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Ethanol, Marijuana, and Other Drug Use in 600 Drivers Killed in Single-Vehicle Crashes in North Carolina, 1978–1981

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ABSTRACT: Although the use of ethanol, marijuana, and other drugs may be detrimental to driving safety, this has been established by direct epidemiological evidence only for ethanol. In this study, the incidences of detection of ethanol (and other volatile substances), delta-9-tetrahydrocannabinol (THC), barbiturates, cocaine and benzoylecgonine, opiates, and phencyclidine were determined in an inclusive population of 600 verified single-vehicle operator fatalities that occurred in North Carolina in 1978 to 1981. The incidence of detection of amphetamines and methaqualone were determined for drivers accepted for study during the first two years ($n = 340$) and the last year ($n = 260$), respectively. Blood concentrations of 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (9-carboxy-THC) were determined in THC positive drivers. EMIT cannabinoid assays were performed on blood specimens from all drivers accepted for study during the third year, and the feasibility of using the EMIT cannabinoid assay as a screening method for cannabinoids in forensic blood specimens was investigated. The incidence of detection of ethanol (79.3%) was far greater than the incidences determined for THC (7.8%), methaqualone (6.2%), and barbiturates (3.0%). Other drugs were detected rarely, or were not detected. Blood ethanol concentrations (BECs) were usually high; 85.5% of the drivers whose bloods contained ethanol and 67.8% of all drivers had BECs greater than or equal to 1.0 g/L. Drug concentrations were usually within or were below accepted therapeutic or active ranges. Only a small number of drivers could have been impaired by drugs, and most of them had high BECs. Multiple drug use (discounting ethanol) was comparatively rare. Ethanol was the only drug tested for that appears to have a significantly adverse effect on driving safety.

KEYWORDS: toxicology, motor vehicle accidents, alcohol, marijuana

It is accepted that ethanol use has a detrimental effect on the performance of drivers because it impairs sensory input and perception, judgement and cognition, motor control, and their integration and coordination. It is also known that the use of ethanol is strongly associated with traffic fatalities. Nationally, between 40 and 55% of all drivers involved in fatal crashes have blood ethanol concentrations (BECs) greater than or equal to 1.0 g/L [*1*],[3] the

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[3]1.0 g/L = 100 mg/dL = 100 mg% = 0.10%.

BEC that most states define as being the concentration where a driver may be considered to be "under the influence of ethanol." During the past 13 years (1970 to 1982 inclusive), BECs have been determined in 4041 blood specimens taken from drivers who have died in single-vehicle crashes in the state of North Carolina. Of these drivers, 2337 (57.8%) had BECs greater than or equal to 1.0 g/L.

There has also been great interest in determining whether the use of other drugs, especially marijuana, can adversely affect driver performance. It is believed that marijuana use may be a potential highway safety problem because of its widespread use, and because it has been shown to produce changes in cognitive and perceptual abilities and changes in the ability to perform complex integrated and coordinated psychomotor tasks. However, both the ability to determine relationships between plasma concentrations of drugs of abuse or cannabinoids with either subjective psychological effects or induced decrements in performance and the ability to interpret the potential impairment in performance that resulted from a given concentration of that drug in plasma are restricted by many factors. Compared to ethanol, both the pharmacokinetic behavior and the analytical techniques used for the quantitation of these substances are complex. The relationships between plasma concentrations and either subjective self-reported psychological effects or induced decrements in performance are also complex, and are in many cases unknown.

Information concerning marijuana-induced impairment of performance has been obtained through three types of studies: clinical studies of the correlations between cannabinoid plasma concentrations and subjective self-reported psychological effects; driving, driving simulator, or other behavioral studies that attempt to correlate either the dose of delta-9-tetrahydrocannabinol (THC) administered or the resulting THC plasma concentrations with quantitated objective impairment in the performance of skills; and epidemiological studies that examine the incidence of drug use in various at-risk populations.

Clinical studies have determined that when marijuana is smoked, plasma concentrations of THC, the major active compound in marijuana [*2*], exhibit only a poor to moderate correlation with subjective self-reported psychological effects [*3–9*]. Plasma concentrations of 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (9-carboxy-THC) showed slightly better correlation with effects [*8*]. However, this THC metabolite is nonpsychoactive [*10*]. Correlations of hemolyzed blood or plasma THC concentrations and effects would be expected to be even poorer in forensic science situations. Chronic marijuana smokers exhibit tolerance to the physiological and psychoactive effects of marijuana [*11–14*], while it is also possible that they accumulate significant residual plasma concentrations of THC and 9-carboxy-THC. After a heavy passive exposure to marijuana smoke, one subject achieved THC plasma concentrations up to 2.2 μg/L [*15,16*] and experienced no psychoactive effects. Yet to be determined is the relationship between subjective effects and performance decrements.

The effects of marijuana use on both the performance of tasks associated with driving and on performance during driving on test tracks, on closed courses, or on driving simulators have been extensively reviewed [*17–19*]. An early study indicated that above a threshold dose [*20*], increasing doses of THC produced dose-dependent decreases in proficiency in some mental performance tests that used delayed auditory feedback, such as counting, verbal output, and visual stimulus discrimination [*21*]. Motor control was impaired in tests of stance and hand stability [*21*]. The effects of orally administered THC (0.2, 0.4, and 0.6 mg/kg) on either the proficiency or variability of performance as measured in a battery of objectively scored sensory, perceptual, cognitive, or psychomotor tests were minimal [*22*]. However, when individual test scores and variabilities were combined and corrected to standardized scores to allow for the analysis of overall performance, THC did have a small but consistent detrimental effect on both proficiency and performance variability [*22*]. Another performance study using orally administered THC (0.21 mg/kg) showed that standing steadiness, perceptual speed, manual dexterity, reasoning, and reaction time were markedly impaired [*23*]. Ethanol administered at 0.54 g/kg, a dose required to produce BECs of about 0.7 g/L,

produced no such impairment in these tests [*23*]. Finally, orally administered THC (0.32 mg/kg) induced a significant impairment of performance when measured in a battery of perceptual, cognitive, and psychomotor tests [*24*]. The impairment noted was of lower magnitude than that noted in subjects with BECs at 0.8 g/L [*24*].

The effects of THC on various aspects of visual perception also have been studied. Static visual acuity to an immobile image on a video screen was unimpaired by either marijuana smoking (8- or 15-mg THC cigarettes) or by ethanol (1 mL of 95% ethanol/kg) in either high or low contrast light [*25*]. When the image, a small spot, moved laterally with increasing frequency in either a smooth and pendular or a saccadic manner, the frequency at which coordinated eye tracking could not be maintained was markedly reduced in subjects receiving ethanol, but not in subjects who smoked marijuana [*26*]. These studies indicated that the perceptual impairment caused by THC is due to impaired central integration of information, and not because of impaired motor control [*26*]. A more recent study used compensatory cursor tracking on a video screen as an impairment indicator [*27*]. Either marijuana or ethanol, or the two drugs taken in combination adversely affected tracking performance. These effects were not observable without sophisticated devices for data collection and analysis.

The effects of marijuana use on risk acceptance were studied in a simulated passing test on a driving simulator [*28*]. Unlike the subjects receiving ethanol, the subjects receiving marijuana were less likely to accept the increased risk associated with passing in a hazardous situation. No change from control was noted in the number of attempted or completed passes, the number of simulated crashes, or the lateral control of the vehicle. The time required to make a decision to pass was not affected in emergency situations, but increased in nonemergency situations. A driving simulator study required subjects to drive while monitoring traffic signal lights [*29*]. Marijuana produced a small but significant delay in response to the lights, but did not otherwise affect tracking or vehicle control. A later driving simulator study used a car on a chassis mounted dynamometer, and a projected landscape to simulate a 50-km (31-mile) driving task [*30*]. Braking, acceleration, and steering wheel handling were unaffected by marijuana smoking. However, its use did cause a dose-related delay in response to signals in the driver's peripheral vision fields [*30*]. Driving simulator studies showed that higher doses of marijuana can cause performance impairment in some tasks involving visual search and recognition [*31*]. However, 25 other indices of driver performance were not affected in these same studies.

A closed-course driving study showed that the effects of marijuana on driver performance can be differentiated from placebo effects only by using complex multivariate analyses of responses from sensitive transducers monitoring the driver [*32*]. The effects were only barely noticeable by direct observation. Double-blind driving studies have also been performed using dual-control vehicles on test tracks and city streets [*33*]. The test track drivers were scored objectively, using the number of cones hit, and the street drivers were scored subjectively by observers in the front seat of the test vehicle. For the test track drivers, performance impairment was noted only after smoking the higher of the two doses of THC (8.4 mg), and not after the low dose (4.9 mg). Subjects who drove on the street were noted to be impaired in three of eleven subjective scores: judgement, care, and concentration. However, in both the subjective or objective tests, significant numbers of subjects either showed no performance impairment or their performance improved. A third notable driving study used both objective and subjective scoring to examine the performance of drivers who had smoked marijuana (0.02- or 0.09-mg/kg THC) or who had ingested ethanol (BEC = 0.7 g/L). Observers either in the car or on the 10.6-km (6.6-mile) course were unable to determine that the performance of the marijuana users was in any way impaired [*30*]. However, the group that had used the higher dose of THC (5.9-mg average) hit 27% more cones than did the placebo group. The group that had smoked the lower dose of THC (1.4-mg average) showed no such increase. The group that had ingested ethanol hit 32% more cones than did its requisite control group [*34*]. Finally, the performances of nine subjects familiarized with a closed-

course driving task were evaluated both by observers inside the dual-control vehicles, and by observers in vehicles following the test subjects [35]. The subjects received ethanol sufficient to produce a BEC of 0.6 g/L, marijuana (2% THC in a marijuana cigarette, dose not indicated), or both drugs. In this dual-treatment, dual-placebo, Latin square design experiment, both sets of observers determined that neither the subjects who received ethanol alone, nor the subjects who received THC alone were impaired at the doses given. However, "the use of both drugs simultaneously resulted in significant driving impairment" [35].

Many other factors may modify the impairment of performance noted in some studies. Subjects allowed to practice three different visual stimulus discrimination tasks for four days before smoking marijuana (18 mg of THC) and repeating the tasks on the fifth day exhibited no increase in reaction time on the fifth day [36]. A second set of subjects practiced the tasks and smoked marijuana for four days before repeating the tasks without smoking on the fifth day. The subjects' reaction times stabilized at the nondrugged level after two days of practice, and did not change afterwards [36]. Therefore, it appears that practice may increase resistance to some aspects of marijuana induced impairment. The concurrent use of ethanol and marijuana may also alter the degree of impairment induced by marijuana use. In several studies, the performance decrements produced by the use of marijuana and ethanol were roughly additive [23,24,32,35]. However, the magnitude of the additive effect may not be consistent either between subjects, or even in the same subject. Time-dependent decreases in the relative impact of this additive effect have been noted [23]. Whether or not individuals who have developed tolerance to some of the effects of marijuana [11-14] are less likely to exhibit reduced performance abilities versus nontolerant individuals has not been determined.

