

## Neurobehavioral Effects from Acute Exposures to Methyl Isobutyl Ketone and Methyl Ethyl Ketone

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Subjects were tested for neurobehavioral performance in an environmental chamber to detect the presence of subclinical central nervous system effects from 4-hr exposures to methyl isobutyl ketone (MIBK) at 100 ppm, methyl ethyl ketone (MEK) at 200 ppm, MIBK at 50 ppm with MEK at 100 ppm, or a placebo (i.e., a 5-min presentation of 25 ppm MEK-MIBK at each exposure period outset). Subjects were 68 males and 75 females recruited from local universities; ages ranged from 18 to 32 years. Ethanol by ingestion (95% - 0.84 ml/kg) was used as a positive control. Five psychomotor tests (choice reaction time [CRT], simple reaction time [SRT], visual vigilance, dual task [auditory tone discrimination and tracking], memory scanning), one sensorimotor test (postural sway), and a test of mood (profile of mood states) were used to measure neurobehavioral effects. Additionally, chemical measurements (blood and breath) and reports of sensory and irritant effects were measured. The chemical exposures produced statistically significant performance effects on only 4 of 32 measures (% correct responses-visual vigilance, movement time-CRT, SRT, % incorrect responses-dual task). These effects, however, were not substantial and could not be attributed directly to the chemical exposures. Alcohol ingestion, however, produced significant decrements on every performance test except memory scanning and mood. An interaction occurred between gender and alcohol ingestion, such that more statistically significant performance decrements were found for females than for males. Significant odor sensations and irritant effects were reported by the subjects during the chemical exposures. The MEK results agree with earlier MEK experiments at comparable exposure conditions, and the MIBK results are consistent with a recent Swedish study that used MIBK exposures and showed no significant behavioral performance decrements from single MIBK exposures at 50 ppm with 50 W exercise. Additionally, the MIBK-MEK combination exposure showed no evidence of any interaction effects on either the behavioral or chemical measurements. The principal effects resulting from exposures to MEK and MIBK at the durations and concentrations used in the study are limited to sensory and irritant effects. © 1992 Society of Toxicology.

The ketones are widely used as industrial solvents, extractants, chemical intermediates, and, in some cases, flavor and fragrance ingredients (Krasavage *et al.*, 1982). Total U.S. production of the ketones in 1985 was over 2 billion pounds. This total included over 537 million pounds of methyl ethyl ketone (MEK) and approximately 131 million pounds of methyl isobutyl ketone (MIBK) (USITC, 1985). Provisional data from the NIOSH National Occupational Exposure Survey (1981-1983) reported an estimated 1,447,456 workers exposed to MEK, of which 245,372 were female. Estimated workers exposed to MIBK totaled 612,921, of which 110,397 were female. Estimated workers exposed to both MEK and MIBK totaled 1,625,530, which includes 284,673 female workers.

In occupational settings, the primary routes of exposure to the ketones (MEK and MIBK) are inhalation and skin contact (Krasavage *et al.*, 1982). The primary health hazards from MEK and MIBK inhalation are mucous membrane irritation of the eyes, nose, and respiratory tract at low concentrations (<500 ppm) and central nervous system depression at higher concentrations (Papa and Sherman, 1981).

A number of controlled human exposure studies have investigated the subclinical neurobehavioral effects from acute exposures to various ketones. These include exposures to acetone (Nakaaki 1974; Matsushita *et al.*, 1979; Dick *et al.*, 1989), methyl ethyl ketone (Nakaaki 1974; Dick *et al.*, 1984; Dick *et al.*, 1989), and methyl isobutyl ketone (Hjelm *et al.*, 1990). Studies investigating the neurobehavioral effects of MEK and MIBK have failed to show significant central nervous system depressant effects from short-duration exposures (Dick *et al.*, 1984; Dick *et al.*, 1989; Hjelm *et al.*, 1990), nor has MEK demonstrated any interaction effects in a coexposure with toluene (Dick *et al.*, 1984) or acetone (Dick *et al.*, 1989). The Nakaaki (1974) study reported decrements on a time estimation test from MEK exposures, but only four subjects were used. Also, MIBK did not demonstrate any interaction effects in a coexposure with toluene (Hjelm *et al.*, 1990). In the studies using MEK and MIBK, the concentrations ranged from 10 to 270 ppm.

TABLE 1  
Subjective II Questionnaire Ratings under Various Treatment Exposure Conditions

Condition	Male			Female			Total <sup>a</sup>	% <sup>d</sup>
	No. reported exposed <sup>b</sup>	No. reported not exposed <sup>c</sup>	% <sup>d</sup>	No. reported exposed <sup>b</sup>	No. reported not exposed <sup>c</sup>	% <sup>d</sup>		
MEK	12	(1)	92	11	(0)	100	23 (1) <sup>e</sup>	96
MIBK	10	(0)	100	7	(6)	54	17 (6)	74
MEK-MIBK	11	(1)	92	12	(0)	100	23 (1)	96
Chemical control	8	(3)	27	9	(5)	36	8 (17)	32
Alcohol	10	(1)	91	12	(2)	86	22 (3)	88
Alcohol control	3	(8)	73	1	(10)	9	4 (18)	82
Total	54	(14)	68	52	(23)	75	97 (46)	143

<sup>a</sup> Excludes five subjects rejected for 9-carboxy THC (confirmed by GC/MS > 50 ng/ml).

<sup>b</sup> Number of subjects who reported they were exposed to a chemical or had a drink containing ethanol.

<sup>c</sup> Number of subjects who reported that they were not exposed to a chemical or had a drink containing no alcohol.

<sup>d</sup> Percentage of subjects who correctly identified the treatment condition.

<sup>e</sup> Total number of subjects in each treatment condition can be calculated by summing the number in parenthesis to the number not in parenthesis.

This work represents the third in a series of studies investigating the neurobehavioral effects of the ketones and the use of MEK in combination with common solvents. MEK was selected for an experimental series because the chemical occurs frequently in combination with other solvents, and animal research has shown that MEK potentiates the peripheral neuropathic effects of methyl normal butyl ketone and *n*-hexane (Spencer *et al.*, 1980).

In the present study, subjects were tested during a simulated 8-hr workday with the chemical exposures occurring during the middle 4 hr. Exposures took place during a 1-year period (June 1987–June 1988) and did not exceed the Occupational Safety and Health (OSHA) permissible exposure limits in effect during the experiment, and the combination exposures were constrained by the OSHA additivity formula which limits exposures to (solvent) mixtures in the workplace (U.S. Printing Office, 1981). Applying the OSHA constraints, the combination exposure concentrations were at one-half the single exposure concentrations. Before, during, and after exposures, neurobehavioral measurements were collected to determine whether performance decrements or improvements resulted from the exposures. Chemical measurements from blood and breath samples were collected before, during, and after exposures to document body-burden concentrations and to investigate relationships between individual blood concentrations and neurobehavioral test performance.

## EXPERIMENTAL PROCEDURES

### Subjects

Sixty-eight males and 75 females were recruited from local universities for this experiment; ages ranged from 18 to 32. Initial telephone screening eliminated smokers and subjects with previous work histories of solvent

exposure. Prior to testing, subjects were required to pass a medical examination. Medical disqualification criteria included obesity, pregnancy, hypertension, elevated values on liver function tests, diabetes, abnormal EKG, and substance abuse. Subjects were required to be drug free (i.e., tested for 10 drugs of abuse at the medical exam, and repeated on exposure day if results from the medical exam were positive), to abstain from alcohol for at least 12 hr (i.e., tested on the day of exposure), and to be free of medication (unless approved by the examining physician) for 24 hr prior to the experiment. Five subjects were eliminated from data analysis for substance use (9-carboxy THC confirmed by GC/MS > 50 ng/ml). Subjects were required to eat a breakfast before the exposure test session and to eat two lunches (i.e., sandwich and noncaffeinated pop or juice) during the test session (one-half hour before the exposure/alcohol ingestion, and at the end of the 4-hr exposure period).

### Experimental Design

Subjects were randomly assigned to one of six treatment groups: (1) control-placebo; (2) MEK-200 ppm; (3) MIBK-100 ppm; (4) MEK-100 ppm-MIBK-50 ppm; (5) 95% ethanol-0.84 ml/kg; and, (6) alcohol-placebo. Random assignment was compromised only as necessary to maintain equal numbers of subjects for each treatment condition by gender or to avoid violating the State of Ohio drinking age regulations (i.e., subjects had to be over 21 years old to consume alcohol). (A one-way ANOVA showed no significant age differences between the six treatment groups;  $F[5,137] = 0.27, p = 0.93$ .) The alcohol group was used as a positive control for determining the sensitivity of the neurobehavioral tests. Two additional control groups were used: One (the chemical-control group) served as a control for the chemical exposure groups, and the other (alcohol-control group) served as a control for the alcohol ingestion group. The chemical-control exposure consisted of a 5-min, 25 ppm MEK-MIBK mixture presented at the beginning of each 2-hr exposure period. The alcohol-control group consumed the alcohol drink mixture without ethanol. Table 1 provides the total number of subjects in each treatment group.

The experimental test sessions took place on 3 consecutive days and consisted of a 2-hr practice session the day before the exposure session (Day 1), an 8-hr exposure session on Day 2, and a 2-hr postexposure session on Day 3. On the exposure day (i.e., Day 2), subjects reported to the laboratory at 7:45 AM for preexposure breath testing. The test session commenced with a 2-hr preexposure period (Pre), followed by a 4-hr exposure period (divided into two, 2-hr periods, Exp-1 and Exp-2), and a 2-hr postexposure period

(Post-1). Subjects returned the next day at 7:45 AM for the last 2-hr test period (Post-2). Neurobehavioral tests, which were sedentary in nature (i.e., required no physical exertion) were administered during each of the 2-hr test periods. The number of subjects run per test session varied between 2 and 4.

Five expired breath samples and five venous blood samples were collected from the subjects in accordance with the following schedule: (1) Preexposure (collected the afternoon prior to the exposure session for blood, and immediately prior to the exposure session for breath); (2) after 2 hr of exposure (Exp-1); (3) after 4 hr of exposure (Exp-2); (4) 90 min after the exposure ended (Post-1); and, (5) prior to the Post-2 test session. The 4-hr exposure (Exp-1 and Exp-2) was continuous except for a brief period when subjects exited the chamber to provide blood samples. Table 2 outlines the test regimen, indicating the approximate times of the blood and breath samples, lunch periods, performance testing, and questionnaire administration.

Experimental sessions were conducted double blind (i.e., only the chamber operator had knowledge of the exposure condition). In accordance with the guidelines of the National Institute for Occupational Safety and Health (NIOSH) Human Subjects Review Board and the ethical principles of the American Psychological Association (American Psychologist, 1990), subjects were duly informed about the nature of the exposure and test conditions and were required to sign a consent form to that effect. They were paid \$150 for participation. Testing was administered inside an environmental chamber (Forma-Scientific) that measured 2.5-m wide × 5.3-m long × 2.2-m high and was configured with four test stations. Each test station was equipped with one monopanel keyboard (Centralab-MRK12AE2100), one Hewlett-Packard 1311B video display terminal (VDT), one custom-made reaction time panel, one cylindrical microswitch (Switchcraft E-19), one pressure-type joystick (Measurement Systems 735DC), two box-mounted toggle

switches (Switchcraft 41306), one custom-made electrode box, and one set of earphones (Realistic Pro-IIA).

During each 2-hr test period, several neurobehavioral performance tests were administered. Performance measurements were derived from five psychomotor tests (choice reaction time [CRT], simple reaction time [SRT], visual vigilance, dual task, short-term memory scanning), one neurophysiological test (eye blink reflex), and one sensorimotor test (postural sway). A mood questionnaire, the Profile of Mood Scales (POMS), was administered to subjects on Day 1 prior to the exposure test day, at the end of the Post-1 period on Day 2, and prior to the Post-2 period on Day 3. Two additional questionnaires also were administered. The Subjective I questionnaire (i.e., to assess sensory and irritant effects) was administered at the end of the Exp-1 and Exp-2 periods. The Subjective II questionnaire, which asked subjects to identify the exposure conditions and to rate the neurobehavioral tests for irritation (i.e., they find these tests to be disturbing), was administered at the end of the Post-1 period.

