposure period one, and although the same trend was present in exposure period two, it was not significant. The same although not significant trend was also found in the pattern recognition task.

The robustness of this significant finding has to be questioned because of the lack of confirmatory evidence from other studies. Only one other study (Stewart et al. 1975) has detected any significant effects of a toluene exposure level of 100 ppm on behavioral performance. The effect was noted only in females exposed for 7.5 h and also involved an alertness type task (see Introduction). Two studies (Gamberale and Hultengren 1972; Winneke 1982) failed to find any effects at less than 300 ppm; and another (Suzuki 1973) found no effects at

200 ppm. The Winneke (1982) study also included a bisensory vigilance task and a 100-ppm exposure level for three and one-half hours. The Stewart et al. (1975) study also had a 3.5 h exposure period, and in that condition no differences were found with either male or female subjects. Furthermore, the results are not consistent with the other treatment conditions where detection of critical events (percentage hits) was not affected. Mild CNS depressents like the ones used in this study would be expected to show some consistency on the measures used. In addition with the large number of measurements taken on the subjects, only one measurement was significant. Some possible reasons for the differences may be in the experimental design and analysis used. Other studies generally used designs where the same subjects received all exposure levels, whereas the present study used different subjects at each exposure level. The latter type of design requires more subjects, which can increase the precision of the experiment and statistical power of the analysis. We can only conclude that a compelling case has not been made for the likelihood that toluene produces significant cognitive decrements at 100 ppm.

In general, the results indicated that neither toluene at 100 ppm or MEK at 200 ppm seriously impaired behavioral performance on the tasks used in this study. The effects of toluene were at most marginal and were not as great as the effects of ingested alcohol (0.80 ml/kg), which affected both the visual-vigilance task and the choice reaction time task. Similar findings where alcohol caused more impairment than a low level exposure to an organic solvent have been reported in studies with xylene (Riihimaki and Savolainen 1980). These authors felt that the solvent effects were most prevalent during the period of the most rapid increase in body burden levels. This conclusion also seems relevant in this study, because the most pronounced effects were noted in the first 2 h of exposure which was the most rapid period of increase in body burden levels. Further, the combination of MEK (50 ppm) and toluene (100 ppm) failed to produce any significant effects on the same performance measures, although the total organic solvent exposure concentration was higher (150 ppm) than the toluene single exposure (100 ppm) concentration. This evidence coupled with the biochemical evidence discussed earlier suggests that neither chemical at these exposure levels exerted a potentiating effect on one another, and that their effects were probably not even additive.

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