The performance decrements produced by marijuana use [27] were present for roughly the same time period as noted for the production of subjective effects in other studies. Like the correlation between subjective effects and THC plasma concentrations, the temporal correlation between THC plasma concentrations and centrally mediated performance decrements should also be rather poor because of the dispositional and pharmacokinetic properties of THC. Recently, performances in three roadside sobriety test tasks were used to examine the correlation between serum concentrations of THC and impaired motor function in 58 subjects who smoked marijuana ad libitum [9,37]. It was reported that 94 and 60% of the subjects failed to pass one of the three test tasks (Romberg, finger-nose, or one-foot stance steadiness) when the tests were administered 90 and 150 min, respectively, after smoking stopped [9]. If the THC concentrations measured 5 min after smoking were ignored, then failure in one or more of the tests was "inevitably" associated with THC plasma concentrations above 25 to 30 μg/L [9]. Later it was reported that the serum THC concentrations correlated poorly with the performance scores [37], and that the subjective psychological effects and performance impairment scores correlated poorly because the physical effects lasted far longer than did the psychological effects [37].

The value of the conclusions of this study are limited by many factors. The dose administered was not controlled, and no control subjects (placebo marijuana) were used. Objective evaluation of performance abilities was not possible because the study was not performed in a double-blind manner, and because potentially biased observers (California Highway Patrol Officers) participated as the test evaluators [9]. Only sobriety test "results that showed either the clear presence or absence of impairment were used" to evaluate the impairment-concentration relationship. Therefore, only some (32, 47, and 70%, respectively) of the results from the three component tests were reported. Considered individually, the three tests did not reliably detect THC-induced motor impairment, as roughly 20, 18, and 50%, respectively, of the three tests administered resulted in failure. Independent evaluation of the use of these tests as a battery was not possible because results from the tests were not compiled with respect to either the subject or the time of blood sampling or performance testing. Furthermore, a recent interlaboratory method comparison study [38] showed that the tritium-based

radioimmunoassay (RIA) method used [*39*] lacks sensitivity (10 μg/L in serum) and only recovered between 16 and 43% of the THC in control serum specimens [*38*]. If these conditions were operable during the performance experiment, then the THC concentrations detected would be lower than they should have been, resulting in a lower presumptive cutoff concentration. For all the above reasons, the presumption of physical impairment at THC serum concentrations greater than 25 to 30 μg/L cannot be substantiated from the data presented.

A report to Congress on the effects of marijuana on highway safety [*40*] summarizes the current state of knowledge concerning marijuana-induced performance impairment.

> Experimental research, taken as a whole, indicates that certain dose levels of marijuana can impair tracking and perceptual functions involved in driving [*17*]. Perception and other complex mental functions appear to be more affected than simple motor or sensory tasks that demand little processing of information. The few studies involving actual car handling on closed courses support the implications of laboratory tests that marijuana use by drivers, especially in higher doses, can increase the likelihood of traffic crashes. However, whether the differences found in the laboratory are large enough to have impact in an actual driving situation is unknown [*40*].

In other words, the relationships between testing procedures and "real life situations," and the potential effects that decrements in performance measured by those procedures have on the performance of complex integrated and coordinated tasks outside the laboratory are not known.

Epidemiological or incidence studies have been completed in attempts to determine if marijuana use is detrimental to the safe operation of motor vehicles. Basically, these studies have attempted to show that marijuana use is overrepresented in drivers that are at-risk on the highways. However, to prove overrepresentation, the incidence of use must not only be known in the primary at-risk group: the operators of motor vehicles who have died as the result of crashes, but must also be known in two other groups of drivers: all operators of motor vehicles and the operators who are victims in nonfatal crashes. The major problem encountered during the performance of incidence studies has been that it has been very difficult and may be impossible to obtain blood or plasma specimens from a representative sample of drivers in either of the latter two populations. Access to blood specimens from the total population of motor vehicle operators at large is restricted by ethical and legal constraints. No systematic procedures are available to collect blood specimens from a representative sample of the population of drivers involved in nonfatal crashes. However, access to blood specimens from the population of drivers involved in fatal automobile crashes is guaranteed in some instances, for example where specimens are required to be submitted to a city, county, or state agency for routine forensic toxicological examination. If it can be determined that the incidence of use of a drug in this at-risk group is very low or that the drug is present in concentrations below those required for activity or both, then the frequency of use in the general population becomes relatively unimportant.

One of the earliest incidence study of marijuana use in drivers [*41*] reported that 43 of the 267 drivers (16.1%) examined were "under the influence of marijuana." Unfortunately, these results were based only on interviews of the friends and relatives of the deceased. No analyses for cannabinoids were performed. Only 13 of the drivers (5%) were said to have used marijuana alone. Of the 43 drivers who were said to be under the influence of marijuana, 25 (58%) were said to have also used ethanol. Later Teale and Marks [*42*] reported a single motor vehicle death where a high concentration of "cross-reacting cannabinoids" was found by RIA in both the blood and urine of a driver. In a larger study [*43*], these authors reported that 6 of 66 (9%) blood specimens obtained from fatally injured drivers contained cannabinoids by RIA. Only one of these six specimens contained ethanol. THC was quantitated in three of the six specimens. One of the victim's bloods contained THC at 3.4 μg/L

and an ethanol concentration of 3.4 g/L. The other two victims were motorcyclists who crashed into cars. Their bloods contained THC at 1.5 and 4.4 μg/L, respectively, and no ethanol. These THC concentrations are too low to insure that any detrimental effects on the operation of a motor vehicle were experienced. The number of specimens analyzed is small, and the authors suggest that there was a significant bias in their selection. In a widely cited study, Reeve et al [*44,45*] reported on the examination of 1792 blood specimens that were selected from a total population of over 19 000 blood specimens taken from drivers arrested for driving under the influence. Blood specimens were analyzed for THC by RIA. They reported that 285 (15.9%) of these blood specimens contained THC in excess of 5.0 μg/L [*44*], and that 258 drivers (14.4%) had blood THC concentrations greater than or equal to 5.5 μg/L [*45*]. However, 111 of these 285 specimens contained ethanol at concentrations greater than 1.0 g/L [*44*]. Therefore, only 174 (9.7%) of these drivers could possibly have been adversely affected by marijuana alone.

This study was subject to many methodological errors, the most basic of which was a very strong bias toward intoxicated drivers with BECs less than 1.0 g/L. All of the blood specimens with BECs in this range were analyzed for THC [*44*]. These 1027 drivers' bloods represented about 5.4% of the 19 000 specimens submitted, but comprised 57.3% of the specimens analyzed (n = 1792). The other 765 specimens in the study population contained BECs greater than 1.0 g/L, and were randomly selected from the over 17 000 specimens with high ethanol concentrations. These specimens comprised roughly 90% of the total specimen population (n = 19 000) submitted. Only 4% of them (n = 765) were selected for inclusion in the study group, of which they comprised 42.7%. Therefore, the sample population used is not representative of impaired drivers, to say nothing of either the population at large or of any at-risk groups. The authors showed that there was a very strong negative correlation between the presence of THC in blood and the incidence of traffic crashes. The specimens were routinely analyzed only for THC and ethanol. It was reported [*9,37,45*] that all of the drivers whose bloods contained THC also failed standard roadside sobriety tests, and that this evidence supports or corroborates the hypothesis that *Cannabis* use impairs driving skills. However, all 1792 subjects were stopped and arrested because their driving was impaired [*44*]. Of the 1385 drivers who were given the sobriety tests, 1381 drivers failed [*44*]. Although all of the 234 drivers whose bloods contained THC and whose test results were known failed the test, all of the 77 drivers whose bloods contained neither drugs nor alcohol also failed the test [*44*]. Based on this data, the hypothesis that *Cannabis* use was responsible for the production of impairment in driving skills cannot be accepted. For these reasons, it is doubtful that this study provides useful data concerning the potential effects of marijuana on highway safety.

A Canadian study [*46*] reported the incidence of use of many different drugs in 401 fatally injured drivers. THC was detected in blood specimens from 15 (3.7%) of these drivers. Two of the blood specimens contained THC at a concentration of 5 μg/L. One of these two specimens also contained ethanol at a concentration of 2.4 g/L, while the other contained no ethanol. The 13 other specimens all contained THC at concentrations less than 3.0 μg/L. Eight of the fifteen drivers had BECs greater than 1.0 g/L. THC was also detected in 2 of 367 (0.5%) drivers that were excluded from the incidence study [*46*]. One of these two cases was excluded because a urine specimen was not available. The blood specimen from this driver contained THC and ethanol at concentrations of 35 μg/L and 1.6 g/L, respectively. The high concentration of THC may have impaired the ability of this driver to operate a motor vehicle safely. However, the high BEC in this driver would have seriously impaired his ability to perform even in the absence of any THC.

In summary, the few meaningful incidence studies that have been performed tend to indicate that if marijuana use does adversely affect the safe operation of motor vehicles, the number of persons so affected is relatively small, and most were also affected by ethanol [*47*]. To further study the incidence of ethanol, marijuana, and drug use in motor vehicle opera-

tors, blood specimens from 600 drivers that were submitted to the Office of the Chief Medical Examiner for the State of North Carolina over a three-year period have been analyzed. Because blood specimens from all motor vehicle fatalities are required by the regulations of the Medical Examiner System to be submitted, an inclusive population of drivers from a defined geographical area has been studied. Because access to appropriate records is guaranteed in most cases, the circumstances surrounding these deaths have been verified. Furthermore, this study of the incidence of ethanol, marijuana, and drug use has been restricted to the population of drivers who have died following single-vehicle crashes. Drivers in this group would have a greater probability of being directly culpable for crashes that were caused by the impaired operation of a motor vehicle than would drivers killed in multiple-vehicle crashes. Preliminary results from this study [*4,47,48*] have been reported. A summary of the toxicological findings from the entire study has also been presented [*49*].

Experimental Methods and Materials

Selection of Cases

All cases submitted to the Toxicology Laboratory of the Office of the Chief Medical Examiner between 1 Oct. 1978 and 30 Sept. 1981 were examined to see if they were suitable for further investigation. The following criteria were used to select cases for study [*48*]:

1. The victim was the operator of a motor vehicle, who died in an accidental or suicidal manner, as the result of a crash involving only that vehicle and no other. Furthermore, the vehicle was either a car or a truck. Victims of crashes involving either motorcycles or farm vehicles were not accepted. Pedestrian deaths were also excluded.
2. The specimen submitted was suitable for examination. That is, that it contained greater than 5 mL of either cardiac, arterial, or venous whole blood or plasma.
3. The specimen submitted was representative of the composition of the blood of the driver at the time of death. Either the driver was killed in the crash, or lived for less than 1 h after the crash occurred. This restriction decreased the effects of either drug metabolism or elimination on the composition of the specimen. The victim must not have received any vigorous medical treatments including medications, surgery, or transfusions.
4. Complete documentation was available to verify the pertinent information. The required documents were the toxicology request submitted with the specimen, the medical examiner's report, the pathologist's report if an autopsy was performed, the death certificate, and the motor vehicle crash report from the North Carolina Division of Motor Vehicles.

Determination of Ethanol and Other Volatile Substances

Sodium fluoride (10 g/L) was added to all blood specimens as a preservative. Blood specimens from all cases accepted for study were tested for ethanol and other volatile substances by diffusion into and reduction of a potassium dichromate solution [*50*]. The sensitivity of this determination has been reported to be 0.2 g/L for ethanol. The presence of a volatile substance was confirmed, and the substance identified and quantitated using a gas chromatographic procedure [*51*] with *n*-propanol as the internal standard. All ethanol concentrations were rounded down to the next nearest whole tenth of a gram per litre, and reported as such. For example, an ethanol concentration of 0.47 g/L would be reported as 0.4 g/L. All ethanol concentrations less than 0.20 g/L were reported as none detected.