#### Performance and Subjective Tests

The Subjective questionnaires (I and II) and the POMS were self-administered paper and pencil tests. The neurobehavioral performance tests were administered through a minicomputer (IBM Series I), and the postural sway test was microcomputer-controlled (Northstar Horizon). Tests were presented simultaneously to the subjects (except for the postural sway test), and the order of test presentation (see Table 2) was the same in each test period. Trial order within a test, however, differed for each subject, and the trial order varied for each successive administration of the same test. Postural sway testing was conducted on the force platform mounted in the chamber floor. Subjects were required at the practice session to reach 80% criterion

TABLE 2  
Experimental Test Schedule<sup>a</sup>

Period:	Day 1—Practice	Day 2—Exposure					Day 3—No exposure	
		Pre	Exp-1	Exp-2	Post-1		Post-2	
Time <sup>b</sup> :	1330–1530	0745	1030	1230	1450	1510	1710	0745–1030
Test <sup>c</sup>								
Vis-vig	XXXx <sup>d</sup>	XXXx	XXXx	XXXx	XXXx			XXXx
CRT	x	x	x	x	x			x
Dual task	XX	XX	XX	XX	XX			XX
SRT	x	x	x	x	x			x
Sway	x	x	x	x	x			x
Memory	XXx	XXx	XXx	XXx	XXx			XXx
Eye blink		Xx	Xx		Xx			Xx
POMS	x						x	x
Subj I			x	x				
Subj II							x	
Chemical								
Breath								
	x	x		x	x		x	x
Blood	x			x	x		x	x
Other								
	Consent form		Lunch		Lunch		Med <sup>e</sup> check	Release

<sup>a</sup> Test presentations and chemical sample collections are listed in order of administration.

<sup>b</sup> Times listed represent approximate times that test presentations, sample collections, and other events occurred.

<sup>c</sup> Vis-vig, visual vigilance; CRT, choice reaction time; SRT, simple reaction time; POMS, profile of mood states; Subj I, subjective questionnaire 1; subj II, subjective questionnaire 2.

<sup>d</sup> Testing/sampling time durations are designated as: X, approximately 10 min; x, 5 min or less.

<sup>e</sup> Medical examination for release from the exposure test day.

levels on tests using correct responses as the performance measure; a score of 90 (i.e., range 0–308) or less was required for the 3-min tracking test. Subjects received 40 practice trials on the CRT test, 30 practice trials on the SRT test, 60 practice trials on the memory scanning test, and one practice trial on the postural sway test. The eye blink test was demonstrated to each subject. The visual-vigilance, dual task, CRT, memory scanning, postural sway, and POMS tests used the same forms/equipment and were administered in the same manner, as in a previous study (Dick *et al.*, 1989). Only brief descriptions of each previously used test will be described below. The SRT test (which was new to this battery) and the questionnaires will be described in more detail. The eye blink reflex test results have been reported previously (Russo *et al.*, 1990) and are not presented here.

**Visual vigilance.** The visual-vigilance test is a computerized version of the Mackworth clock test (Mackworth, 1961). Subjects were required to follow a moving clockhand and respond when the clockhand jumped twice instead of once. The test took 36 min to complete and was divided into four 9-min test periods. Measurements recorded were response time (msec) for correct responses and the number of correct responses and incorrect responses.

**Dual task.** The dual task required subjects to perform an auditory tone discrimination test, followed by a compensatory visual tracking task, and then to perform the two tasks simultaneously. Measurements were taken in both single and dual task conditions. The auditory tone test required the detection of a 760 Hz tone from a series of 750 Hz tones. The compensatory tracking task consisted of two 4-cm arrows displayed on a VDT screen, one pointing upward and moveable, and one pointing downward and stationary. Subjects used a joystick to reposition the moving arrow underneath the fixed arrow. The dual test was modified from our previous experiments (Dick *et al.*, 1989), primarily to shorten the total test time from 30 to 20 min. The measurements recorded were response time (msec) for correct responses, number of correct responses, number of incorrect responses, and tracking error (i.e., root mean square error and modulus mean error).

**Choice reaction time.** The CRT test requires subjects to depress a lighted green button at all times except when one of eight red buttons is lighted. The test is the same as the test described in Dick *et al.* (1989). The measurements recorded were: (1) release time (i.e., the interval between the onset of the stimulus [red light] and release of the subject's finger from a green button) and (2) movement time (i.e., the interval between release of the green button and depression of the lit red button).

**Simple reaction time.** For the simple reaction time test, subjects were seated in front of the video display terminal with the preferred index finger resting on the "5" key of a monopanel keyboard. The reaction time stimulus was a  $1.3 \times 1.3$ -cm blank square that appeared in the center of the screen. The stimulus (square) appeared quasi-randomly, with intertrial intervals ranging from 2000 msec (minimum) to 6000 msec (maximum). Subjects responded to the presentation of the square by depressing the 5 key. Sixty-eight trials were administered, with the first four trials and the last four trials discarded (to reduce practice and fatigue effects, respectively). The measurement recorded was the time (msec) to respond to the presence of the stimulus. The test took 6 min to complete.

**Memory scanning.** The memory scanning test is a computerized version of the Sternberg short term memory scanning test (Sternberg, 1975) and is described in more detail in a previous publication (Dick *et al.*, 1989). Subjects were presented single digits in list lengths of two, four, or six to memorize. At the end of each list presentation, a test digit appeared. Subjects responded yes (positive response) or no (negative response) whether the test digit matched a number in the previously presented list. The measurements recorded were the mean reaction times for each set size (i.e., list length) and probe type (positive or negative). These times were used to generate the four scores used for data analysis. The scores are positive slope, negative slope, positive intercept, and negative intercept.

**Postural sway (steadiness) test.** The postural sway test used a biomechanics platform system manufactured by Advanced Mechanical Technology, Inc. to take samples of postural stability. Two 30-sec samples (10/sec

sample rate) were taken, one with the subjects standing on the platform with their eyes closed and the other with eyes open. The measures reported are: (1)  $R_m$  (mean radius of sway [in cm]); (2) length (length of sway path [in cm]); (3)  $A_0$  (area of sway path [cm<sup>2</sup>]); and (4) velocity (mean velocity along the sway path [cm/sec]).

**Profile of mood states (POMS).** The POMS test (McNair *et al.*, 1981) is a factor analysis derived inventory that measures mood states. The six mood scales measured are: (1) tension-anxiety; (2) depression-dejection; (3) anger-hostility; (4) vigor-activity; (5) fatigue-inertia; and (6) confusion-bewilderment.

**Subjective questionnaires.** The Subjective I questionnaire consisted of items which used a dichotomous (i.e., "yes/no") format. The items reported were: (1) presence of odor; (2) strong odor; (3) objectionable odor; (4) headache; (5) nausea; (6) throat dryness or coughing; (7) tearing; and (8) unpleasant exposure. The Subjective II questionnaire required subjects to use the same dichotomous response format to indicate whether they had been exposed to a chemical-exposure condition or a chemical-control condition. Subjects who had been administered a drink (i.e., alcohol or alcohol-control) indicated whether or not the drink contained alcohol. The Subjective II questionnaire, using a yes/no response, also asked the subjects to answer the question "Did you find any test particularly irritating;" this and other test items were listed with a space for a yes/no response.

## METHODS

### *Atmosphere Generation and Monitoring*

The MEK and MIBK used in generation of the chamber atmospheres were 99.5% pure as verified by independent analysis (i.e., gas chromatography). The two chemicals were drawn from a reservoir through a dual high-pressure metering pump (Eldex-Model AA) into a mixing flask (2 liter three vertical neck) which forced (using prepurified air) the chemical air mixture into the environmental chamber at the desired concentration. The atmosphere generation and monitoring procedures were the same as those procedures described in previous reports (Dick *et al.*, 1984, 1989), with the following revisions: (1) A Perkin-Elmer 8500 gas chromatograph (GC) replaced a Perkin-Elmer 3920 gas chromatograph, which malfunctioned after the first 54 subjects were tested; (2) the gas chromatograph and the Miran IA infrared analyzers used chamber air samples extracted from separate independent lines (in previous studies, the same line was used); and, (3) a  $183 \times 0.32$ -cm OD stainless steel column packed with 0.2% Carbowax-C 1500 60–80 mesh was used. Detection limits were 0.02 ppm for MIBK and 0.01 ppm for MEK. Concentrations were monitored on-line continuously from four sample ports located at each subjects test station by Miran IA infrared analyzers. Confirmation was performed every 30 min from two additional sample ports by gas chromatography. Infrared analyzer and gas chromatograph measurements were required to agree within 10% or else the exposure was terminated (there were no terminations). After allowing one-half hour for the chamber atmosphere to stabilize, chamber concentrations for Hours 2, 3, and 4 were within 10% of target concentrations (see Table 3).

### *Sampling and Analysis of Breath and Blood Specimens/Ethanol Administration*

The sampling and analysis procedures for the blood and breath specimens were the same as those described in previous studies (Brown *et al.*, 1987; Dick *et al.*, 1989) except: (1) subjects were pretrained at the practice day session on a spirometer to provide forced evacuation breath samples; (2) during the exposure session, the breath samples were collected from within the chamber through a one-way breathing valve system (i.e., subjects were instructed to hold their breath for 30 sec before evacuating their lungs into a disposable mouthpiece connected to a one-way breathing valve [Collins-21003], with the first liter of air collected into a discard bag and the remaining sample collected into a sample bag); and (3) tedlar bags were used rather than mylar bags. The blood sample analyses were performed on a Hewlett-

TABLE 3  
Chamber Exposure Concentrations for Methyl Ethyl Ketone (MEK) and Methyl Isobutyl Ketone (MIBK)

Condition	Sample values <sup>a</sup> (ppm)				
	Hour 1	Hour 2	Hour 3	Hour 4	4-hr mean
MEK (200 ppm)					
Exposure <sup>b</sup> = 8					
Mean	160.2	197.3	197.4	198.3	188.3
SD <sup>c</sup>	22.4	4.6	3.2	1.5	6.8
MIBK (100 ppm)					
Exposures = 8					
Mean	71.5	91.4	93.5	96.5	88.2
SD	14.4	7.9	4.2	2.6	6.3
Combination (MEK and MIBK)					
Exposures = 8					
MEK (100 ppm)					
Mean	91.2	103.1	101.2	104.6	100.0
SD	6.4	3.9	4.1	3.6	4.0
MIBK (50 ppm)					
Mean	41.2	51.3	50.5	52.4	48.9
SD	4.5	4.5	4.9	4.4	4.2

<sup>a</sup> Values represent mean hourly sample readings and standard deviations from four sample ports in the environmental chamber; readings are from the Miran IA analyzer.

<sup>b</sup> Exposures refers to number of times this treatment condition was administered.

<sup>c</sup> SD, standard deviation.

Packard 5890 using a gas liquid chromatography head-space technique, with ethanol as the internal standard. Correlation coefficients between standard concentrations and areas under the curve were 0.996 for MEK and 0.999 for MIBK. Detection limits were 0.2  $\mu\text{g}/\text{ml}$  for MEK and 0.3  $\mu\text{g}/\text{ml}$  for MIBK. The blood and breath concentrations for MEK, MIBK, and ethanol are presented in Tables 4 and 5.

A postexperiment statistical analysis revealed a difference in the breath sample measurements between the two gas chromatographs used in the experiment in certain exposure conditions. The older Perkin-Elmer GC (3920) measured higher MEK breath concentrations in subjects that received the combination exposures and higher MIBK breath concentrations in subjects who received the MIBK single exposures. The mean values measured by the older GC were 36% higher than the values measured by the newer Perkin-Elmer GC (8500). Consequently, the breath values reported below are subject to measurement variability and most likely represent relative values rather than absolute values.

The ethanol administration procedures were the same as those procedures described in Dick *et al.* (1989).

## RESULTS

Two statistical analyses were performed. Analysis of mean differences among treatment groups was conducted using the multiple analysis of variance (MANOVA)/analysis of variance (ANOVA) SAS (SAS, 1989) general linear model and BMDP4V (Dixon, 1990) programs. Analysis of the relationship between subjects' neurobehavioral performance measures and their respective blood concentrations was performed using SAS multiple regression analysis. In all analyses, the four chemical groups that received an inhalation exposure were analyzed separately from the two ethanol groups which received an ingested dose.

The basic experimental design was a mixed model, repeated measures design consisting of a 4 (chemical groups) or 2 (alcohol groups)  $\times$  2 (gender)  $\times$  5 (periods) factorial. The repeated measures factor was periods; the most critical test statistic was computed on the periods  $\times$  group interaction. The expectation was that the neurobehavioral test performance scores would differ from controls in measures taken during the exposure periods (i.e., when the blood concentrations of the chemicals were at the highest levels). In the MANOVA/ANOVA analyses of measures consisting of time blocks (i.e., visual vigilance, CRT, SRT), a fourth factor (time) was included in the analysis. In the regression analysis, tests were performed to determine if a significant linear relationship existed between male and female blood concentrations of MEK and MIBK and performance on the neurobehavioral tests. In addition, tests were performed to determine differences between male and female slopes (i.e., regression coefficients), increases between MEK and MIBK concentration(s), and differences in the MEK-MIBK interaction between males and females.