After the ethanol determination, the specimens were centrifuged to remove cells or other suspended materials, and the supernatant fluids were stored in glass vials with screw top closures at −20°C until other analyses could be performed.

Determination of Cannabinoids

All specimens were analyzed in duplicate for the presence of THC using a specific RIA method designed for use with hemolyzed blood specimens [*52*]. Specimens positive for THC were reanalyzed in duplicate on two other occasions, and the two results averaged. Although the limiting sensitivity of this method for THC is 0.1 μg/L in plasma and 0.4 μg/L in hemolyzed blood [*4,52*], a cutoff concentration for the distinction of positive and negative specimens was imposed at 3.0 μg/L [*4,16,47,48,52*]. Specimens containing THC at concentrations less than 3.0 μg/L were reported as none detected. All specimens determined to contain THC at concentrations greater than 2.9 μg/L were also analyzed in duplicate for 9-carboxy-THC using a specific RIA method [*53,54*]. The sensitivity of this assay was reported to be 2 μg/L (kit instructions, Research Triangle Institute, Research Triangle Park, NC 27709). In addition, all of the blood or plasma specimens accepted for study during the third year were analyzed in duplicate for cannabinoids using a modification of the Syva EMIT®-DAU Assay for Cannabinoids [*55*] (Syva Co., Palo Alto, CA 94304). The modifications used were similar to those proposed by Peel and Perrigo [*56*]. Briefly, 250-μL aliquots of the blood specimens and standards were pipetted to silanized (Surfasil, Pierce Chemical Company, Rockville, Fl 61105) 10- by 75-mm disposable borosilicate culture tubes. Proteins were precipitated and the THC extracted [*48*] by adding 500 μL of methanol (distilled in glass, Burdick and Jackson Laboratories Inc., Muskegon, MI 49224) to the center of the tube, while rapidly vortexing, using a Pipettor-Dilutor (Cavro Scientific Instruments, Model 1500, Los Altos, CA 94022). Vortexing continued for 15 s after the addition of the methanol. The tubes were capped using No. 1 corks, allowed to incubate for 30 min, centrifuged at 1000 g for 10 min, and the supernatant fluids decanted to 2-mL disposable plastic sample cups. The EMIT tests were performed using a Perkin-Elmer KA-150 Automated Kinetic Analyzer with the following instrumental parameters:

cell temperature = 30°C,
high absorbance threshold = 1.5,
low absorbance threshold = 0.0,
incubation time = 24 s,
preincubation = on,
wavelength = 340 nm,
reaction = up, substrate,
sensitivity = low,
sampler = synch,
scale factor = 415,
name = EMIT,
mode = slow, and
duplicates = on.

The use of a scale factor of 415 on this instrument produces results expressed as the change in milliabsorbance units that occurred during a 30-s interval multiplied by 2.667 [*57*], the same units in the manual EMIT-DAU method [*56,58*]. All EMIT reagents were prepared such that their relative concentrations in the spectrophotometer cell were identical to those in the cell in the manual method [*56,58*], and their actual concentrations in the cell were 90% of those in the cell in the manual method. The EMIT reagents were prepared in the following manner:

Buffer: dilute to a total volume of 117 mL with distilled water.
Reagent "A": dilute as written with distilled water, then dilute 1:5 (1 + 4) with buffer before use.
Reagent "B": dilute as written with distilled water, then dilute 1:5 (1 + 4) with distilled water before use.

9-Carboxy-delta-9-THC standards were prepared in cannabinoid-free hemolyzed blood [*52*] at 0, 20, and 75 μg/L, and analyzed before and after every 15 specimens. All unknown specimens and standards were analyzed in duplicate, and their results averaged. The average responses from the standards run before and after a set of specimens were averaged. The

average response of the 20-μg/L 9-carboxy-THC blood standard was used to discriminate positive from negative specimens within the sample set.

Determination of Other Drugs

Commercially available RIA kits (Abuscreen® Radioimmunoassays, Roche Diagnostics; a Division of Hoffman La-Roche Inc., Nutley, NJ 07110) were used to screen the specimens for amphetamines, barbiturates, cocaine and its metabolite benzoylecgonine, methaqualone, opiates, and phencyclidine. These analyses were performed both because it is believed that the use of these drugs may possibly have adverse effects on driver safety, and because a simple and fast screening technique was available. The detection limit (concentration cutoff) for amphetamines was 1.0 mg/L. The detection limits for barbiturates, cocaine and benzoylecgonine, methaqualone, and phencyclidine were 0.1 mg/L. The detection limit for opiates was 0.04 mg/L of morphine. These detection limits are sufficiently sensitive to detect the concentrations of these drugs and their metabolites that would be produced by either therapeutic or recreational use.

The presence of a barbiturate in a blood specimen giving a positive result in the screening test was confirmed, and the barbiturate identified and quantitated using a gas chromatographic procedure [*59*]. Specimens producing positive results in the methaqualone screening test were treated in a similar manner. Briefly, 4-mL aliquots of unknown blood specimens and methaqualone blood standards were spiked with 20 μL of a solution containing benztropine (internal standard) at 1 g/L. Specimens and standards were brought to pH 9 with ammonium hydroxide and extracted with 10 mL of butyl chloride. Nine millilitres of the organic (top) phase was extracted with 5-mL 2*N* hydrochloric acid, the organic phase was discarded, and the aqueous phase was filtered through water wet Whatman No. 5 filter paper. The filtrate was made basic with 50% sodium hydroxide solution, extracted with 3 mL of chloroform, filtered through sodium sulfate over glass wool, reduced to dryness under nitrogen, and reconstituted in 20 μL of methanol. One-microlitre aliquots were injected into a Varian 2100 Aereograph equipped with a flame ionization detector and a 0.9-m (3-ft) glass column (2-mm inside diameter) packed with 3% OV-17 on Chromasorb W. The column temperature was programmed, starting at 200°C for 1 min, then rising at 20°C/min to 265°C. Injector and detector temperatures were 280 and 300°C, respectively. The flow rate for the nitrogen carrier gas was 20 mL per minute. In some cases the volume of the specimen required for methaqualone confirmation exceeded the volume of the specimen remaining after all screening tests had been performed. In these cases, the Abuscreen test for methaqualone was modified in a fashion similar to that used by Honigburg et al [*60*] for the analysis of hydromorphone. Briefly, standard solutions of methaqualone were prepared in blood at concentrations between 0.5 and 5 mg/L. Unknown specimens and standards were then diluted 1:10 (1 + 9) with methaqualone-free blood. The analysis was performed using 12- by 75-mm disposable borosilicate culture tubes. Each standard or specimen tube received 20 μL of the appropriate diluted standard or unknown specimen, along with 300 μL of the methaqualone radioligand solution and 200 μL of the antibody solution. The determination of zero dose binding was performed in a similar manner, using a 20-μL aliquot of methaqualone-free blood. Nonspecific binding was determined using a 200-μL aliquot of an antibody solution specific for barbiturates in place of the methaqualone antisera. The barbiturate antiserum was taken from another Abuscreen kit. Total counts tubes were prepared using only the 300-μL aliquot of the methaqualone radioligand. All tubes for specimens, standards, zero dose binding, nonspecific binding, and total counts determinations were prepared in duplicate. Equilibrium radioligand binding was insured by incubation at 4°C overnight. Antibody bound radioactivity was precipitated by adding 500 μL of saturated ammonium sulfate to all but the total counts tubes, which were set aside until counting. All remaining tubes were

briefly vortexed, incubated for 15 min at room temperature, and centrifuged for 10 min at 1000 g. The supernatant fluids were removed by aspiration. The pellets were then washed by adding 250 μL of distilled water and briefly vortexing. Bound radioactivity was immediately precipitated using the procedure above. Results for unknown specimens were interpolated from the standard curve, using the linear regression line that was calculated from the logit binding-log dose data [*61*].

Statistical Tests and Procedures

The level of significance α, was chosen to be 0.05 for all hypothesis tests and confidence interval estimates. Procedures used to test statistical inference include the chi-square test for association, and two-sided hypothesis tests for the equivalency of normally distributed means with known variances [*62*]. When appropriate, the normal approximation to the binomial distribution was used in two-sided hypothesis tests concerning the equivalency of binomial parameters, either between populations, or during the comparison of a sample population to the entire study population [*62*]. Distributions were tested for normalcy using the chi-square test and for skewness using the a_3 skewness test [*62*].

Results and Discussion

Case Selection

During the three years between 1 Oct. 1978 and 30 Sept. 1981, approximately 21 000 cases were submitted to the Office of the Chief Medical Examiner for toxicological investigation. After preliminary screening, 850 cases were determined to fit the primary study requirements that the specimens were obtained from operators of cars and trucks involved in single vehicle crashes. This study population can be considered to be inclusive. In North Carolina, during calendar years 1979 and 1980, there were 212 and 242 single vehicle operator fatalities, respectively [*63,64*]. During these two years, 220 and 280 cases were received that fit the primary study requirements. Differences between these two sets of data were caused by the use of slightly different crash classification criteria. Of the 850 cases that satisfied the primary study requirements, 596 cases (70.1%) were found to satisfy fully the secondary study requirements that the specimen submitted was suitable for examination and was representative of the composition of the blood of the driver at the time of death. These specimens were accepted for further investigation. The first 4 cases reviewed during Oct. 1981 that met all study criteria were also accepted, bringing the total number of accepted cases to 600. Of the 254 cases (29.9% of 850 cases) that did not satisfy the secondary requirements 84 cases (33.1%) were rejected because the submitted specimen volume was less than 5 mL; 49 cases (19.3%) were rejected because the specimen submitted was neither blood nor plasma, was of unspecified origin, or was taken after embalming; and 121 cases (47.6%) were rejected because the subjects lived longer than 1 h after the crash or received vigorous medical treatment that could have altered the concentrations of drugs or ethanol in the drivers' bloods. During the three consecutive years of the study, 169, 171, and 260 cases were accepted, respectively. The increase in the number of cases accepted during the third year resulted from improvements in the methods used to search for and review cases, and not from alterations in the criteria for case acceptance.

Study Population

The age distribution for the 600 accepted cases is shown in Fig. 1. When the drivers' ages were classified into five-year intervals, the age distribution was shown to be both nonnormal ($P < 0.0005$) and strongly and positively skewed ($P < 0.01$) towards drivers in the younger

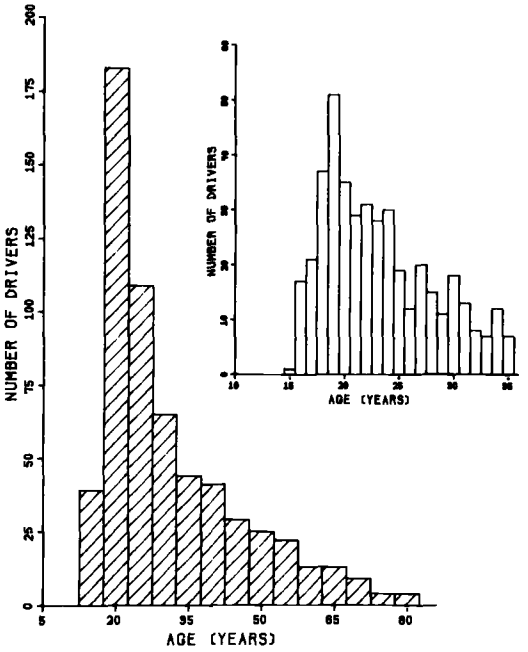

FIG. 1—*Distribution of ages of 600 drivers.*

age groups. Drivers that were 19 years old comprised the mode age of the distribution (51 cases of 600, 8.5%). More than one quarter of the drivers (n = 162, 27.0%) were younger than 21 years old. The median age of the drivers was 26 years. The mean age (and standard deviation sd) of all drivers was 31.2 ± 14.5 (sd) years. The drivers younger than the mean age (n = 388) comprised 64.7% of the population. The study population was predominantly comprised of whites (n = 485, 80.9%), while blacks comprised 16.3% (n = 98) of the population. All other races comprised 2.8% (n = 17) of the study group. Males (n = 520, 86.7%) heavily predominated over females (n = 80, 13.3%). Not surprisingly, white males (n = 416, 69.4%) comprised the majority of the population studied. Black males (n = 87) accounted for 14.5% of the study group, while white females (n = 19, 11.5%) comprised the next largest group. Males of other races comprised 2.8% (n = 17) of the population, while black females accounted for only 1.8% (n = 11) of the total. No females from other races were noted. The majority of these drivers had their fatal crashes during the evening or night hours. Using the third-year specimens (n = 260) as an example, 64% (n = 166) of the crashes occurred between 6 p.m. and 4 a.m. A large number of crashes (n = 120, 46.2%) occurred between 10 p.m. and 4 a.m. The motor vehicle crash reports indicated that the drivers accepted during the third year exceeded the posted speed limits in the areas where their crashes occurred by an average of 31.1 ± 37.1% (sd). Seat belt or restraint system use could not be determined in six of the drivers who died during the third year. Only 2 of the remaining 254 drivers (0.77%) were reported to be using either lap or combined lap and shoulder belt restraints.

Incidence of Ethanol and Drug Detection

The incidence of ethanol and drug detection is presented in Table 1. Ethanol was the most common substance detected in the study population. It was present in 79.3% (n = 476) of

the blood specimens tested, and was the only substance detected in 68.4% ($n = 410$) of the specimens. Ethanol was not detected in only 20.7% ($n = 124$) of the drivers' bloods. The incidence rate for ethanol use by fatally injured drivers determined in this study is greater than previous incidence estimates. Turk et al [*65*] detected ethanol in 50 of 72 drivers (69.4%) killed in single-vehicle crashes in North Carolina. Garriott et al [*66*] determined that the blood specimens from 78 of 127 drivers (61.4%) who died in Dallas County, Texas, contained detectable concentrations of ethanol. Cimbura et al [*46*] reported that ethanol was detected in blood specimens taken from 229 of 401 drivers (57.1%) who died in either single- or multiple-vehicle crashes in Ontario Canada.

Compared to the incidence of ethanol detection, the incidence of drug detection determined in this study was low. Drugs were detected in only 83 blood specimens (13.8%) taken from the drivers in the study population. Sixty-six cases (11.0%) were noted where both ethanol and drugs were detected, while only seventeen specimens (2.8%) contained drugs but did not contain ethanol. The incidence of drug use reported in this study is greater than that reported by some authors, but far less than that reported by others. Turk et al [*65*] detected drugs in 4 of 72 drivers (5.6%), while Garriott et al [*66*] and Cimbura et al [*46*] reported drug incidence rates of 18.1% (23 of 127) and 26.2% (105 of 401), respectively. Finally, only 107 of the drivers' blood specimens (21.8%) examined in this study contained neither ethanol nor drugs. This is less than the incidence of fatally injured drivers whose bloods contained no ethanol or drugs (30 to 31%), as reported in the three studies cited above [*46,65,66*]. Using the data in Table 1, a relationship between ethanol and drug use in drivers in this study could not be demonstrated ($P < 0.95$). Incidences of drug and ethanol use in various test populations were not significantly different from incidences noted in appropriate reference populations (Table 2). The drivers who had used drugs had age and sexual distributions similar to those noted for the entire study population (Table 2). The mean, median, and mode ages among these drivers were 30.1 $\pm$ 14.9 (sd) years, 24 years, and 18 years, respectively.

Incidence rates for the detection of specific drugs are presented in Table 3. The most commonly detected drugs were THC (47 of 600, 7.8%) methaqualone (16 of 260, 6.2%), and barbiturates (18 of 600, 3.0%). Phencyclidine, opiates, cocaine and benzoylecgonine, and other volatile substances were detected only rarely. Amphetamines were not detected in any of the 340 blood specimens tested during the first two years of the study. For this reason, amphetamine screening was terminated. The methaqualone RIA became commercially available shortly before the end of the second year of the study, and was used to screen all third-year specimens. A more complete discussion of these results is presented below.

The incidence of multiple drug use is presented in Table 4. The large majority of the drivers who had used drugs had used either one drug and ethanol (60 of 83, 72.3%), or had used one drug with no ethanol (14 of 83, 16.9%). The use of more than one drug, either with or without ethanol (9 of 83, 10.8%), was comparatively rare.

The blood specimens in this study were not screened for many drugs or classes of drugs

TABLE 1—*Incidence of ethanol and drug use.*

	Drugs					
	Present		Absent		Totals	
Ethanol	*n*	%[a]	*n*	%[a]	*n*	%[a]
Present	66	11.0	410	68.4	476	79.3
Absent	17	2.8	107	17.8	124	20.7
Totals	83	13.8	517	86.2	600	100.0

[a]Percent of the 600 drivers' bloods tested.

TABLE 2—*Statistical comparisons of population characteristics: ethanol and drug users.*

No.	Test Char. *n* (%)	Test Pop. *n*	versus	Test Char. *n* (%)	Ref. Pop. *n*	$P <$[a]
1	drugs 66 (13.8)	EtOH 476		drugs 83 (13.8)	A.D.[b]	0.98
2	drugs 17 (13.7)	no EtOH 124		drugs 83 (13.8)	A.D.	0.96
3	drugs 66 (13.8)	EtOH 476		drugs 17 (13.7)	no EtOH 124	0.92
4	EtOH 66 (79.5)	drugs 83		EtOH 476 (79.3)	A.D.	0.96
5	EtOH 410 (79.3)	no drugs 517		EtOH 476 (79.3)	A.D.	0.99
6	EtOH 66 (79.5)	drugs 83		EtOH 410 (79.3)	no drugs 517	0.96
7	age > 31.2 yrs. 25 (30.1)	drugs 83		age > 31.2 yrs. 212 (35.3)	A.D.	0.30
8	females 8 (9.6)	drugs 83		females 80 (13.3)	A.D.	0.25
9	no EtOH 17 (20.5)	drugs 83		no EtOH 124 (20.7)	A.D.	0.96
10	BEC 0.2-0.9[d] 15 (18.1)	drugs 83		BEC 0.2-0.9 69 (11.5)	A.D.	0.12
11	BEC ≥ 1.0 51 (61.4)	drugs 83		BEC ≥ 1.0 407 (67.8)	A.D.	0.23
12	BEC ≥ 1.0 51 (77.3)	drugs + EtOH 66		BEC ≥ 1.0 407 (85.5)	EtOH 476	0.11

[a] $P < 0.05$ significance.
[b] All drivers ($n = 600$).
[c] Mean age of all drivers.
[d] Blood ethanol concentration, g/L.

that have been previously detected at high incidence rates in impaired drivers, that have high abuse potential, or that could potentially have a significant adverse effect on driver performances. These drugs or drug classes included the benzodiazepines such as diazepam and chlordiazepoxide; other sedative-hypnotic drugs such as methyprylon and glutethimide; the tricyclic antidepressants imipramine and amitriptyline; the phenothiazines and other neuroleptic drugs such as meperidine; antiepileptic medications such as phenytoin (diphenylhy-

TABLE 3—*Incidence of detection of specific drugs.*

Drug	Specimens Analyzed	Number Detected	Percent Detected[a]
THC	600	47	7.8
Methaqualone	260	16	6.2
Barbiturates	600	18	3.0
Phencyclidine	600	3	0.5
Opiates	600	3	0.5
Cocaine and benzoylecgonine	600	2	0.3
Other volatile substances	600	1	0.2
Amphetamines	340	0	0.0

[a] Percent of 600 drivers in the study population (except methaqualone and amphetamines).

TABLE 4—*Incidence of multiple drug use.*

Number[a] of Drugs	No Ethanol		With Ethanol		Total	
	n	%[b]	*n*	%[b]	*n*	%[b]
1	14	2.3	60	10.0	74	12.3
2	2	0.3	5	0.8	7	1.2
3	1	0.2	1	0.2	2	0.3
Totals	17	2.8	66	11.0	83	13.8

[a]Other than ethanol.
[b]Percent of 600 drivers in the study population.

dantoin); other centrally acting analgesics such as propoxyphene, methadone, and pentazocine; hallucinogens such as LSD or mescaline; centrally acting muscle relaxants such as meprobamate; and certain antihistamine drugs such as diphenhydramine; and so forth. Neither the time, equipment, personnel, nor budget ($50/case) were available that would be required to complete an exhaustive extraction style gas chromatographic or gas chromatographic/mass spectrometric study of this magnitude. Screening methods for some of these drugs were not readily available. For these reasons, the study was limited in scope to ethanol and to those drugs that could be detected using available RIA methods and could be confirmed when necessary.

Ethanol Concentrations

The distribution of ethanol concentrations found in the 600 accepted cases is shown in Fig. 2. Only 69 (11.5%) of the 600 blood specimens contained ethanol concentrations between 0.2 and 0.9 g/L, while 407 (67.8%) of the bloods contained ethanol concentrations greater than or equal to 1.0 g/L. Therefore, of the 476 drivers who had used ethanol, 85.5% had BECs greater than or equal to 1.0 g/L. The mean BEC for the total population of drivers (n = 600) was 1.43 ± 0.98 g/L (sd), a mean concentration and standard deviation almost indentical to those reported for the first year of the study [*4,48*]. When the BECs in all speci-

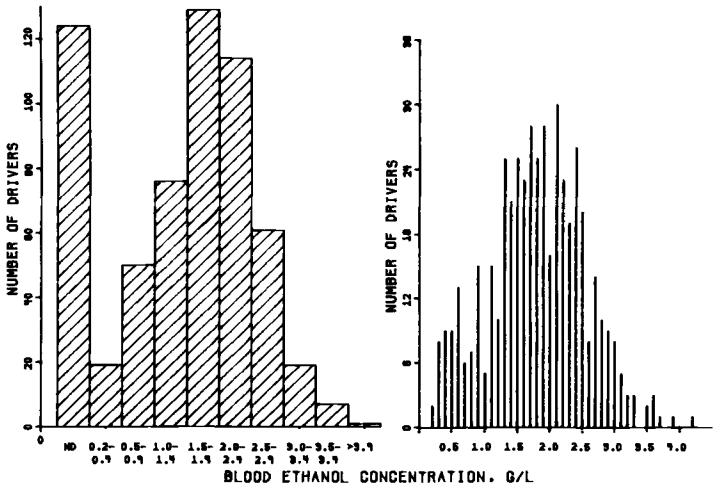

FIG. 2—*Distribution of blood ethanol concentrations in 600 drivers.*

mens that contained ethanol ($n = 476$) were classified using 0.5-g/L increments, the resulting distribution (Fig. 2) was not significantly different from the normal distribution ($P < 0.50$). The mean BEC among these drivers was 1.81 ± 0.74 g/L (sd), a concentration likely to impair the performance of a vast majority of the driving public.