In tests involving multiple dependent measures, ANOVA was used if the MANOVA was significant at  $\alpha = 0.05$ . The MANOVA tests used are the Wilk's Lambda or the Hotelling  $T^2$ . In the regression analysis, a multivariate test was performed initially on the regression coefficients. Regression coefficients for each measure were significant if both the multivariate test and the performance measure regression coefficients were significant at  $\alpha = 0.05$ . If the MANOVA

TABLE 4  
Blood and Breath Concentrations for the Chemical Conditions

Condition	Pre		2 hr		4 hr		90-min post		20-hr post	
	Bl <sup>a</sup>	Br	Bl	Br	Bl	Br	Bl	Br	Bl	Br
Single exposures										
Male: MEK-200 ppm, <i>N</i> = 13 <sup>b</sup>										
Mean	ND <sup>c</sup>		3.3	17.2	4.0	20.2	1.0	1.3		ND
SD			0.9	4.0	3.3	7.1	0.3	1.0		
Female: MEK-200 ppm, <i>N</i> = 10,										
Mean	ND		2.5	19.9	3.3	19.2	0.9	1.4		ND
SD			0.6	6.3	1.1	6.7	0.4	0.6		
Combined:										
Mean	ND		3.0	18.4	3.7	19.7	0.9	1.3		ND
SD			0.9	5.2	1.1	6.8	0.4	0.9		
Male: MIBK-100 ppm, <i>N</i> = 13,										
Mean	ND		0.7	11.7	0.6	10.7	0.1	0.2		ND
SD			0.5	3.5	0.4	3.1	0.3	0.3		
Female: MIBK-100 ppm, <i>N</i> = 12,										
Mean	ND		0.6	9.5	0.5	10.0	0.1	0.2		ND
SD			0.4	3.3	0.4	3.2	0.2	0.4		
Combined:										
Mean	ND		0.6	10.6	0.6	10.5	0.1	0.2		ND
SD			0.5	3.5	0.4	3.2	0.3	0.2		
Combination exposures										
Male: MEK-100 ppm, <i>N</i> = 12,										
Mean	ND		0.9	12.0	1.1	10.9	0.1	0.7		ND
SD			0.2	4.4	0.3	3.1	0.2	0.7		
Female: MEK-100 ppm, <i>N</i> = 12,										
Mean	ND		0.9	8.0	0.9	11.1	0.1	0.5		ND
SD			0.2	2.9	0.4	5.7	0.1	0.7		
Combined:										
Mean	ND		0.9	10.1	1.0	11.0	0.1	0.6		ND
SD			0.2	4.1	0.4	4.4	0.2	0.7		
Male: MIBK-50 ppm, <i>N</i> = 12,										
Mean	ND		0.3	3.5	0.2	4.0	ND	0.1		ND
SD			0.2	1.1	0.2	1.2		0.3		
Female: MIBK-50 ppm, <i>N</i> = 12,										
Mean	ND		0.3	3.3	0.3	4.2	ND	0.1		ND
SD			0.2	1.7	0.4	2.0		0.3		
Combined:										
Mean	ND		0.3	3.4	0.2	4.1	ND	0.1		ND
SD			0.2	1.4	0.3	1.7		0.3		

<sup>a</sup> Bl, blood in  $\mu\text{g/ml}$ ; Br, breath in ppm. All subjects were tested for MIBK, MEK, and ethanol. Values are means and standard deviations (SD) under exposure conditions and correspond to the chemical detected for the designated exposure. Samples were collected at the beginning of the exposure, except for the preexposure samples. Preexposure blood samples were taken the day before exposure, and preexposure breath samples were collected on the morning of exposure.

<sup>b</sup> *N*, number of subjects. The actual number of blood samples varied for each sample period because blood samples were not obtained from some subjects.

<sup>c</sup> ND, 100% of the sample values were below detectable limits.

or the multivariate test was not significant, then the ANOVA test statistic or the regression coefficient for each measure was considered significant only if  $\alpha = 0.05/d$ , with *d* being the number of dependent variables for that test. The Greenhouse-Geisser estimate of epsilon was used to adjust the degrees of freedom for the ANOVA within-subject main ef-

fects, as well as interactions. If a treatment condition main effect, or an interaction involving treatment conditions, was found to be significant in either the chemical or the alcohol groups, contrasts were performed comparing each exposure group or the alcohol group to the respective control group. A significant contrast level was  $\alpha = 0.05$ . Percentage data

TABLE 5  
Blood and Breath Concentrations for the Alcohol Exposures

Condition	Pre		2 hr		4 hr		90-min post		20-hr post	
	Bl <sup>a</sup>	Br	Bl	Br	Bl	Br	Bl	Br	Bl	Br
Alcohol ingestion										
Male: 0.84 ml/kg, <i>N</i> = 11,										
Mean	ND		0.06	115.6	0.03	53.8	0.005	11.1		ND
SD			0.01	22.2	0.01	21.2	0.011	5.8		
Female: 0.84 ml/kg, <i>N</i> = 13,										
Mean	ND		0.06	106.9	0.02	39.9	0.003	7.9		ND
SD			0.01	20.6	0.01	24.2	0.007	8.2		

<sup>a</sup> Bl, blood in w/v%; Br, breath in ppm. Values are means and standard deviations (SD). Samples were collected 2 hr and 4 hr after the beginning of ingestion, except for the preexposure samples. Preexposure blood samples were collected the day before exposure, and preexposure breath samples were collected on the morning of exposure.

<sup>b</sup> *N*, number of subjects. The actual number of blood samples varied for each sample period because blood samples were not obtained from some subjects.

<sup>c</sup> ND, 100% of the sample values were below detectable limits.

were calculated as follows: % correct responses = correct responses divided by expected responses  $\times$  100; % incorrect responses = incorrect responses divided by the sum of incorrect responses and correct responses  $\times$  100. Data from the preexposure test period were compared with data from postexposure Period 2 to assess learning or practice effects. Only the choice reaction time test showed consistent learning effects in both the chemical and alcohol analysis. Additional analysis confirmed the absence of significant differences among the four test stations.

In an effort to compress the outcomes of the aforementioned data analyses, two tables (6 and 7) listing the probability values for the various statistical treatments were developed, and only the most notable results will be acknowledged for each test. Table 6 presents the MANOVA/ANOVA probabilities for the period  $\times$  group interactions for each test measure (except for the Subjective I questionnaire data, which are presented as main effect probabilities). Tables (9–13) of means and standard deviations for the performance measures listed in Table 6 are presented in the Appendix. Table 7 presents the regression coefficient probability values for each test measure. Data from the Subjective II questionnaire pertaining to exposure conditions are reported in Table 1. Subjective II questionnaire data describing attitudes toward the neurobehavioral tests showed no significant interactions with the treatment conditions and therefore will not be discussed further.

#### Visual Vigilance

**Chemical groups.** Only the MANOVA for the period  $\times$  time  $\times$  group  $\times$  sex interaction was significant ( $F[108,159.64] = 1.40, p = 0.03$ ). A significant ANOVA was obtained for the percentage correct responses ( $F[36,1056] = 1.53, p = 0.04$ ). Examination of the contrasts revealed no

consistent trends that could be attributed to the chemical treatments. Regression analysis for the chemical groups revealed significant multivariate tests for the MIBK-exposed females ( $p = 0.015$ ) and the MEK–MIBK interaction term for males ( $p = 0.008$ ). The female percentage correct responses showed a small, positive linear slope ( $b = 10, p = 0.02$ ) with the blood concentration of MIBK. The MEK–MIBK interaction term for response time was significant for males ( $b = 260, p = 0.001$ ).

**Alcohol groups.** The ANOVA for response time was significant ( $F[4,176] = 4.61, p = 0.006$ ). The mean response time was significant ( $F[4,176] = 4.61, p = 0.006$ ). The mean response time in the alcohol group (883 msec) was significantly longer than for the alcohol-placebo group (793 msec) in Exp-1 ( $p = 0.03$ ). Regression analysis revealed significant multivariate tests for both males ( $p = 0.03$ ) and females ( $p = 0.01$ ). Positive linear relationships between blood concentrations and response times were significant for both males ( $b = 2069, p = 0.003$ ) and females ( $b = 2201, p = 0.002$ ).

In summary, no significant effects for group treatment means were detected in the chemical groups (period  $\times$  group) for the visual vigilance task, but some isolated chemical effects were detected in the regression analysis. The only linear concentration effect was for females (i.e., females exposed to MIBK showed a small increase in percentage correct responses with increasing blood concentrations of MIBK). A decrease in percentage correct responses, however, would have been predicted with increasing blood concentrations of a CNS depressant substance. This result, therefore, has to be considered isolated and possibly spurious. The increase in response times for males shown by the MEK–MIBK interaction term does not reflect a simple linear concentration/response relationship, but a three-dimensional response surface. A plot of these results did not reveal an interpretable

TABLE 6  
Summary of Significant MANOVA/ANOVA Results<sup>a</sup>

Performance test	Chemical groups		Alcohol groups	
	MANOVA	ANOVA	MANOVA	ANOVA
Visual Vigilance	0.46		0.08	
Response time		0.43		0.01 <sup>b</sup>
% Correct response		0.50		0.06
% Incorrect response		0.26		0.35
Choice reaction time	0.44		0.04	
Release time		0.72		0.00 <sup>c</sup>
Movement time		0.36		0.62
Simple reaction time		0.05 <sup>d</sup>		0.11
Dual task	0.05		0.20	
Auditory-response time		0.91		0.12
Auditory-% Incorrect response		0.67		0.27
Auditory-% Correct response		0.14		0.85
Tracking		0.26		0.05
Postural sway	0.62		0.04	
<i>R<sub>m</sub></i>		0.72		0.34
Length		0.28		0.00 <sup>e</sup>
Area		0.57		0.01
Velocity		0.17		0.00 <sup>f</sup>
Memory scanning	0.13		0.83	
Intercept-positive		0.01 <sup>g</sup>		0.64
Intercept-negative		0.47		0.99
Slope-positive		0.14		0.50
Slope-negative		0.73		0.34
Profile of mood scales	0.65		0.92	
Tension-anxiety		0.41		0.57
Depression-dejection		0.35		0.33
Anger-hostility		0.58		0.59
Vigor-activity		0.01 <sup>h</sup>		0.70
Fatigue-inertia		0.05		0.29
Confusion-bewilderment		0.93		0.42
Subjective I <sup>i</sup>	0.00		0.03	
Odor		0.91		0.00
Odor-strong		0.00		0.05
Odor-objectionable		0.26		0.01
Headache		0.09		0.07
Nausea		0.14		0.26
Throat irritation		0.04 <sup>j</sup>		0.56
Tearing		0.74		0.56
Unpleasant		0.49		0.12

<sup>a</sup> Probability levels are for the period  $\times$  group interactions. Significant three- and four-factor interactions are reported in the text. Significant results that met acceptance criteria are italic.

<sup>b</sup> Mean response time for the alcohol group was longer than for the alcohol-control group in Exp-1 ( $p = 0.0335$ ).

<sup>c</sup> Mean release time for the alcohol group was longer than for alcohol-control group in both Exp-1 ( $p = 0.0210$ ) and Exp-2 ( $p = 0.0392$ ).

<sup>d</sup> The only significant contrast was between the MEK-MIBK group and the chemical-control group for the preexposure period.

<sup>e</sup> Mean length of sway path for the alcohol group was longer than for the alcohol-control group in Exp-1 ( $p = 0.0500$ ).

<sup>f</sup> Mean velocity of sway for the alcohol group was faster than the alcohol-control group in Exp-1 ( $p = 0.0503$ ).

<sup>g</sup> The only significant contrast was between the MEK-MIBK group and the chemical-control group for the preexposure period.

<sup>h</sup> The significant contrast was between the MEK group and the control group for Post-2.

<sup>i</sup> Probabilities are for main group effects.

<sup>j</sup> No contrasts were significant for the three chemical groups versus the control group.