The large number of drivers with high blood ethanol concentrations found in this study illustrates the serious negative impact that ethanol use has on highway safety. Turk et al [*65*] reported that 41 of 72 (56.9%) drivers killed in single-vehicle crashes had BECs greater than or equal to 1.0 g/L, and that 41 of the 50 (82.0%) blood specimens containing ethanol had BECs greater than or equal to 1.0 g/L. The mean BEC in drivers who had used ethanol was 1.79 g/L. Garriott et al [*66*] reported that the 78 blood specimens taken from dead drivers who had ingested ethanol had a mean BEC of 2.07 g/L. They did not report the number of these specimens that had BECs greater than or equal to 1.0 g/L. Cimbura et al [*46*] reported that the mean BEC in the drivers in their study was 1.63 g/L, and that 196 of these 401 drivers (48.9%) had BECs greater than 0.8 g/L. The incidence of operators who died in single-vehicle crashes in North Carolina between 1970 and 1982, and who had BECs greater than 0.9 g/L is presented in Table 5. The incidence ranged from a minimum of 51.1% in 1978 to a maximum of 64.4% in 1970. The mean incidence was 58.0 ± 4.5% (sd). The upper 95% confidence limit for the mean, determined using the sample variance, is 60.7%, an incidence rate less than that reported in our study. During the majority of the specimen collection period (1979 to 1981), the average incidence rate was 61.5 ± 0.6% (sd), a rate close to the upper 95% confidence limit for the average for the last 13 years. However, the incidence rate for drivers with BECs greater than 0.9 g/L determined here (67.8%) is still considerably higher.

The increase in the incidence of drivers with high ethanol concentrations may be attributed to the use of stringent case selection methods, and is probably not due to an actual increase in either the number of ethanol consumers or the amount of ethanol ingested, or both. The yearly incidence figures were collected solely from information supplied with the toxicology request forms submitted with the specimens. By examining the medical examiners' records as a part of this study, it was determined that the yearly incidence figures contain some cases in which the victims died of natural causes; lived longer than 1 h after the crash; received vigorous medical treatments such as transfusions; or possibly were involved

TABLE 5—*Single vehicle operator fatalities in North Carolina (1970-1982) classified by ethanol concentrations.*[a]

BEC,[b] g/L	1970	1971	1972	1973	1974
N.D.	53 (24.2)	88 (29.0)	134 (33.8)	121 (36.8)	88 (30.1)
0.2-0.9	25 (11.4)	29 (9.6)	44 (11.1)	36 (10.9)	25 (8.6)
≥1.0	141 (64.4)	186 (61.4)	218 (55.1)	172 (52.3)	179 (61.3)
Total	219	303	396	329	292
	1975	1976	1977	1978	1979
N.D.	104 (36.1)	107 (36.8)	123 (38.3)	120 (38.3)	86 (26.4)
0.2-0.9	25 (8.7)	24 (8.2)	29 (9.0)	33 (10.5)	41 (12.6)
≥1.0	159 (55.2)	160 (55.0)	169 (52.6)	160 (51.1)	199 (61.0)
Total	288	291	321	313	326
	1980	1981	1982	1970-1982	
N.D.	91 (27.6)	86 (24.4)	78 (27.8)	1279 (31.7)	
0.2-0.9	37 (11.2)	47 (13.4)	30 (10.7)	425 (10.5)	
≥1.0	202 (61.2)	219 (62.2)	173 (61.6)	2337 (57.8)	
Total	330	352	281	4041	

[a]Percentages in parentheses.
[b]BEC = blood ethanol concentration and N.D. = none detected.

as pedestrians, passengers, operators in multiple vehicle crashes, or operators of motorcycles or farm vehicles. All of these factors should reduce the incidence of operators with high ethanol or drug concentrations. Unless each case in a study of this nature is carefully examined to insure valid inclusion in the study group, the predicted incidence of ethanol or drug use will probably be less than the actual value.

The mean BEC in all drivers who had used drugs ($n = 83$) was 1.29 ± 0.96 g/L (sd). The mean BEC in drivers who had used both drugs and ethanol ($n = 66$) was 1.63 ± 0.79 g/L (sd), a BEC not significantly different than that determined for all drivers with ethanol ($P < 0.97$). BECs in drug users were distributed in a manner similar to that noted in the entire study population (Table 2).

Cannabinoids

THC was detected at concentrations greater than 3.0 μg/L in 47 (7.8%) blood specimens. Forty-four of these specimens contained detectable concentrations of 9-carboxy-THC. The THC and 9-carboxy-THC concentrations detected in these specimens as well as the EMIT test results from 24 THC positive specimens detected during the third year of the study are presented in Table 6.

The 47 drivers who had used *Cannabis* products did not differ from the entire study population with regard to either their sexual distribution or any aspect of ethanol use. However, *Cannabis* users were generally younger and had a much greater incidence of multiple drug use than other drivers (Table 7). Marijuana and ethanol use were not related in the study population ($P < 0.10$). The mean BEC in drivers who had THC blood concentrations greater than 3.0 μg/L ($n = 47$) was 1.47 ± 0.94 g/L (sd), a mean and variance almost exactly the same as that determined for all 600 drivers. The mean BEC in drivers who had used *Cannabis* and ethanol ($n = 41$) was 1.69 ± 0.80 g/L (sd), a concentration not significantly different from that determined for all drivers who had ingested ethanol in the study population ($P < 0.97$). The mean, median, and mode ages of drivers who had used *Cannabis* were 26.5 ± 11.70 (sd) years, 23 years, and 18 years, respectively. All three are lower than the ages determined in all drivers. A cross-classification of all drivers with respect to the presence or absence of THC and age less than or greater than the population mean (31.2 years) showed that age and THC use were related ($P < 0.05$). Among THC positive drivers, the proportion younger than the mean age of the study population (37 of 47, 78.7%) is significantly greater than that noted among all drivers ($P < 0.02$). Finally, in six of the nine cases where two or more drugs were used, either with or without ethanol, one of the drugs detected was THC. The incidence of multiple drug use in the THC positive sample population (6 of 47, 12.7%) is significantly greater than the incidence rate for multiple drug use in the study population ($P < 0.02$).

Major analytical and physiological factors that affected the cannabinoid determinations included the inevitable variability in the analytical results caused by the precision of the determinations, the relative specificities of the antisera used in the three immunoassay techniques, the route of drug administration and its effects on the distribution and disposition of THC and its metabolites, and the degree of hemolysis of the specimen.

The RIA for THC has been reported to be a specific and quantitative method for the determination of THC in plasma and hemolyzed blood [*52*]. The relative reactivity of the antiserum used in this method is primarily dependent on changes in antigenic structure occurring in the cyclohexene ring of the tetrahydrocannabinol nucleus. The antiserum does not cross-react with 9-carboxy-THC, and the relative cross-reactivity of 11-hydroxy-THC is only 18% of that of THC [*52*]. This does not affect THC determinations unless THC is orally administered. In that case, THC plasma concentrations are much lower, and 11-hydroxy-THC concentrations may be as great as THC plasma concentrations [*67*], while they were found to be only 5 to 10% of peak THC concentrations after marijuana smoking [*10*]. Therefore, after oral administration of THC, the RIA method detects both THC and its equipotent

TABLE 6—*THC and 9-carboxy-THC concentrations and EMIT responses in 47 blood specimens.*

No.	A/S[a]	BEC,[b] g/L	THC, μg/L	9-COOH-THC,[c] μg/L	EMIT[d] Response	Other Drugs and Notes
1	38 M	2.7	3.1	5.8	−	...
2	36 M	2.1	3.1	10	−	...
3	36 M	1.3	3.5	0	...	phencyclidine positive
4	32 M	1.4	3.5	0	...	...
5	56 F	N.D.	3.5	6.5	−	phenobarbital 39 mg/L, phenytoin 11 mg/L
6	71 F	N.D.	3.5	6.8	−	...
7	22 M	0.7	3.5	53	+	...
8	18 F	1.1	3.6	38	+	...
9	19 M	0.9	3.6	58	+	...
10	46 M	N.D.	3.7	0	...	...
11	22 M	0.7	3.8	59	+	phenobarbital 5 mg/L, methaqualone 1.7 mg/L
12	23 M	2.1	3.9	16	...	...
13	18 M	3.0	3.9	17	...	...
14	37 M	3.5	3.9	18	−	...
15	21 M	2.8	4.1	30	+/−	...
16	19 M	N.D.	4.4	12	...	marijuana found in vehicle
17	21 M	1.4	4.4	61	+	...
18	22 M	1.7	4.7	10	...	marijuana found in vehicle
19	18 M	1.6	4.7	45	...	...
20	22 M	0.9	5.0	45	...	...
21	25 M	0.7	5.3	3.1	...	...
22	24 M	N.D.	5.3	18	...	...
23	16 M	2.2	5.3	76	+	...
24	25 M	0.7	5.4	30	+/−	methaqualone 1.1 mg/L
25	23 M	1.0	5.5	54	+	...
26	27 M	1.7	5.7	71	...	...
27	24 M	1.2	5.9	36	...	...
28	61 M	2.9	6.1	6.5	...	...
29	27 M	2.4	6.2	2.6	...	...
30	23 F	2.9	6.3	114	+	...
31	19 M	0.7	6.4	76	+	...
32	25 M	1.2	6.5	8.3	...	...
33	21 M	1.3	6.6	79	+	...
34	18 M	1.7	7.2	30	...	...
35	20 M	2.1	7.4	75	...	...
36	18 F	2.3	9.0	1.8	...	...
37	21 M	2.3	9.8	27	+	...
38	24 M	1.1	13	18	...	...
39	21 M	1.6	13	56	+	marijuana found in vehicle
40	22 M	2.2	13	116	+	...
41	30 M	0.2	17	25	...	...
42	16 M	0.8	18	123	+	...
43	26 M	2.2	23	8.4	...	...
44	18 M	2.2	23	93	+	marijuana cigarette butt in gastric contents
45	24 M	1.1	32	157	...	...
46	18 M	N.D.	33	72	+	methaqualone 4.0 mg/L
47	32 M	2.7	37	3.2	+/−	phencyclidine positive

[a]Age/sex.
[b]BEC = blood ethanol concentration and N.D. = none detected.
[c]9-carboxy-THC.
[d]EMIT response for blood specimens from third-study year (n = 260). See Table 9, p. 1009.

TABLE 7—*Statistical comparisons of population characteristics, marijuana users.*

No.	Test Char. n (%)	Test Pop. n	versus	Test Char. n (%)	Ref Pop. n	$P^{<a}$
1	females 5 (10.6)	THC 47		females 80 (13.3)	A.D.[b]	0.54
2	no EtOH 6 (12.8)	THC 47		no EtOH 124 (20.7)	A.D.	0.10
3	EtOH 41 (87.2)	THC 47		EtOH 476 (79.3)	A.D.	0.10
4	BEC 0.2-0.9[c] 9 (19.1)	THC 47		BEC 0.2-0.9 69 (11.5)	A.D.	0.18
5	BEC ≥ 1.0 32 (68.1)	THC 47		BEC ≥ 1.0 407 (67.8)	A.D.	0.97
6	BEC ≥ 1.0 32 (78.0)	THC+EtOH 41		BEC ≥ 1.0 407 (85.5)	EtOH 476	0.25
7	age < 31.2 yrs.[d] 37 (78.7)	THC 47		age < 31.2 yrs. 388 (64.7)	A.D.	0.02
8	mult. drug use[e] 6 (12.7)	THC 47		mult. drug use 9 (1.5)	A.D.	0.02

[a] $P < 0.05$ significance.
[b] All drivers, ($n = 600$).
[c] Blood ethanol concentration, g/L.
[d] Mean age of all drivers.
[e] Two or more drugs, ethanol discounted.

psychoactive metabolite, but the determined concentration will be less than the sum of the 11-hydroxy-THC and THC concentrations. However, THC is administered by smoking far more often than by the oral route. Finally, both THC [*52*] and 9-carboxy-THC[4] are detected in plasma at concentrations roughly double those determined in hemolyzed blood. For THC, this phenomenon has been attributed to be the result of its high lipophilicity and its extensive partitioning into plasma lipoproteins [*68,69*]. The very large majority of the specimens containing THC were blood specimens that were completely hemolyzed. Only small amounts of suspended materials were removed by centrifugation.

The RIA method for 9-carboxy-THC has also been reported to be a specific quantitative technique [*53,54*]. This assay probably does not detect the glucuronide ester conjugate of 9-carboxy-THC because this important urinary metabolite [*70*] has not yet been isolated from plasma or blood, because no hydrolysis step was included in the extraction, and because the relative affinity of the antibody-antigen interaction is strongly dependent on the antigenic structure at the 11-carbon [*53,54*]. The large steric bulk of the glucuronide moeity probably makes significant cross reaction unlikely. Other metabolites that could interfere with this assay have been isolated, but their capacities to do so are at present unknown. Polar acid metabolites, acidic metabolites of intermediate polarity, and conjugated metabolites have been detected in plasma [*10*], but their structures have not been determined. Compounds similar to 9-carboxy-THC that contain either hydroxylated side chains or shortened alkylcarboxy side chains have been isolated from human urine [*71,72*], but not from blood or plasma. If they are present in human blood or plasma, then they probably would cross-react to a significant, but at present unknown degree.

The EMIT-DAU cannabinoid assay [*55*] is a semiquantitative technique [*58*] designed to detect cannabinoids in urine. As such, its antibody cross-reacts with a wide variety of THC metabolites [*55*] including 9-carboxy-THC, its glucuronide [*73*], and to a lesser extent the

[4] C. E. Cook, Vice-President of Chemistry and Life Sciences Division, Research Triangle Institute, Research Triangle Park, NC, personal communication, 1983.

11- or 8-hydroxy and 8,11-dihydroxy metabolites. The method is potentially cross-reactive to the dicarboxylic acids and 9-carboxy-THC metabolites with hydroxylated alkyl side chains detected in urine [*71, 72*]. Because of the semiquantitative and cross-reactive nature of the EMIT assay, its use is usually limited to situations where only the presence or absence of cannabinoids is to be determined, such as during drug screening.

All of these three methods, being immunoassays, are presumptive tests. As such, their results are, at best, mutually supportive or corroborative, but not mutually confirmatory. Ideally, the results from the THC and 9-carboxy-THC assays should be independently confirmed using alternative nonimmunological techniques. These confirmatory analyses were not performed primarily because these methods were not available in our laboratory. It should be stressed that results from this study were not used in any adversarial proceedings where the use of appropriate confirmatory techniques is mandatory [*74*].

The THC concentrations in Table 6 are distributed in a manner that appears to be nonnormal. The distribution is heavily and positively skewed towards lower concentration values. This skewing may have been exacerbated by the imposition of the cutoff concentration at 3.0 μg/L of THC. The THC concentrations range from 3.1 to 37 μg/L. The mean THC concentration was 8.70 ± 8.25 μg/L (sd), and the median concentration was 5.4 μg/L. Nineteen (40.8%) of the specimens contained THC at concentrations less than 5.0 μg/L. Thirty-seven (78.7%) of the specimens contained THC at concentrations less than 10 μg/L. Therefore, most of the THC concentrations determined were relatively low. For the 47 specimens, the deviation of an analytical result from its respective mean between the two THC determinations ranged from ±0 to ±3.0 μg/L. The mean deviation was ±0.42 ± 0.53 μg/L (sd). If the deviations are normalized as a percentage of the mean concentrations, then the deviation ranged from ±0 to ±19% of the determined THC concentrations, and the mean deviation was ±5.22 ±4.14% (sd) of the determined concentrations.

The 9-carboxy-THC concentrations presented in Table 6 appear to be distributed in a nonnormal platykurtic manner, and are generally much higher than the THC concentrations, ranging from 0 to 157 μg/L. Many of the 9-carboxy-THC concentrations detected are far higher than those reported in a recent study [*8*] where subjects smoked moderate doses of marijuana, and the blood specimens were analyzed by the same method. The mean 9-carboxy-THC concentration was 39.8 ± 38.0 μg/L (sd). The median 9-carboxy-TCH concentration was 30 μg/L. Precision and recovery of 9-carboxy-THC from control hemolyzed blood specimens were determined during the third year of the study, and the results are presented in Table 8. Precision and accuracy were considered to be acceptable given the nature of the study. The recovery results from the analysis of the specimens containing no 9-carboxy-THC were all less than the stated sensitivity of the method. Four standard curves, each comprised of six 9-carboxy-THC concentrations between 2 and 100 μg/L, were determined to have correlation coefficients r between 0.991 and 0.999. During the second year of the study, eight hemolyzed blood specimens from subjects older than 60 years were selected from the general study population. These subjects had no noted history of *Cannabis* use and

TABLE 8—*Precision and recovery of 9-carboxy-THC determinations in control blood specimens.*

9-COOH-THC,[a] μg/L	0.0	8.0	30.0	80.0
x,[b] (n = 4), μg/L	0.87	6.87	34.8	92.7
sd,[c] μg/L	0.70	0.92	5.45	5.80
cv,[d] %	79.9	13.4	15.6	6.26
Recovery, %	...	85.9	116.2	115.9

[a]Concentration added, 9-carboxy-THC.
[b]Mean concentration detected.
[c]Standard deviation.
[d]Coefficient of variation, (sd/x)·100.

their THC blood concentrations were all determined to be 0.0 μg/L. 9-Carboxy-THC concentrations in seven of these specimens were determined to be 0.0 μg/L. The last specimen contained 1.1-μg/L 9-carboxy-THC, a concentration below the cutoff for the assay. Similar results were reported following the first year of the study [*48*]. Twenty-two THC negative blood specimens were determined to contain no detectable concentrations of 9-carboxy-THC [*48*].

Three of the 47 blood specimens contained low concentrations of THC (3.5, 3.5, and 3.7 μg/L) and contained no detectable concentrations of 9-carboxy-THC. While it is possible that these findings represent false positive results for THC, it is not highly probable that this occurred. The concentrations detected are far above the statistical sensitivity limit for the assay, and positive results were obtained in duplicate on three separate occasions. Similarly, the apparent absence of 9-carboxy-THC in these three specimens could be construed as resulting from false negative findings. More likely, 9-carboxy-THC was present in these specimens, but was present at concentrations below the sensitivity limit for the assay.

No direct data were available for any of the 47 drivers concerning the dose of THC ingested, the route by which it was administered, or the elapsed time between the administration of the dose and the death of the driver. Therefore, interpretations of the potentially adverse effects experienced by these drivers must be based solely on the results from the analyses of single blood specimens with varying degrees of hemolysis and on the temporal correlation between THC plasma concentrations and impairment of driving skills, an uncharacterized relationship. The relationship between THC concentrations and subjective self-reported effects has been fully characterized, but as previously noted, the temporal correlation between these two variables is not strong. Therefore, at present, performance impairment must be interpreted from THC concentrations using the only correlation available, that between concentrations and subjective effects. One must assume that subjective effects and objectively measured performance impairment produced by marijuana use exhibit significant temporal correlation.

The relative utility and value of imposing an assumption of this type on the concentration-effects interpretation can be increased if an important restriction is also imposed; that the interpretation be used to determine only those drivers who could possibly have been most adversely affected by the use of marijuana. This restriction would strengthen the concentration-subjective effects and concentration-impairment correlations by eliminating from consideration those drivers with low THC plasma concentrations who should experience only slight and declining effects. Furthermore, the interpretation of effects from THC concentrations should also be restricted to determining which drivers could possibly have been the most affected by marijuana alone, in the absence of significant effects caused by the use of ethanol or other drugs. It is evident that compared to the effects of ethanol, the effects caused by marijuana use are far more subtle and far less profound. Additional marijuana-induced impairment in a driver who is already grossly impaired by ethanol would be of little additional importance. However, some drivers with low blood ethanol concentrations may have experienced some additional effects from marijuana use.

A recent study of subjective self-reported psychological effects and plasma concentrations of THC after smoking moderate doses of THC in marijuana cigarettes showed that 2 h after smoking began, the average value for the subjective effects reported by the subjects were roughly 40, 25, and 50% of their respective peaks for the three doses administered [*8*]. Therefore, after 2 h, the average subjective effects had declined to between one quarter and one half of peak values. The greatest effects, as well as the large majority of the effects, were experienced before that time. At 2 h, average THC plasma concentrations were between 7.0 and 9.6 μg/L. Blood concentrations would probably have ranged from roughly 3.5 to 5.0 μg/L. Therefore, a conservative limit for the imposition of a significant degree of marijuana-induced effects during forensic science interpretation of THC concentrations could be set at 5 μg/L in blood or 10 μg/L in plasma. A more conservative limit could be set at double these

THC concentrations; 10 μg/L in blood or 20 μg/L in plasma. One complicating factor in this model is the issue of tolerance. There is no available data on chronic smokers using high doses of THC, the potentially very high residual blood concentrations of THC and 9-carboxy-THC that result, or the magnitude of the effects that may have resulted. Based on present data, it is impossible to estimate the extent of tolerance effects based on cannabinoid blood concentrations.