TABLE 7  
Summary of Probability Values of Regression Coefficients for Slope Using Subject Blood Concentrations

Performance test	MIBK			MEK			MEK × MIBK			Ethanol		
	M <sup>a</sup>	F <sup>b</sup>	D <sup>c</sup>	M	F	D	M	F	D	M	F	D
Visual vigilance <sup>d</sup>	0.82	0.02	0.10	0.09	0.06	0.53	0.01	0.43	0.23	0.03	0.01	0.71
Response time	0.43	0.01	0.38	0.41	0.59	0.94	0.00	0.22	0.22	0.00	0.00	0.87
% Correct response	0.84	0.02	0.03	0.62	0.24	0.16	0.16	0.37	0.11	0.79	0.27	0.46
% Incorrect response	0.60	0.90	0.82	0.02	0.07	0.95	0.70	0.92	0.74	0.73	0.13	0.30
Choice RT	0.32	0.29	0.46	0.00	0.45	0.02	0.36	0.22	0.91	0.00	0.00	0.51
Release time	0.99	0.16	0.24	0.22	0.30	0.08	0.16	0.12	0.83	0.00	0.00	0.33
Movement time	0.13	0.52	0.66	0.00	0.50	0.03	0.81	0.47	0.71	0.25	0.70	0.54
Simple RT	0.47	0.67	0.91	0.20	0.96	0.40	0.12	0.04	0.60	0.03	0.00	0.00
Dual task	0.09	0.71	0.38	0.62	0.01	0.05	0.94	0.22	0.74	0.06	0.00	0.00
Auditory-response time	0.12	0.87	0.25	0.52	0.40	0.22	0.63	0.96	0.72	0.00	0.37	0.09
Auditory-% incorrect response	0.03	0.45	0.43	0.71	0.00	0.02	0.88	0.95	0.96	0.69	0.33	0.61
Auditory-% correct response	0.51	0.42	0.26	0.61	0.27	0.18	0.87	0.57	0.59	0.88	0.20	0.33
Tracking	0.16	0.40	0.10	0.25	0.17	0.66	0.87	0.57	0.59	0.87	0.00	0.00
Postural sway	0.83	0.89	0.96	0.80	0.28	0.28	0.73	0.98	0.88	0.08	0.00	0.17
R <sub>m</sub>	0.44	0.83	0.74	0.23	0.98	0.42	0.38	0.82	0.45	0.08	0.35	0.49
Length	0.85	0.42	0.58	0.37	0.35	0.14	0.46	0.66	0.41	0.02	0.00	0.14
Area	0.98	0.76	0.81	0.30	0.80	0.34	0.19	0.80	0.29	0.13	0.04	0.70
Velocity	0.82	0.39	0.57	0.40	0.72	0.36	0.50	0.60	0.40	0.02	0.00	0.20
Memory scanning	0.72	0.90	0.62	0.80	0.76	0.86	0.55	0.81	0.78	0.43	0.88	0.24
Intercept-positive	0.64	0.99	0.75	0.35	0.44	0.95	0.70	0.74	0.99	0.40	0.65	0.27
Intercept-negative	0.65	0.38	0.30	0.66	0.61	0.45	0.24	0.29	0.98	0.30	0.68	0.22
Slope-positive	0.77	0.87	0.74	0.77	0.41	0.58	0.65	0.53	0.44	0.76	0.83	0.65
Slope-negative	0.70	0.57	0.82	0.77	0.80	0.97	0.49	0.34	0.80	0.53	0.72	0.82
Subjective I	0.69	0.99	0.78	0.38	0.75	0.68	0.55	0.94	0.96	0.94	0.58	0.74
Odor	0.20	0.39	0.15	0.41	0.58	0.78	0.10	0.51	0.81	0.93	0.29	0.36
Odor-strong	0.27	0.50	0.24	0.79	0.58	0.85	0.80	0.45	0.43	0.99	0.13	0.23
Odor-objectionable	0.73	0.72	0.92	0.06	0.82	0.18	0.36	0.66	0.94	0.54	0.10	0.47
Headache	0.55	0.71	0.97	0.30	0.80	0.51	0.47	0.75	0.93	0.45	0.64	0.28
Nausea	0.23	0.95	0.53	0.29	0.98	0.40	0.35	0.96	0.68	0.49	0.41	0.19
Throat irritation	0.95	0.99	0.98	0.82	0.05	0.23	0.52	0.75	0.97	0.39	0.29	0.98
Tearing	0.99	0.72	0.78	0.55	0.85	0.54	0.51	0.32	0.24	0.68	0.09	0.35
Unpleasant	0.26	0.93	0.47	0.98	0.64	0.72	0.92	0.67	0.67	0.40	0.80	0.53

<sup>a</sup> M, males.

<sup>b</sup> F, females.

<sup>c</sup> D, difference between males and females.

<sup>d</sup> Significant probability values of regression coefficients ( $p \leq 0.05$ ) for slope scores are italic; significant coefficients are positive, except for the CRT performance test in the MEK test condition.

relationship. These chemical effects, however, are not as consistent as the alcohol effects. In the alcohol group analysis, both the multivariate and regression analyses produced consistent results. These results showed that response times on the visual-vigilance task increased significantly with alcohol ingestion.

#### Choice Reaction Time

**Chemical groups.** The MANOVA for the time × group interaction was significant ( $F[18,235.24] = 1.91, p = 0.02$ ). The ANOVA for movement time also was significant

( $F[9,264] = 4.16, p = 0.0002$ ), but none of the contrasts were significant. The MANOVA for the period × time × group interaction also was significant ( $F[72,195.11] = 1.47, p = 0.02$ ). The ANOVA for release time was significant ( $F[36,1056] = 1.73, p = 0.01$ ). The three-factor interaction, however, was difficult to interpret and demonstrated no consistent treatment-related trend. The regression analysis resulted in only one significant chemical effect: Males exposed to MEK showed a significant negative linear trend with MEK blood concentration (multivariate;  $p = 0.0002$ ). This significant regression coefficient was for movement time ( $b = -3.4,$

$p = 0.0001$ ); the slope value also differed significantly ( $p = 0.03$ ) from the female slope value ( $b = -0.7$ ).

**Alcohol groups.** The MANOVA for the period  $\times$  group interaction was significant ( $F[8,37] = 2.29, p = 0.04$ ). The ANOVA for response time was significant ( $F[4,176] = 5.36, p = 0.001$ ). The mean reaction time of the alcohol group in Exp-1 (336 msec,  $p = 0.02$ ) and Exp-2 (324 msec,  $p = 0.04$ ) was significantly longer than the alcohol-control group times in Exp-1 (319 msec) and Exp-2 (307 msec). Regression analysis produced significant multivariate tests for both males ( $p = 0.0001$ ) and females ( $p = 0.0004$ ). Significant, positive slopes for males ( $b = 314, p = 0.0001$ ) and females ( $b = 244, p = 0.0001$ ) were found between release time and ethanol blood concentrations. Residual plots showing the alcohol release time results are presented in Figs. 1 (females) and 2 (males).

In summary, the alcohol group analysis shows consistent performance decrements caused by alcohol ingestion on the choice reaction time task, whereas the chemical group analysis does not show conclusively any consistently interpretable chemical treatment effects. The only significant results from the MANOVA/ANOVA chemical analysis was on a complex, uninterpretable three-factor interaction, and these results were inconsistent with the regression analysis results. Regression analysis for the chemical groups resulted in a

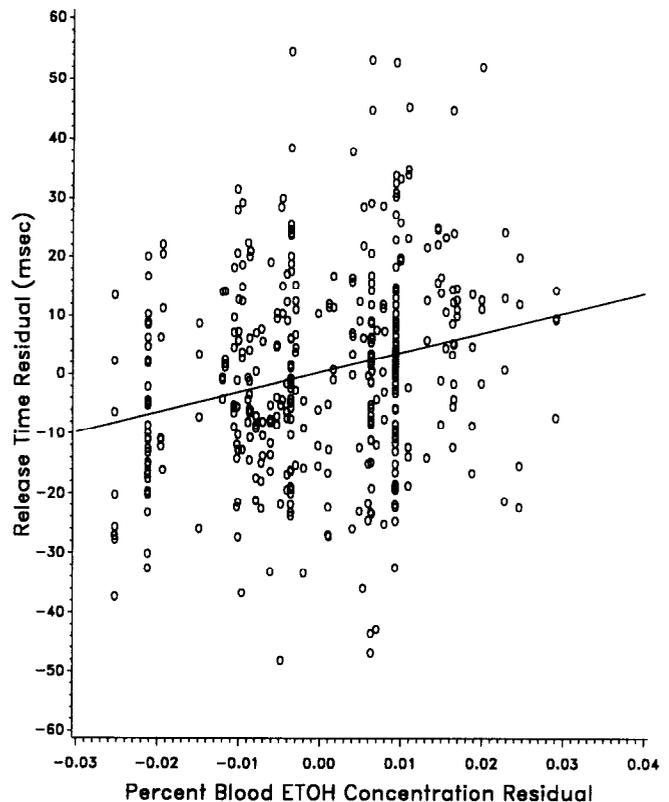


FIG. 2. Partial regression leverage plot for release time on the CRT test among male subjects who ingested alcohol.

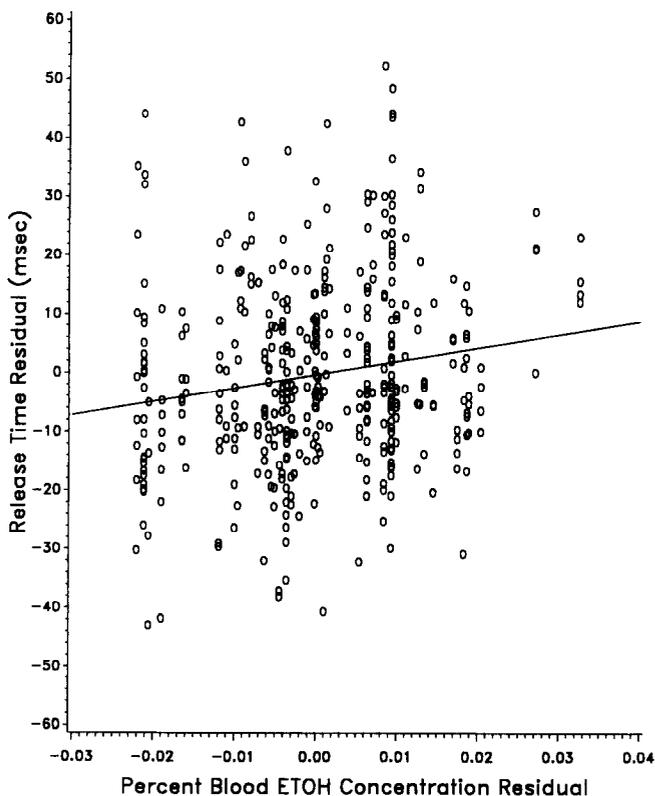


FIG. 1. Partial regression leverage plot for release time on the CRT test among female subjects who ingested alcohol.

significant, negative movement-time slope for males exposed to MEK (i.e., a negative slope on the CRT test represents performance improvement). As noted in the performance and subject tests section, the CRT test was the only performance test that demonstrated significant learning effects. The significant movement-time decrease in males, therefore, is likely a learning effect and not a treatment effect.

#### Simple Reaction Time

**Chemical groups.** The period  $\times$  group interaction was significant ( $F[12,340] = 1.86, p = 0.05$ ). The mean of the MEK-MIBK group (310 msec) was significantly larger ( $p = 0.03$ ) than the mean in the control group (280 msec) for the preexposure period. Regression analysis showed a significant MEK-MIBK interaction term ( $b = -31, p = 0.04$ ) for the females. A residual plot of the MEK-MIBK interaction was generated, but no interpretable relationship was evident.

**Alcohol groups.** The ANOVA analysis failed to identify significant effects. Regression analysis, however, showed significant positive relationships between reaction time and blood concentrations for both males ( $b = 224, p = 0.03$ ) and females ( $b = 557, p = 0.0001$ ). The female slope was twice as large the male slope ( $p = 0.005$ ).

In summary, no significant linear relationships between reaction time and blood concentrations under the chemical

treatment conditions were detected. The ANOVA analysis showed no performance decrements with alcohol ingestion, while the alcohol regression analysis showed some evidence of alcohol effects in both sexes; these effects were more pronounced for the females than males.