Seven of the forty-seven drivers with THC blood concentrations greater than 2.9 μg/L had BECs less than or equal to 0.2 g/L, and should not have been influenced by their ethanol use. Four of these blood specimens contained THC at concentrations less than 5.0 μg/L, concentrations too low to predict with acceptable certainty that these drivers experienced any adverse effects. The other three specimens (Table 6, Nos. 22, 41, and 46) contained THC at 5.3, 17, and 33 μg/L, respectively. Because one of these drivers' bloods also contained a rather high concentration of methaqualone, there is a maximum of two, and probably only one driver (Table 6, No. 41) who could have possibly experienced significant adverse effects because of the use of marijuana in the absence of significant concentrations of ethanol or other drugs. There are eight cases where the driver's blood ethanol concentration ranged from 0.7 to 0.9 g/L. These drivers' behaviors were probably at least influenced by ethanol use. Of these, five drivers (Table 6, Nos. 20, 21, 24, 31, and 42) had THC blood concentrations greater than or equal to 5.0 μg/L, and may have experienced some additional degree of impairment because of marijuana use. Only one of these drivers (Table 6, No. 42) had a THC blood concentration high enough (18 μg/L) to indicate that the driver definitely should have experienced some subjective effects. There are 32 cases where the driver's BEC was greater than or equal to 1.0 g/L, and all of these drivers were probably impaired by their use of ethanol. Only 20 of these drivers had THC blood concentrations above 5.0 μg/L and only 7 had THC blood concentrations above 10.0 μg/L. Therefore, at most 20, but at least 7 of these drivers could have been impaired by ethanol and could have experienced some additional adverse effects from marijuana use.

In summary, of the 47 drivers (7.8% of 600) who had THC blood concentrations greater than 2.9 μg/L, there were at least 9 (1.5%), but no more than 28 (4.7%), drivers who could have experienced significant adverse effects, either with or without the additional effects of ethanol or other drugs, because of marijuana use (Table 6; 9 cases, Nos. 38–45 and 47: 28 cases, Nos. 20–47). Probably only one driver experienced significant adverse effects from marijuana in the absence of significant concentrations of ethanol or other drugs.

While the THC concentrations detected in this study are greater than the concentrations detected in other studies of fatally injured drivers [*43,46*], the incidence of THC detection is not remarkable by comparison. Is this incidence rate significant, or are users of *Cannabis* products overrepresented in this at-risk population of drivers? This question can not be definitely answered. The incidence rate for *Cannabis* use in all drivers on the highways of North Carolina during the case collection period is unknown. However, the incidence rate determined in the at-risk population was low, and the number of persons potentially affected by marijuana use was even lower. These rates are especially low when compared with the respective rate for ethanol use, and the incidence of drivers impaired by ethanol.

By examining the toxicology request forms and medical examiners' reports, it was determined that of the 600 accepted cases, there were 9 cases where marijuana was found either in the possession of the driver, or in the vehicle that crashed. In one case, a partially burned marijuana cigarette was found in the driver's gastric contents. In one other case, a "strong odor of marijuana smoke" was reported to be in the vehicle after the crash. Of these eleven cases, THC was detected at 3.0 μg/L or greater in only four (36%). In the case where the odor of marijuana smoke was reported, THC was not detected. These results are similar to results reported by Lundberg et al [*75*]. In a study of 736 impaired drivers, it was reported that the ability to predict correctly which drug a subject had taken was about 50%, based upon the drugs that were in the driver's possession [*75*]. In three other cases, analyses for

THC or "marijuana" were specifically requested when there was no stated history that the subject had used a *Cannabis* product. THC was not detected in these three drivers' bloods.

In some cases, the relative concentrations of THC and 9-carboxy-THC contained in these specimens may be used to facilitate the interpretation of effects experienced by these drivers by providing crude estimates for the time elapsed since the last dose of THC was administered. Using general concentration-time patterns for THC and 9-carboxy-THC [*8*], it can be surmised that those drivers with high THC concentrations where 9-carboxy-THC concentrations are comparatively low (Table 6, Nos. 43 and 46) probably died within roughly 15 min after smoking. Effects in these drivers were increasing at the times of their deaths. Those drivers whose THC and 9-carboxy-THC blood concentrations were roughly equivalent (Table 6, Nos. 4 and 38) died roughly 30 min after smoking, and experienced near peak effects at the times of their deaths. Finally, there were many cases where 9-carboxy-THC concentrations were much higher than THC concentrations and where 9-carboxy-THC concentrations were quite high. These drivers probably smoked marijuana within the last few hours before they died, smoked marijuana chronically, or both. Effects experienced by these drivers may have ranged from negligible to significant.

The automated EMIT assay for cannabinoids in hemolyzed blood was faster and easier to perform than the manual EMIT method. Duplicate EMIT response rate determinations were precise. Hemolyzed blood specimens containing 9-carboxy-THC at either 0, 20, or 75-μg/L were analyzed 27 times in duplicate during a 5-day period. The mean differences between duplicate response rates (expressed in milliabsorbance units, mA) were 3.0 $\pm$ 3.1 mA (sd), 2.7 $\pm$ 2.6 mA (sd), and 5.0 $\pm$ 4.3 mA (sd), respectively, for the three calibrators. Between-day precision of the 27 mean EMIT response rate determinations was quite good. Mean EMIT response rates for the 27 determinations were 379.8 $\pm$ 10.2 mA (sd), 402.9 $\pm$ 9.6 mA (sd), and 444.1 $\pm$ 8.4 mA (sd), respectively, for the determinations at the three 9-carboxy-THC calibrator concentrations.

All 260 specimens accepted for study during the third year were analyzed using the EMIT method. Besides the 24 specimens that contained THC at concentrations greater than 2.9 μg/L, there were only 13 other specimens that either demonstrated EMIT reactivity significantly greater than that of cannabinoid-free hemolyzed blood or contained detectable concentrations of THC. THC and 9-carboxy-THC concentrations and EMIT results for these 13 specimens are presented in Table 9. These specimens were not included in the incidence study because all of their THC concentrations were less than 3.0 μg/L. Given the relatively high concentrations of 9-carboxy-THC and the very low concentrations of THC contained in these specimens, it is most probable that none of these drivers had smoked marijuana within the last several hours before their deaths. The THC and 9-carboxy-THC concentrations detected in these drivers might be representative of the residual cannabinoid concentrations produced in chronic marijuana users. Although the THC concentrations in some of these specimens are low enough, their high 9-carboxy-THC concentrations preclude the possibility that any of these specimens were obtained from drivers who had been passively exposed to marijuana smoke [*15,16*], and who had not actively smoked marijuana.

The EMIT response rates for the 37 cannabinoid containing blood specimens (Tables 6 and 9) collected during the third year of the study were far more dependent on 9-carboxy-THC concentrations (Fig. 3) than they were on THC concentrations (Fig. 4). This should be expected given the three- to four-fold increase in reactivity of the EMIT assay for the carboxylic acid metabolite versus that of the parent compound [*55,56,58,73*]. Correction of the 9-carboxy-THC concentrations by addition of the THC concentration multiplied by an appropriate factor (0.3 [*73*]) derived from the relative cross-reactivity of THC did not strengthen the concentration-response relationship to any large degree. In Fig. 3, only eight of the data points would have been altered by an apparent increase in 9-carboxy-THC concentration of more than 2.0 μg/L. However, THC and 9-carboxy-THC probably comprise only a fraction of the EMIT reactive cannabinoids in any blood specimen. Much better correlation would be

TABLE 9—*THC and 9-carboxy-THC concentrations and EMIT responses in 13 third-year blood specimens not included in incidence study.*

No.	A/S[a]	BEC,[b] g/L	THC, μg/L	9-COOH-THC,[c] μg/L	EMIT[d] Response	Other Drugs and Notes
1	24 M	N.D.	0.0	18	+/−	butalbital 6.0 mg/L
2	24 M	2.3	0.0	24	+/−	...
3	19 M	1.2	0.1	25	+	...
4	27 M	1.9	0.1	27	+	...
5	19 M	2.2	0.3	29	+/−	...
6	18 F	1.0	0.4	48	+	methaqualone 9.0 mg/L
7	19 M	2.1	0.7	23	+/−	...
8	27 M	1.7	0.8	29	+/−	...
9	17 M	0.3	0.9	37	+/−	methaqualone 2.0 mg/L
10	19 M	2.3	1.5	49	+	...
11	22 M	1.3	1.8	101	+	...
12	30 M	1.7	2.1	61	+	...
13	23 M	0.9	2.3	41	+	...

[a]Age/sex.
[b]BEC = blood ethanol concentration and N.D. = none detected.
[c]9-Carboxy-THC.
[d]EMIT responses.

+ = Specimen EMIT response greater than that of 20-μg/L 9-carboxy-THC blood calibrator.
+/− = Specimen EMIT response less than that of 20-μg/L 9-carboxy-THC blood calibrator, but greater than that of negative blood calibrator.
− = Specimen EMIT response equivalent to that of negative blood calibrator.

expected if both the concentrations and relative reactivities of these other species were accounted for.

Of the 260 blood specimens that were tested using the EMIT assay, 23 (8.8%) exhibited response rates greater than that of the 20-μg/L 9-carboxy-THC calibrator. All of these specimens contained 9-carboxy-THC at concentrations greater than or equal to 25 μg/L. Therefore, there were no false-positive EMIT results. Positive results in the EMIT assay are produced with 95% confidence at 50-μg/L 9-carboxy-THC [*56, 58, 73*]. Even with the dilution introduced during the methanolic protein precipitation-extraction, all 21 specimens contain-

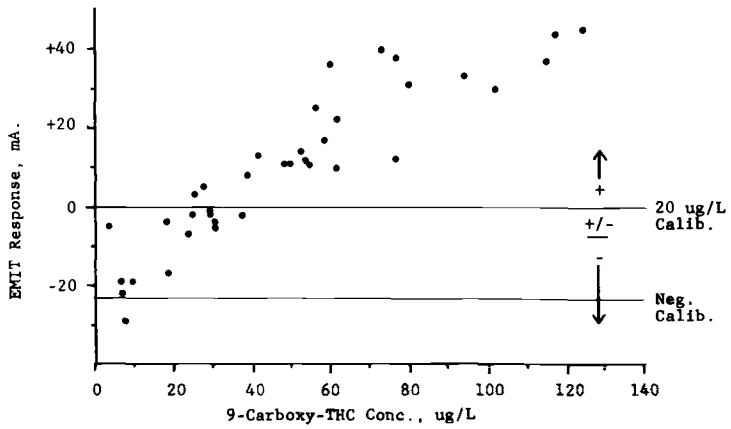

FIG. 3—*EMIT responses and 9-carboxy-THC concentrations in 37 third-year blood specimens.*

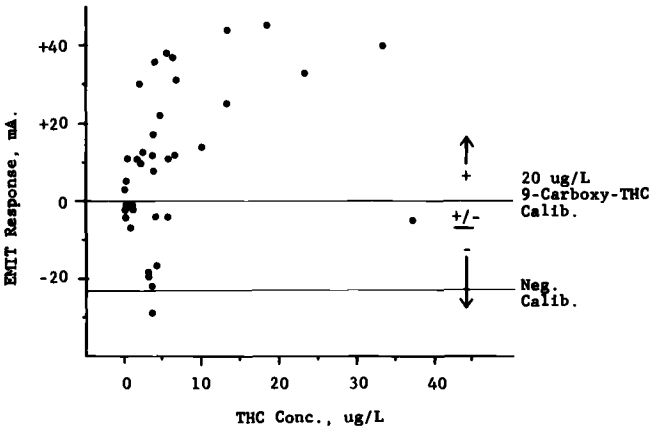

FIG. 4—*EMIT responses and THC concentrations in 37 third-year blood specimens.*

ing 9-carboxy-THC at concentrations equal to or greater than 38 μg/L were positive in the EMIT assay. A proper sensitivity determination would entail repetitive determinations of EMIT reactivity in spiked blood specimens. However, it appears that the sensitivity of the EMIT assay, when applied to the detection of cannabinoids in hemolyzed blood, may be as low as 38-μg/L 9-carboxy-THC (with appropriate other reactive cannabinoids including 3.6-μg/L THC) because all specimens containing greater concentrations of 9-carboxy-THC were positive.