#### Dual Task

**Chemical groups.** The MANOVA for the period  $\times$  group interaction was significant ( $F[48,203.04] = 1.43, p = 0.05$ ), but no significant ANOVAs were found for the group factor. Regression analysis of the chemical groups showed a significant multivariate test value for females ( $p = 0.01$ ); a significant difference also was obtained between males and females ( $p = 0.05$ ). The single significant regression coefficient was for percentage incorrect responses. The female slope showed a small, positive linear relationship ( $b = 3, p = 0.004$ ) with MEK blood concentrations. The female slope for percentage incorrect responses also was significantly different ( $p = 0.05$ ) from the male slope ( $b = 0.3$ ). These results are presented in Figs. 3 (females) and 4 (males).

**Alcohol groups.** The MANOVA for the period  $\times$  group interaction was not significant ( $F[16,27] = 1.43, p = 0.20$ ). Evidence was found, however, of an alcohol-related decre-

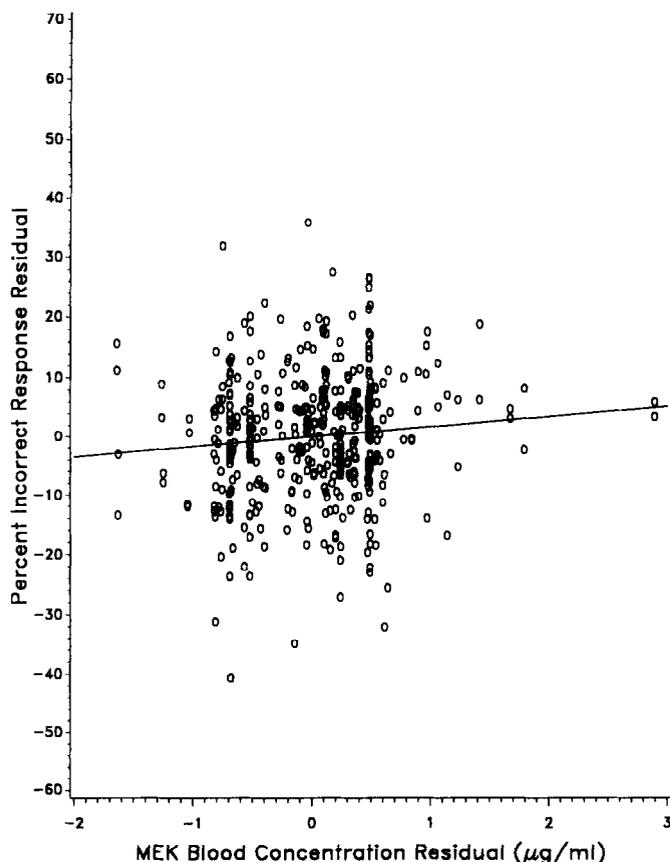


FIG. 3. Partial regression leverage plot for percentage incorrect responses on the dual task for female subjects who were exposed to MEK at 200 ppm.

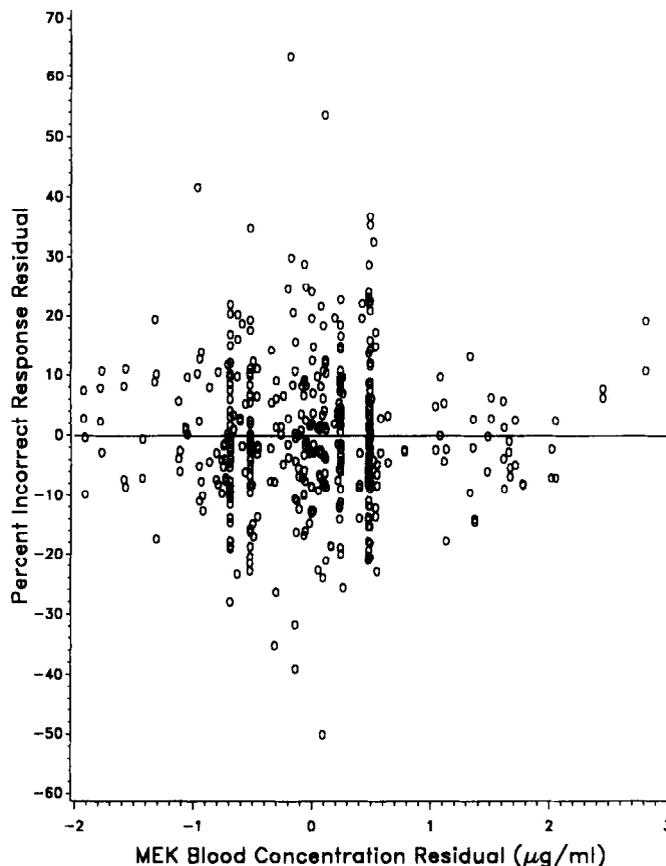


FIG. 4. Partial regression leverage plot for percentage incorrect responses on the dual task for male subjects who were exposed to MEK at 200 ppm.

ment on tracking performance. The ANOVA for the period  $\times$  group interaction for tracking performance (root mean square) was  $F(2.56,107.61) = 2.88, p = 0.05$ . Using combined score means (single and dual tracking scores), tracking error scores for the alcohol group increased from a baseline score of 110 to 132 in Exp-1 ( $p = 0.07$ ) versus the control group value of 107 at baseline, and 108 in Exp-1. Regression analysis showed a significant multivariate test on the dual task measures for females only ( $p = 0.0001$ ). A significant difference ( $p = 0.0001$ ) also was found between males and females for tracking performance (i.e., females showed a positive linear slope [ $b = 1177, p = 0.0001$ ] between blood ethanol concentrations and tracking performance). The female slope also was significantly different ( $p = 0.0001$ ) from the male slope ( $b = 32$ ).

In summary, only one dual task performance measure was impaired significantly by the chemical exposures, and this effect was limited to females. This measure was percentage incorrect responses for the MEK exposures. Alcohol ingestion resulted in a significant performance decrement on tracking scores, with this effect being most pronounced for females.

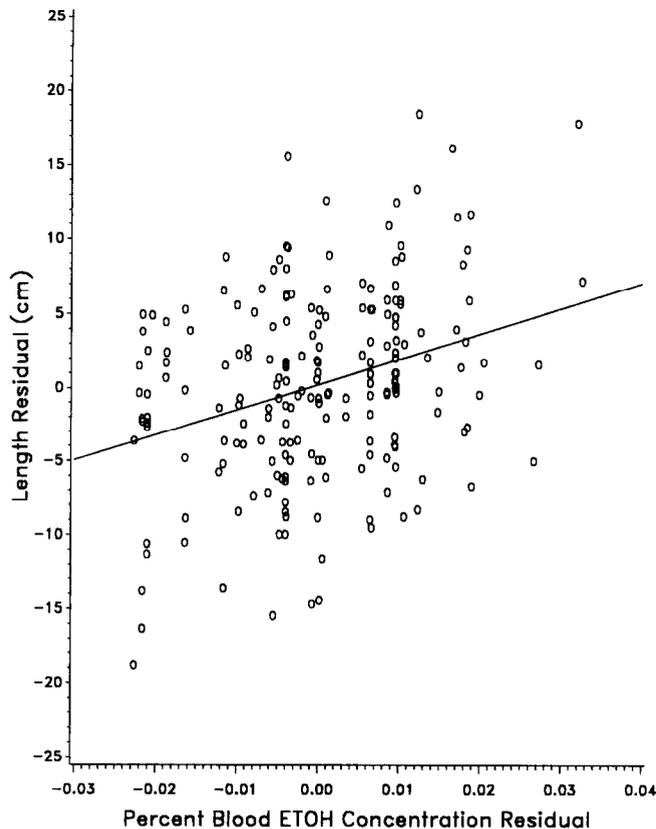


FIG. 5. Partial regression leverage plot for the length measure on the postural sway test for female subjects who ingested alcohol.

### Postural Sway

**Chemical groups.** No significant effects were found involving the group factor. Regression analysis failed to detect any significant linear relationships with blood concentrations in the chemical groups.

**Alcohol groups.** The MANOVA for the period  $\times$  group interaction was significant ( $F[16,26] = 2.12, p = 0.05$ ). The ANOVAs for length ( $F[4,164] = 7.67, p = 0.0000$ ), area ( $F[4,164] = 3.63, p = 0.01$ ), and velocity ( $F[4,164] = 6.84, p = 0.0002$ ) also were significant. Contrasts showed significant differences between the alcohol group and the control group in Exp-1 for length (44 cm versus 36 cm,  $p = 0.03$ ), area (11 cm<sup>2</sup> versus 9 cm<sup>2</sup>,  $p = 0.0000$ ), and velocity (1.47 cm/sec versus 1.23 cm/sec,  $p = 0.05$ ). In the regression analysis, only the multivariate tests for females ( $p = 0.0005$ ) were significant. Significant positive linear relationships occurred with area, length, and velocity for females. Although the multivariate test for males was not significant ( $p = 0.08$ ) at the predetermined 0.05 level, the regression coefficients for length and velocity were significant for males at  $p < 0.05$  (see Table 7). The significant female slopes were: length, 154 ( $p = 0.0001$ ); area, 44 ( $p = 0.04$ ); and velocity, 5 ( $p = 0.0001$ ). The males slopes were: length, 83 ( $p = 0.02$ ); and velocity, 3 ( $p = 0.02$ ). To illustrate the effects of the alcohol ingestion,

residual plots of the male and female results for length are presented in Figs. 5 (females) and 6 (males).

In summary, no chemical effects were detected on the postural sway measures. In both the MANOVA/ANOVA and regression analysis, the ingestion of alcohol resulted in performance decrements on two of the postural sway measures (i.e., length and velocity). Regression analysis detected significant effects for length, area, and velocity; these effects, however, were significant only for females.

### Memory Scanning

**Chemical groups.** No significant effects were found involving the group factor during Exp-1, Exp-2, or Post-1. The ANOVA for the positive intercept, however, was significant ( $F[12,352] = 2.27, p = 0.01$ ). The mean positive intercept score of the MEK-MIBK group (594 msec) was significantly greater ( $p = 0.04$ ) than the mean score for the control group (501 msec) during the preexposure period. No significant regression coefficients for slope were found for the chemical analyses.

**Alcohol groups.** No significant effects involving the group factor were found, and no significant regression coefficients were obtained for the slopes.

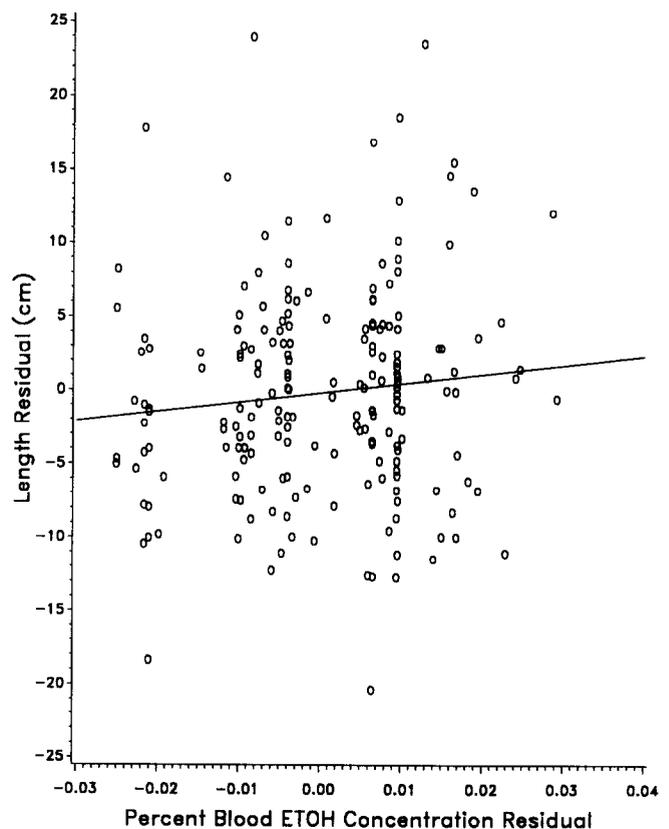


FIG. 6. Partial regression leverage plot for the length measure on the postural sway test for male subjects who ingested alcohol.

In summary, no significant alcohol or chemical treatment effects were found on the memory scanning measures.

### *Profile of Mood Scales (POMS)*

**Chemical groups.** The MANOVA period factor was significant at  $p = 0.0001$ , and ANOVAs for each of the six mood scales also were significant for the period factor ( $p < 0.02$ ). The MANOVA for the period  $\times$  group interaction was not significant ( $p = 0.65$ ), but the ANOVA period  $\times$  group interaction for "Vigor" was significant ( $F[6,176] = 3.13, p = 0.01$ ). The mean score for Vigor for the MEK group (57) was significantly larger ( $p = 0.004$ ) than the mean score for the control group (49) in Post-2. (Regression analysis was not performed on these data because the administration of the POMS did not correspond to the collection of blood samples within a reasonable time period.)

**Alcohol groups.** The MANOVA period factor was significant at  $p = 0.0001$ , and the ANOVAs for each of the six mood scales also were significant for the period factor ( $p < 0.02$ ). No significant ANOVAs were found involving the period  $\times$  group interaction.

In summary, the significant effects for the period factor on the POMS measures, coupled with the lack of any significant chemical or alcohol treatment effects at the end of the exposure test day, indicate that the experimental situation per se, regardless of the treatment or control conditions imposed, elevated the mood scale Vigor.

### *Subjective Effects*

**Chemical groups.** The MANOVA for the main group effect was significant ( $F[24,235.53] = 2.14, p = 0.002$ ). The ANOVA for reporting a strong odor (St-odor) was significant ( $F[3,88] = 8.90, p = 0.0000$ ). Table 8 presents the percentage data; the percentages (contrasts) which differ significantly from controls  $<0.05$  are italic. The ANOVA for reporting throat irritation also was significant, but none of the contrasts were significant. Regression analysis was performed using the 2- and 4-hr sensory and irritant effects reports and the 2- and 4-hr blood concentrations for each chemical group. No significant multivariate tests or regression coefficients were significant for the odor or irritant effect items (see Table 7).

**Alcohol groups.** The MANOVA for the main group effect was significant ( $F[8,36] = 2.43, p = 0.03$ ). The ANOVAs were significant for odor ( $F[1,43] = 14.0, p = 0.0005$ ), St-odor ( $F[1,43] = 4.04, p = 0.05$ ), and objectionable odor ( $F[1,43] = 6.88, p = 0.01$ ). Table 8 summarizes the results for the alcohol Subjective I questionnaire. Regression analysis detected no significant multivariate tests or regression coefficients in the alcohol group analysis.

The statistical tests to determine differences in reporting sensory and irritant effects from the 2- to 4-hr reporting periods showed significant differences for the chemical groups only. A significant MANOVA was found for period ( $F[8,81]$

$4.65, p = 0.0001$ ). The ANOVAs were significant for the presence of odor ( $F[1,88] = 6.33, p = 0.01$ ), St-Odor ( $F[1,88] = 17.0, p = 0.001$ ), headache ( $F[1,88] = 4.66, p = 0.03$ ), and unpleasant odor ( $F[1,88] = 4.22, p = 0.04$ ). Adaptability, therefore, was restricted primarily to reports regarding odor. Response percentages are presented in the bottom of Table 8.

Examination of Table 8 shows that a sizeable percentage of subjects reported various sensory and irritant effects during the 4-hr exposures. The only effect, however, that differed significantly between the three chemical exposure groups and the control group was for St-odor. The subjects exposed to MIBK reported the highest percentage for St-odor (70%), followed by the subjects exposed to the MIBK-MEK mixture (69%), and the subjects exposed to MEK alone (48%). Interestingly, the alcohol-control group reported the presence of St-odor more frequently than the alcohol group. This difference indicates that the alcohol-control subjects perceived they were receiving a chemical exposure even though the consent form and verbal instructions stated that they would not be exposed to a chemical if they received a drink.

Reports of headache increased significantly from Exp-1 to Exp-2 for the chemical groups. Although not significant, reports of headache also increased for the chemical-control group and the two alcohol groups from Exp-1 to Exp-2. These increases, across all treatment and control groups, suggest that test taking for 4 hr per se was accounting for these headache effects.

## DISCUSSION

This research was designed to detect whether or not sub-clinical neurobehavioral effects are present in a simulated 8-hr workplace exposure to solvents. Single acute exposures to MEK or MIBK, and acute exposures to MEK and MIBK in combination, were at concentrations deemed safe for a working lifetime of continuous exposures (U.S. Printing Office, 1981). In addition to the neurobehavioral measurements taken, chemical measurements of MEK, MIBK, and ethanol were determined from blood and breath samples. The blood and breath results will be discussed only briefly, as a more extensive presentation of these data is being prepared for future publication.

Statistical analyses found no significant differences between the male and female blood and breath concentrations at each of the sample points, although the male blood concentrations tended to be higher than the female blood concentration values during the MEK and MIBK single exposures (2- and 4-hr samples, see Table 4). These blood differences were not evident in the Post-1 sample or during the MEK-MIBK combination exposures. No evidence was found of chemical interactions (i.e., nonadditive blood and breath values) for the MEK-MIBK combined exposures on the MEK and MIBK blood and breath values when com-

TABLE 8  
Subjects Reporting of Sensory and Irritant Effects and Adaptation to the Sensory and Irritant Effects

Item	Odor Presence	Strong Odor	Objectionable Odor	Headache	Nausea	Throat Irritation	Tearing	Unpleasant Odor
Condition <sup>a</sup>								
Alcohol	4	2	2	28	20	26	22	14
Alcohol-control	36	18	23	9	9	33	16	30
Chemical-control	94	22	40	12	6	34	24	34
MIBK	93	70	35	24	20	30	13	39
MEK	96	48	48	7	19	50	17	44
MEK-MIBK	94	69	52	27	8	17	17	50
Adaptation <sup>b</sup>								
2 hour	97	63	47	20	10	30	19	47
4 hour	91	41	41	30	10	35	17	36

<sup>a</sup> Values reported are mean percentage averaged from both the 2- and 4-hr periods. Group comparisons are alcohol versus alcohol-control, and chemical-control versus chemical exposures. Significant differences ( $p < 0.05$ ) are italic.

<sup>b</sup> Values reported are mean percentage averaged for the chemical exposure groups only. No significant differences (2- versus 4-hr) were found between these chemical groups. Significant differences ( $p < 0.05$ ) are italic.

bined exposures (i.e., airborne exposures at one-half the single exposure concentrations) were compared to single exposures. For example, in the combination MEK-MIBK exposures, average MEK and MIBK blood concentrations, and MIBK breath concentrations, for all subjects (males and females) were less than half the single exposure concentrations; the MEK breath concentrations in the MEK-MIBK exposures at the 2-hr sample and the 4-hr sample were slightly more than one-half the corresponding MIBK single-exposure values, while the 90-min postexposure sample for MIBK was less than one-half the MIBK single-exposure sample mean (see Table 4).

Tables 6 and 7 present the significant probabilities for the large number of measurements taken on the subjects. Examination of these two tables reveals few significant probabilities that represent neurobehavioral performance decrements in the chemical-exposure groups. For example, of the 72 probabilities (18 ANOVAs and 54 regression coefficients involving six neurobehavioral tests and two genders, with the POMS and Subjective I questionnaires excluded), only six significant differences were found for the chemical-exposure conditions (i.e., near the level expected by chance). The MANOVA/ANOVA analyses also failed to demonstrate any significant period  $\times$  group treatment differences that could be attributed to the chemical exposures, except for one performance test (i.e., the CRT) that differed significantly between the chemical groups and the control group. These statistically significant effects consisted of three-factor interactions involving exposure period, chemical groups, and a response-block factor (i.e., a response measure derived for the CRT); only a small number of contrasts were significant, and no chemical group treatment effect was evident with the significant contrasts.

Regression analyses produced six coefficients that showed a significant linear relationship between neurobehavioral performance and blood concentrations for MEK, MIBK, or the MEK-MIBK interaction term. Only two coefficients, however, demonstrated a positive linear dose-response relationship between an increase in blood concentrations and neurobehavioral performance: MIBK-exposed females showed a small increase in percentage correct responses on the visual-vigilance task with increased levels of MIBK, while MEK-exposed females showed a small increase in percentage incorrect responses on the auditory portion of the dual task with increased MEK levels. In the visual-vigilance task, males showed a positive, linear relationship between response times and the MEK-MIBK interaction term. The other significant regression coefficients were small, negative relationships between movement time on the CRT test and MEK blood concentrations among males, and between response time on the SRT test and the MEK-MIBK interaction term for females. While these results may suggest possible gender differences, these significant effects appeared for a limited number of measures, and the slope values were either small or in the unexpected direction (i.e., negative versus positive). Additionally, the lack of agreement between the MANOVA/ANOVA analyses and the regression analyses argues against any reliable subclinical CNS effects resulting from the chemical exposures.

The alcohol analyses demonstrated moderate agreement between the MANOVA/ANOVA results and the regression analyses on most of the neurobehavioral performance measures. MANOVA/ANOVA results show significant performance decrements on the visual-vigilance test (i.e., response time), the CRT (i.e., release time), and the postural sway test (i.e., length and velocity measures). Not only did the regres-

sion analyses show performance decrements on the same measures as in the MANOVA/ANOVA analyses, but the regression analyses also detected performance differences on simple RT, dual task tracking performance, and the length, area, and velocity measures of the postural sway test. Regression analysis, which used each individual's blood concentration values, may therefore be a more sensitive analysis than MANOVA/ANOVA (which used group values). This sensitivity may be due to: (1) use of a continuous variable (i.e., blood concentration) and (2) increased degrees of freedom for the error terms.

In comparison with our previous research (Dick *et al.*, 1984, 1989) the alcohol condition resulted in significant performance decrements in more performance tests, and there is good agreement between the studies. The visual-vigilance test detected effects after ethanol ingestion in previous studies (Dick *et al.*, 1984, 1989), as has the dual task (Dick *et al.*, 1989) and the choice reaction time test (Dick *et al.*, 1984). The memory scanning test did not detect effects in a previous study (Dick *et al.*, 1989) or in this study. This is the second study to use postural sway measures, and whereas the previous study (Dick *et al.*, 1989) showed nonsignificant decrements, this study did show marked decrements from ethanol ingestion. The change was probably due to moving the postural sway test forward in the test order nearer the subjects peak blood alcohol concentrations.

The significant performance differences demonstrated by the alcohol analyses confirm the use of alcohol as a positive control for the purpose of demonstrating that the neurobehavioral tests used in this experiment could detect mild central nervous system depression. While the MANOVA/ANOVA analyses failed to demonstrate gender differences on the neurobehavioral tests after alcohol ingestion, the regression analyses showed several significant gender-related performance decrements under this condition. Females showed a significant regression coefficient on the dual task measures and the postural sway test; a significant gender difference was found between males and females on the SRT test (i.e., females had steeper slopes than males). While gender differences on behavioral performance tasks after ethanol ingestion have been reported previously in the research literature (Erwin *et al.*, 1978; Taberner, 1980; Bhattacharya *et al.*, 1987; Niaura *et al.*, 1987), these data have often been inconsistent. For those studies finding differences between females and males, these differences usually are attributed to females achieving higher blood alcohol concentrations than males at the same relative dose levels (Niaura *et al.*, 1987). In this study, however, the blood alcohol concentration levels did not differ substantially between males and females. These gender differences, therefore, do not appear to be based on differences in blood alcohol concentration levels.

The results of the Subjective I and II questionnaires showed that self-reported sensory and irritant effects varied across the experimental conditions. The only statistically significant effect found between the chemical-control subjects and the chemically exposed subjects was for the presence of strong odor. The subjects exposed to MIBK and MEK-MIBK reported higher levels of strong odor than those subjects exposed only to MEK (70% and 69% versus 48% for MEK). This difference implicates MIBK as the primary chemical contributing to this effect. Approximately 20-30% of the subjects exposed to MIBK reported sensory and irritant effects (i.e., odor, headache, nausea, throat irritation, tearing). These percentage results agree with a recent study by Hjelm *et al.* (1990), who exposed subjects either to 10, 25, or 50 ppm MIBK with 50 W exercise or to 25 ppm MIBK with 40 ppm toluene and 50 W exercise and used a similar dichotomous choice (i.e., yes/no) questionnaire to assess sensory and irritant effects.

In summary, these chemical exposures did not produce any marked neurobehavioral effects. In contrast, the alcohol ingestion group, which served as a positive control for demonstrating the sensitivity of the neurobehavioral tests to the effects of central nervous system depression, showed a performance decrement on at least one measure for each of the neurobehavioral tests (except the memory scanning test).

In this experiment, 4-hr exposures to MIBK at 100 ppm showed no significant neurobehavioral effects. These MIBK results are consistent with a recent study by Hjelm *et al.* (1990), which also failed to detect neurobehavioral effects using measures of simple reaction time and addition performance during exposures to 50 ppm MIBK combined with 50 W of physical exercise. The present study was the third study conducted by NIOSH in which MEK has been used in combination with other solvents at concentrations constrained by the OSHA additivity formula for mixtures. None of these studies has shown any significant neurobehavioral effects from single, 4-hr exposures to MEK at 200 ppm, nor does MEK appear to cause neurobehavioral impairments during combined exposures with toluene (Dick *et al.*, 1984), acetone (Dick *et al.*, 1989), or MIBK. The principal effects resulting from exposures to MEK and MIBK at the durations and concentrations used in this study, therefore, appear to be limited to sensory and irritant effects.<sup>1</sup>

<sup>1</sup> On January 19, 1989, OSHA issued amendments to the air contaminants standards 29 CFR, Part 1910. The permissible exposure limit (PEL) for MIBK was changed from 100 to 50 ppm for an 8-hr time-weighted average. A short-term exposure limit (STEL) of 75 ppm was also set for MIBK. The STEL was issued for prevention of irritant effects. The results of this experiment support the setting of a STEL at 75 ppm for MIBK. The 1989 amendments did not change the PEL for MEK, but a STEL of 300 ppm was set for the prevention of eye and nose irritation. The results of this experiment suggest that a STEL of 300 ppm may not protect all individuals from the possibility of experiencing transient sensory and irritant effects from MEK at exposures above 200 ppm.

## APPENDIX

## Performance Measures Means and Standard Deviations

TABLE 9  
Visual Vigilance and Postural Sway Performance Measurements by Period and Chemical Condition

Condition	Preexposure		Exposure-1		Exposure-2		Post-1		Post-2	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Visual vigilance <sup>a</sup>										
Alcohol, <i>N</i> = 25 <sup>b</sup>										
Response time	796.96	129.37	882.79	155.96	805.43	186.73	751.05	152.12	745.47	144.00
% Correct response	81.02	14.14	70.29	19.10	56.87	23.30	65.01	20.47	81.59	18.83
% Incorrect response	23.86	22.89	22.77	4.14	27.00	22.56	20.45	17.49	18.84	18.34
Alcohol-control, <i>N</i> = 23										
Response time	800.71	145.17	792.53	129.98	870.77	132.26	835.68	166.22	807.63	170.22
% Correct response	84.67	19.99	70.85	21.11	68.33	15.86	71.38	21.92	78.30	18.82
% Incorrect response	16.51	17.68	15.38	15.63	17.32	18.20	20.04	18.29	16.31	17.43
Control, <i>N</i> = 25										
Response time	778.36	137.07	815.70	161.98	806.48	163.67	802.02	193.50	761.48	143.84
% Correct response	82.32	14.83	65.72	22.92	66.44	23.43	64.87	21.63	75.61	18.60
% Incorrect response	21.23	15.64	24.30	18.18	22.24	16.67	22.80	20.42	17.51	15.48
MIBK, <i>N</i> = 23										
Response time	796.25	133.64	821.84	132.34	782.62	210.61	829.35	138.56	799.49	146.60
% Correct response	79.21	17.23	66.85	23.48	70.32	23.27	68.30	21.90	74.24	19.40
% Incorrect response	22.57	20.05	21.95	20.36	20.30	20.05	24.13	23.48	19.62	21.61
MEK, <i>N</i> = 24										
Response time	782.15	156.36	827.48	207.51	751.36	136.37	727.88	164.70	803.59	177.47
% Correct response	81.43	17.34	68.84	23.22	65.76	23.10	64.84	26.55	74.52	21.40
% Incorrect response	16.84	12.41	19.66	19.08	25.81	21.35	20.09	22.95	20.04	18.30
Mix, <i>N</i> = 24										
Response time	801.26	140.48	858.54	155.97	831.36	160.33	821.85	213.62	810.09	139.77
% Correct response	80.22	19.47	72.19	23.56	70.27	21.06	64.29	24.98	80.68	19.41
% Incorrect response	19.61	21.22	19.19	21.53	23.80	22.03	25.98	22.32	15.61	17.42
Postural sway <sup>a</sup>										
Alcohol, <i>N</i> = 25 <sup>b</sup>										
<i>R</i> <sub>m</sub>	0.63	0.15	0.78	0.17	0.69	0.19	0.65	0.20	0.65	0.19
Length	37.96	6.82	44.17	9.82	34.84	7.24	33.86	7.29	34.51	7.68
Area	8.07	2.65	11.33	4.27	7.70	2.85	7.32	3.22	7.55	3.44
Velocity	1.26	0.24	1.47	0.33	1.16	0.24	1.13	0.24	1.15	0.26
Alcohol-control, <i>N</i> = 20										
<i>R</i> <sub>m</sub>	0.64	0.24	0.71	0.24	0.72	0.32	0.68	0.23	0.71	0.22
Length	38.14	10.56	36.49	10.23	35.96	10.18	35.76	8.54	37.06	8.21
Area	8.52	5.46	9.22	7.22	9.03	6.49	8.58	5.14	9.31	4.76
Velocity	1.17	0.37	1.23	0.39	1.20	0.34	1.19	0.29	1.24	0.27
Control, <i>N</i> = 25										
<i>R</i> <sub>m</sub>	0.67	0.25	0.74	0.33	0.70	0.31	0.68	0.27	0.67	0.27
Length	35.55	10.56	37.44	10.75	37.16	11.59	37.26	11.19	35.82	8.68
Area	8.19	5.52	9.57	6.54	9.25	6.59	9.40	7.81	8.23	4.93
Velocity	1.17	0.37	1.25	0.36	1.24	0.39	1.24	0.37	1.20	0.29
MIBK, <i>N</i> = 22										
<i>R</i> <sub>m</sub>	0.66	0.25	0.74	0.29	0.73	0.22	0.71	0.24	0.70	0.21
Length	36.20	9.56	35.94	9.71	34.43	6.79	32.67	6.56	35.30	8.50
Area	8.12	4.60	8.89	5.13	8.40	3.71	7.74	3.85	8.40	4.51
Velocity	1.21	0.32	1.20	0.33	1.15	0.23	1.09	0.23	1.18	0.28

TABLE 9—Continued

Condition	Preexposure		Exposure-1		Exposure-2		Post-1		Post-2	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
MEK, <i>N</i> = 24										
<i>R<sub>m</sub></i>	0.65	0.23	0.70	0.24	0.71	0.21	0.73	0.25	0.66	0.16
Length	36.76	11.52	38.65	9.45	38.63	9.48	37.85	13.05	37.08	10.42
Area	8.33	4.77	9.35	5.48	9.79	4.90	10.11	6.98	8.31	4.09
Velocity	1.21	0.39	1.29	0.32	1.29	0.32	1.26	0.44	1.20	0.31
Mix, <i>N</i> = 23										
<i>R<sub>m</sub></i>	0.62	0.13	0.67	0.25	0.74	0.28	0.64	0.20	0.63	0.20
Length	36.71	9.79	35.20	8.31	36.15	7.86	33.75	7.27	34.11	8.54
Area	7.67	3.68	8.24	5.02	9.24	4.93	7.40	3.68	7.25	3.77
Velocity	1.22	0.33	1.17	0.28	1.21	0.26	1.12	0.26	1.14	0.29

<sup>a</sup> Significant means are italic,  $\alpha = 0.05$ .

<sup>b</sup> Number of subjects. This number is based on the actual number of subjects with usable data for the performance measure.

TABLE 10  
Choice and Simple Reaction Time Performance Measurements by Period and Chemical Condition

Condition	Preexposure		Exposure-1		Exposure-2		Post-1		Post-2	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Choice RT <sup>a</sup>										
Alcohol, <i>N</i> = 25 <sup>b</sup>										
Response time	325.01	27.11	335.73	24.19	324.37	25.33	312.27	23.89	299.61	22.21
Move time	147.36	22.70	144.46	21.89	149.02	26.75	148.65	23.32	135.02	19.72
Alcohol-control, <i>N</i> = 23										
Response time	326.65	30.44	318.63	24.67	307.17	28.20	304.99	23.15	300.20	21.51
Move time	139.53	26.74	138.50	25.46	143.07	29.51	136.75	28.08	127.27	24.82
Control, <i>N</i> = 25										
Response time	339.71	47.54	328.89	46.18	324.49	37.61	315.50	30.78	313.11	27.64
Move time	157.22	31.27	156.26	36.88	153.06	42.05	150.17	38.88	139.83	30.83
MIBK, <i>N</i> = 25										
Response time	323.03	27.58	314.25	18.44	314.30	27.79	304.95	23.47	298.02	21.06
Move time	139.96	27.60	143.18	35.51	148.16	46.42	139.10	38.07	134.87	38.78
MEK, <i>N</i> = 24										
Response time	326.08	37.18	318.63	28.27	315.74	31.32	312.35	28.05	301.09	28.58
Move time	150.65	31.90	145.78	33.76	147.13	36.58	151.71	34.57	138.22	30.76
Mix, <i>N</i> = 24										
Response time	323.92	36.35	309.90	28.88	307.93	33.02	307.64	30.55	303.68	22.66
Move time	164.46	43.47	153.74	34.64	152.77	41.88	156.22	42.12	140.90	35.60
Simple RT <sup>a</sup>										
Alcohol, <i>N</i> = 24 <sup>b</sup>										
RT	266.76	36.30	305.11	52.36	293.61	44.93	280.10	48.01	274.72	46.93
Alcohol-control, <i>N</i> = 23										
RT	278.70	69.90	289.14	14.07	292.46	70.74	288.09	58.36	270.32	37.57
Control, <i>N</i> = 25										
RT	279.62	41.65	296.70	56.78	309.68	54.46	305.43	51.70	298.40	12.63
MIBK, <i>N</i> = 23										
RT	274.65	33.96	293.47	43.85	302.59	50.41	294.52	40.69	278.91	43.31

TABLE 10—Continued

Condition	Preexposure		Exposure-1		Exposure-2		Post-1		Post-2	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
MEK, <i>N</i> = 23										
RT	282.99	52.05	294.25	55.45	295.96	52.60	309.61	61.30	288.84	53.98
Mix, <i>N</i> = 22										
RT	309.68	65.71	309.61	65.78	309.22	57.85	323.00	67.92	303.13	71.88

<sup>a</sup> Significant means are *italic*.  $\alpha = 0.05$ .

<sup>b</sup> Number of subjects. This number is based on the actual number of subjects with usable data for the performance measure.

TABLE 11  
Dual Task<sup>a</sup> Performance Measurements by Period and Chemical Condition

Condition	Preexposure		Exposure-1		Exposure-2		Post-1		Post-2	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Dual task <sup>b</sup>										
Alcohol, <i>N</i> = 23 <sup>c</sup>										
Response time	663.04	109.43	707.66	115.35	713.86	152.80	706.88	170.60	655.06	96.77
% Correct response	78.30	19.28	73.52	26.69	69.22	24.86	72.24	23.54	83.10	15.03
% Incorrect response	31.38	25.87	26.72	25.95	26.94	26.08	26.36	25.21	25.62	23.04
Tracking-RMS	109.90	38.81	131.65	60.56	119.66	32.47	112.70	33.12	101.01	36.59
Alcohol-control, <i>N</i> = 22										
Response time	711.09	153.20	700.28	121.38	702.46	95.75	719.24	131.76	704.70	119.43
% Correct response	83.65	14.62	79.07	18.17	77.32	17.43	76.15	17.97	81.74	17.11
% Incorrect response	21.93	21.13	18.76	23.03	19.52	23.58	20.02	22.86	19.85	22.24
Tracking-RMS	107.27	30.85	107.99	31.12	107.32	31.99	110.23	29.80	106.67	34.94
Control, <i>N</i> = 25										
Response time	679.60	79.25	688.32	89.74	721.56	123.05	712.74	127.56	693.22	82.36
% Correct response	77.44	22.48	79.06	16.94	72.98	19.46	69.80	22.47	78.68	18.71
% Incorrect response	39.04	28.10	29.80	23.57	30.40	25.83	31.96	25.30	30.42	24.95
Tracking-RMS	111.23	17.15	116.11	24.11	130.36	36.17	130.91	45.52	113.25	29.56
MIBK, <i>N</i> = 21										
Response time	677.95	106.27	677.93	121.24	710.83	141.93	683.24	137.69	672.14	108.05
% Correct response	81.52	17.73	79.05	19.93	76.74	21.34	72.24	21.97	81.29	18.50
% Incorrect response	28.71	22.28	26.71	22.77	27.86	24.27	28.62	25.49	27.40	24.30
Tracking-RMS	107.64	28.89	117.14	42.97	123.89	41.50	127.89	39.80	112.89	32.01
MEK, <i>N</i> = 23										
Response time	660.67	121.92	656.87	116.08	686.35	123.69	694.67	116.58	667.50	172.34
% Correct response	87.39	13.97	87.33	14.84	82.17	16.95	79.22	17.56	87.24	16.42
% Incorrect response	30.22	26.00	25.80	25.22	28.04	25.06	27.30	24.10	26.17	24.85
Tracking-RMS	104.19	31.12	106.74	37.22	108.26	34.66	117.51	45.54	99.53	36.70
Mix, <i>N</i> = 22										
Response time	695.73	160.63	703.23	183.45	727.52	129.05	745.67	171.24	699.08	192.91
% Correct response	81.77	19.51	73.83	20.80	75.15	18.06	64.56	22.62	71.75	25.71
% Incorrect response	29.46	29.34	28.29	26.63	27.96	25.55	32.00	28.58	26.06	25.42
Tracking-RMS	107.08	27.18	108.02	32.24	110.36	33.50	116.73	40.07	103.45	33.19

<sup>a</sup> Means represent combined dual and single task conditions.

<sup>b</sup> Significant means are *italic*.  $\alpha = 0.07$ .

<sup>c</sup> Number of subjects. This number is based on the actual number of subjects with usable data for the performance measure.

TABLE 12  
Memory Scanning Task Performance Measurements by Period and Chemical Condition

Condition	Preexposure		Exposure-1		Exposure-2		Post-1		Post-2	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Memory scanning <sup>a</sup>										
Alcohol, <i>N</i> = 25 <sup>b</sup>										
Negative Intercept	577.19	176.67	545.91	173.31	558.83	173.83	562.23	158.83	528.35	145.36
Negative Slope	40.55	17.55	46.90	22.75	42.10	18.85	42.39	26.76	39.16	18.61
Positive Intercept	543.87	177.69	547.79	195.12	504.21	191.25	492.33	142.11	488.99	144.86
Positive Slope	43.42	20.54	36.46	18.40	38.91	24.40	37.72	21.42	32.31	22.39
Alcohol-Control, <i>N</i> = 23										
Negative Intercept	564.19	131.88	533.87	151.50	546.68	159.00	562.67	127.80	516.52	144.41
Negative Slope	47.21	17.70	49.25	21.36	42.07	19.62	35.21	18.38	42.12	21.28
Positive Intercept	527.81	141.55	529.42	139.51	515.62	149.30	512.30	124.49	479.91	144.22
Positive Slope	47.93	12.50	40.17	17.96	35.74	19.82	33.49	21.45	34.86	15.36
Control, <i>N</i> = 25										
Negative Intercept	553.08	176.90	554.77	181.61	566.28	174.41	554.09	208.29	542.65	183.24
Negative Slope	46.25	24.60	50.10	27.28	51.02	30.09	52.52	33.57	44.09	25.88
Positive Intercept	500.51	162.28	481.53	168.81	539.73	204.62	505.76	184.05	498.11	168.92
Positive Slope	56.59	27.81	53.98	26.16	44.30	26.40	47.14	25.05	39.26	20.98
MIBK, <i>N</i> = 23										
Negative Intercept	612.43	184.77	533.33	158.85	563.71	190.70	518.72	128.95	525.41	164.48
Negative Slope	39.03	22.57	49.06	21.47	38.65	26.63	45.46	22.45	38.54	20.09
Positive Intercept	579.23	182.71	549.57	192.68	523.12	192.89	473.57	173.94	474.23	156.95
Positive Slope	44.64	22.68	47.79	23.31	42.76	28.73	50.74	28.00	42.42	26.64
MEK, <i>N</i> = 24										
Negative Intercept	637.79	183.96	577.50	181.06	585.35	155.55	549.99	128.46	537.25	129.56
Negative Slope	44.31	28.09	52.85	25.63	40.99	25.52	43.22	24.34	42.42	22.02
Positive Intercept	582.04	179.41	554.07	163.21	502.22	129.86	524.65	154.06	489.49	158.09
Positive Slope	47.34	24.97	45.46	23.07	50.81	18.50	37.49	19.38	37.49	22.67
Mix, <i>N</i> = 24										
Negative Intercept	613.56	202.07	598.58	196.92	618.93	196.84	573.99	171.84	582.56	177.71
Negative Slope	46.31	25.13	43.51	18.69	40.49	28.66	45.40	27.96	41.11	16.47
Positive Intercept	593.57	164.71	564.86	197.92	543.22	178.08	535.94	178.96	536.39	165.21
Positive Slope	41.14	20.04	39.70	23.75	42.64	20.71	41.50	24.64	34.01	18.99

<sup>a</sup> Significant means are italic.  $\alpha$  0.05.

<sup>b</sup> Number of subjects. This number is based on the actual number of subjects with usable data for the performance measure.

TABLE 13  
Profile of Mood States Scores by Period and Chemical Condition

Condition	Preexposure		Exposure		Postexposure	
	Mean	SD	Mean	SD	Mean	SD
POMS <sup>a</sup>						
Alcohol, <i>N</i> = 24 <sup>b</sup>						
Tension	43.58	5.78	44.38	7.64	40.33	8.50
Depression	42.25	7.59	41.21	6.47	39.88	5.69
Anger	44.42	9.96	42.33	7.57	40.63	6.02
Vigor	54.79	7.94	48.83	10.63	51.96	6.17
Fatigue	42.54	8.84	48.38	9.78	41.08	8.42
Confusion	41.20	6.38	40.58	7.29	37.46	4.94

TABLE 13—Continued

Condition	Preexposure		Exposure		Postexposure	
	Mean	SD	Mean	SD	Mean	SD
Alcohol-control, <i>N</i> = 23						
Tension	47.17	10.50	46.26	8.27	44.65	6.87
Depression	46.87	10.59	43.48	7.85	43.70	4.37
Anger	49.48	10.14	45.35	7.38	43.70	5.49
Vigor	52.57	8.63	46.78	10.65	48.26	9.56
Fatigue	47.09	10.59	50.00	10.77	46.35	9.05
Confusion	46.39	10.50	43.48	6.84	42.17	5.90
Control, <i>N</i> = 25						
Tension	43.36	7.76	42.08	7.20	39.64	6.87
Depression	42.80	5.22	40.96	4.80	40.36	4.37
Anger	44.64	5.95	42.52	6.69	41.84	5.49
Vigor	54.88	7.72	51.48	9.42	48.68	9.56
Fatigue	44.36	6.95	45.60	7.70	44.64	9.05
Confusion	40.16	6.72	39.32	7.48	37.92	5.90
MIBK, <i>N</i> = 24						
Tension	43.00	8.45	42.65	8.10	40.57	6.52
Depression	42.26	4.70	41.13	4.87	41.13	5.40
Anger	44.83	6.69	44.13	7.21	43.22	6.58
Vigor	53.04	10.52	49.48	10.24	49.61	10.08
Fatigue	41.87	7.58	43.35	8.57	40.61	6.72
Confusion	40.09	6.52	39.65	6.55	37.35	6.36
MEK, <i>N</i> = 24						
Tension	45.13	8.17	45.08	6.70	40.25	5.76
Depression	44.50	8.82	42.04	6.61	40.04	4.15
Anger	46.92	10.55	45.96	11.32	42.38	5.75
Vigor	54.79	10.82	49.54	11.94	56.79	10.14
Fatigue	45.17	7.22	49.88	10.46	40.96	6.81
Confusion	40.63	7.20	40.21	5.74	37.71	5.38
Mix, <i>N</i> = 24						
Tension	45.33	5.23	44.00	6.82	42.63	7.22
Depression	43.88	4.08	42.33	4.73	41.96	5.95
Anger	46.83	7.33	46.17	6.73	45.21	7.81
Vigor	58.96	7.96	53.33	9.26	53.50	6.44
Fatigue	44.08	4.09	47.58	7.67	44.46	7.76
Confusion	41.21	4.77	41.25	5.85	39.88	5.42

<sup>a</sup> Significant means are italic.  $\alpha = 0.05$ .

<sup>b</sup> Number of subjects. This number is based on the actual number of subjects with usable data for the performance measure.

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## REFERENCES

- Bhattacharya, A., Morgan, R., Shukla, R., Ramakrishnan, H. K., and Wang, L. (1987). Non-invasive estimation of afferent inputs for postural stability under low levels of alcohol. *Ann. Biomed. Eng.* **15**, 533-550.
- Brown, W. D., Setzer, J. V., Dick, R. B., Phipps, F. C., and Lowry, L. K. (1987). Body burden profiles of single and mixed solvent exposures. *J. Occup. Med.* **29**, 877-883.
- Dick, R. B., Setzer, J. V., Wait, R., Hayden, M. B., Taylor, B. J., Tolos, B., and Putz-Anderson, V. (1984). Effects of acute exposure of toluene and methyl ethyl ketone on psychomotor performance. *Int. Arch. Occup. Environ. Health* **54**, 91-109.
- Dick, R. B., Setzer, J. V., Taylor, B. J., and Shukla, R. (1989). Neurobehavioural effects of short duration exposures to methyl ethyl ketone. *Br. J. Ind. Med.* **46**, 111-121.
- BMDP Statistical Software Manual*, Dixon, W. J. (Ed.) (1990) Vol. 2. Univ. of California Press, Los Angeles.
- Erwin, L. W., Weiner, E. L., Linnoila, M. I., and Truscott, T. R. (1978). Alcohol-induced drowsiness and vigilance performance. *J. Stud. Alcohol* **39**(3), 505-516.
- Hjelm, E. W., Hagberg, M., Iregren, A., and Lof, A. (1990). Exposure to methyl isobutyl ketone: Toxicokinetics and occurrence of irritative CNS symptoms in man. *Int. Arch. Occup. Environ. Health* **62**, 19-2.
- Krasavage, W. J., O'Donoghue, J. L., and Divincenzo, G. D. (1982). Ketones. In *Patty's Industrial Hygiene and Toxicology* (G. Clayton and F. Clayton, Eds.), 3rd ed. pp. 4709-4800. Wiley, New York.

- Mackworth, N.H. (1961). Researches on the measurement of human performance. In *Selected Papers on Human Performance Factors in the Design and Use of Control Systems*, (H. W. Sinaika, Ed.), pp. 174-331. Dover, New York.
- Matsushita, T., Goshima, E., Miyakaki, N., Maeda, K., Takeuchi, Y., and Inoue, T. (1979). Experimental studies for determining the MAC value of acetone. 2. Biological reactions in the "six-day exposure" to acetone. *Sangyo Igaku* **11**, 507-515.
- McNair, D. M., Lorr, M., and Droppleman, L. F. (1981). *EITS Manual for the Profile of Mood States*. Educational and Industrial Testing Service, San Diego.
- Nakaaki, K. (1974). An experimental study on the effect of exposure to organic solvent vapor in human subjects. *J. Sci. Labour* **50**, 89-96.
- Niaura, R. S., Nathan, P. E., Frenkenstein, W., Shapiro, A. P., and Brick, J. (1987). Gender differences in acute psychomotor, cognitive, and pharmacokinetic response to alcohol. *J. Addict. Behav.* **8**(10), 345-356.
- Papa, A. J., and Sherman, P. D. (1981) Ketones. In *Encyclopedia of Chemical Technology*, Kirk-Othmer (M. Grayson, Ed.), pp. 894-941. Wiley, New York.
- Report of the Association (March 1990). Ethical Principles of Psychologists. *Am. Psychol.*, 390-395.
- Russo, J. M., Dick, R. B., Taylor, B. J., and Putz-Anderson, V. (1990). Pre-stimulus inhibition of the human blink reflex during exposures to solvents. *Society of Toxicology, Abstracts of the 29th Annual Meeting*, **10**(1), 302.
- SAS Institute Inc. (1989). *SAS/STAT User's Guide*, Version 6, 4th ed., Vol. 2, 846p. SAS Institute Inc., Cary, NC.
- Spencer, P., Schaumberg, H. H., Sabri, M., and Veronesi, B. (1980). The enlarging view of hexacarbon neurotoxicity. *CRC Critical Rev. Toxicol.* **7**(4), 279-356.
- Sternberg, S. (1975). Memory scanning: New findings and current controversies. *Q. J. E. Psychol.* **27**, 1-32.
- Taberner, P. V. (1980). Sex differences in the effects of low doses of ethanol on human reaction time. *Psychopharmacology* **70**, 283-286.
- USITC (1985). *Synthetic Organic Chemicals*. United States Production and Sales.
- US Printing Office (June 1981). Code of Federal Regulations 29 CFR 1910.1000, tables Z-1, Z-2, Z-3. Washington, DC.