Of the 260 specimens, 237 (91.2%) were not positive in the EMIT assay. Of the 260 specimens, 223 (85.8%) were determined to be nonreactive using the EMIT assay, and contained no detectable concentrations of THC. Nine specimens exhibited significant EMIT reactivity, but not EMIT reactivity greater than that of the 20-μg/L 9-carboxy-THC calibrator. These specimens contained 3.2, 18, 23, 24, 29, 29, 30, 30, and 37 μg/L of 9-carboxy-THC. Seven of these specimens contained more than 20 μg/L of 9-carboxy-THC. Therefore, 7 of the 30 specimens (23.3%) that contained more than 20 μg/L of 9-carboxy-THC exhibited EMIT response rates less than the rate determined for the 20-μg/L 9-carboxy-THC calibrator, and as such, were falsely negative. The surprisingly high EMIT reactivity of the specimen containing only 3.2 μg/L of 9-carboxy-THC was probably produced by its relatively high THC concentration. Finally, five other specimens exhibited EMIT reactivity not significantly different from that of the negative blood calibrator. All of these specimens contained less than 20 μg/L of 9-carboxy-THC and low THC concentrations (Table 6, Nos. 1, 2, 5, 6, and 14).

Because THC and 9-carboxy-THC concentrations in blood specimens are not unrelated, it would be interesting to determine if the EMIT assay can be used to detect specimens with relevant THC concentrations (greater than or equal to 3.0 μg/L). Of the 23 specimens that were positive in the EMIT assay, 16 (69.6%) contained more than 3.0 μg/L of THC, while the other 7 (30.4%) contained THC at concentrations below the cutoff. Therefore, roughly 70% of the EMIT positive specimens would also have been reported as being positive for THC. Of the 237 specimens that were not EMIT positive, only 8 (3.4%) were reported as being positive for THC. These specimens contained 3.1, 3.1, 3.5, 3.9, 4.1, 5.4, and 37 μg/L of THC. According to the above discussion, only the last two of these concentrations could possibly have been associated with significant adverse effects on performance. The other 229 specimens, 96.6% of the 237 specimens not positive by the EMIT test, were reported to be negative for THC. Therefore, the EMIT test could have been used to screen out or exclude THC negative specimens. This would have reduced the size of the specimen population by about 90%. At the same time, only a small number of THC positive specimens would have

been excluded from further analyses. Most of the excluded THC positive specimens would not contain THC at concentrations that could possibly be associated with significant adverse effects. Of those specimens retained, roughly 70% would later be reported positive for THC. Furthermore, the few specimens excluded that had high THC concentrations could have been retained if all specimens with EMIT reactivity significantly above that of the negative calibrator were retained. Following this procedure, the specimens containing 4.1, 5.4, and 37 μg/L of THC would not have been excluded. The reduction in the size of the sample population (228 of 260, 87.7% eliminated) would have been similar, and the proportion of specimens later reported positive for THC (19 of 32, 59.4%) would decrease only slightly. This strategy would help detect specimens obtained from subjects who have died almost immediately after smoking, when THC concentrations are high and 9-carboxy-THC concentrations are low (Table 6, No. 47).

Methaqualone

Methaqualone was quantitated in 16 specimens (6.2% of 260) accepted during the third study year. Pertinent data regarding these specimens are presented in Table 10. Users of methaqualone were significantly younger than drivers in the population accepted for study during the third year, and were exclusively male. Users of methaqualone were not significantly different from the third-year driver population with regard to the incidence of ethanol use, the distribution of ethanol concentrations, or the incidence of multiple drug use (Table 11). Drivers accepted for study during the third year did not differ significantly from drivers accepted for study during the first two years with regard to any tested parameter except for the proportion of drivers who were female (Table 11).

The distribution of ages of the drivers whose bloods contained methaqualone was skewed towards younger age groups. The mean, median, and mode ages for these drivers were 24.7 ± 9.2 years (sd), 22 to 23 years, and 18 years, respectively, while they were 31.6 ± 14.9 years (sd), 26 years, and 19 years for all drivers in the third-year population. The mean, median, and mode ages of the third-year population were equivalent to their respective counterparts from the entire three-year population; 31.2 ± 14.9 years (sd), 26 years, and 19 years. In the

TABLE 10—*Methaqualone concentrations in 16 third-year drivers classified by ethanol concentration.*

No.	A/S[a]	BEC,[b] g/L	Methaqualone, mg/L	Other Drugs and Notes
1	22 M	2.4	1.8[c]	...
2	22 M	2.3	0.2	...
3	54 M	2.1	0.2	...
4	23 M	1.9	0.1[c]	...
5	36 M	1.7	3.8[c]	...
6	27 M	1.7	1.9[c]	...
7	23 M	1.6	1.6	...
8	28 M	1.5	0.9	...
9	24 M	1.4	1.7[c]	...
10	18 M	1.0	0.9[c]	...
11	22 M	0.7	1.7[c]	phenobarbital 5.0 mg/L, THC 3.8 μg/L
12	25 M	0.7	1.1	THC 5.4 μg/L
13	17 M	0.3	2.0	...
14	18 M	N.D.	4.0	THC 33 μg/L
15	18 M	N.D.	3.0[c]	...
16	18 M	N.D.	0.5	...

[a]Age/sex.
[b]BEC = blood ethanol concentration and N.D. = none detected.
[c]Methaqualone concentration determined by RIA.

TABLE 11—*Statistical comparisons of population characteristics: methaqualone users versus third-year drivers and third-year drivers versus first- and second-year drivers.*

	Test Char.	Test Pop. versus	Test Char.	Ref. Pop.	
No.	*n* (%)	*n*	*n* (%)	*n*	$P<^a$
1	age < 31.2 yrs.[b]	methaq.	age < 31.2 yrs.	yr. 3	0.003
	14 (87.5)	16	164 (63.1)	260	
2	age < 31.2 yrs.	yr. 3	age < 31.2 yrs.	yrs. 1+2	0.35
	164 (63.1)	260	224 (65.9)	340	
3	females	yr. 3	females	yrs. 1+2	0.002
	26 (10.0)	260	54 (15.9)	340	
4	no EtOH	methaq.	no EtOH	yr. 3	0.90
	3 (18.7)	16	52 (20.0)	260	
5	no EtOH	yr. 3	no EtOH	yrs. 1+2	0.64
	52 (20.0)	260	72 (21.2)	340	
6	EtOH	methaq.	EtOH	yr. 3	0.90
	13 (81.3)	16	208 (80.0)	260	
7	EtOH	yr. 3	EtOH	yrs. 1+2	0.64
	208 (80.0)	260	268 (78.8)	340	
8	BEC 0.2-0.9[c]	methaq.	BEC 0.2-0.9	yr. 3	0.41
	3 (18.7)	16	28 (10.8)	260	
9	BEC 0.2-0.9	yr. 3	BEC 0.2-0.9	yrs. 1+2	0.50
	28 (10.8)	260	41 (12.1)	340	
10	BEC ≥ 1.0	methaq.	BEC ≥ 1.0	yr. 3	0.58
	10 (62.5)	16	180 (69.2)	260	
11	BEC ≥ 1.0	yr. 3	BEC ≥ 1.0	yrs. 1+2	0.39
	180 (69.2)	260	227 (66.8)	340	
12	BEC ≥ 1.0	methaq.+EtOH	BEC ≥ 1.0	EtOH yr. 3	0.41
	10 (76.9)	13	180 (86.5)	208	
13	BEC ≥ 1.0	EtOH yr. 3	BEC ≥ 1.0	EtOH yrs. 1+2	0.44
	180 (86.5)	208	227 (84.7)	268	

[a] $P < 0.05$ significance.
[b] Mean age of all drivers.
[c] Blood ethanol concentration, g/L.

third-year drivers, age less than the mean and the presence of methaqualone were related ($P < 0.05$). Methaqualone users were exclusively male. If the distribution of the sexes were equivalent between methaqualone users and all drivers accepted during Year 3, then at least one of the drivers in the methaqualone positive drivers should have been female. The proportion of third-year drivers who were female was significantly lower than the proportion of female drivers noted in the population accepted for study during the first two study years (Table 11).

Drivers studied during the third year were not differentiable from drivers accepted for study during the first two years with regard to any aspect of ethanol use (Table 11). The mean BEC determined in all third-year drivers ($n = 260$) was 1.46 ± 0.97 g/L (sd), and determined in all third-year drivers who had detectable BECs ($n = 208$), 1.83 ± 0.71 g/L (sd) were equivalent to the respective means determined in the entire three-year study population. Methaqualone users were not differientable from drivers accepted during the third year with regard to any aspect of ethanol use (Table 11). The mean BEC in the drivers who had ingested methaqualone ($n = 16$, 1.21 ± 0.83 g/L [sd]), and in drivers who had ingested ethanol and methaqualone ($n = 13$, 1.49 ± 0.64 g/L [sd]) were lower than the respective third-year means. However, the latter of these two means was not significantly lower than the mean BEC for drivers in this category who were accepted during the third year ($P < 0.88$). Three of the sixteen specimens containing methaqualone (18.7%) also contained at least one other drug besides ethanol. However, the incidence of multiple drug use determined in driv-

ers studied during the third year (6 of 260, 2.3%) increased over that noted for all drivers because of the addition of methaqualone to the analytical regimen. The incidence of multiple drug use in methaqualone positive drivers is not significantly greater than that determined in third-year drivers ($P < 0.10$).

The modified RIA method for methaqualone was determined to be accurate, precise, sensitive, and linear over the standard concentration range tested, but was not rigorously specific for methaqualone. Nonspecific binding represented 20% of total counts added, but was reproducible ($n = 4$, coefficient of variation [cv] = 3%). Corrected specific binding accounted for 67% ($n = 8$) of total counts added. Average recoveries of methaqualone from control hemolyzed blood specimens spiked at 1.25, 2.50, and 3.75 mg/L each run three times within a day were 103.2, 103.7, and 98.7%, respectively. The 95% confidence intervals around these mean recovered doses represented less than ±5.5% of the recovered dose in each of these three cases. The lowest dose of methaqualone used in the standard curve, 0.5 mg/L (50 pg added/tube) decreased the normalized binding to an average ($n = 2$) of 85% of that determined for four duplicate determinations of binding in methaqualone-free hemolyzed blood. Standard curves comprised of seven concentrations between 0.5 and 5.0 mg/L methaqualone exhibited excellent correlation coefficients $r = 0.995$, 0.999. Finally, both the gas chromatographic (GC) and modified RIA methods were used to determine the methaqualone concentrations in eight specimens where sufficient specimen volume was available. The GC results for these specimens are presented in Table 10. The RIA determined methaqualone concentrations were (Table 10, Nos. 2-4, 7, 8, 12-14, and 16) 0.08, 0.20, 2.09, 0.84, 2.08, 4.02, 8.65, and 0.83 mg/L. The linear regression line for this data, determined using the GC derived data as the independent variable, is represented by the equation $y = 2.24x - 0.61$, and has a correlation coefficient $r = 0.973$. Given the positive regression line slope greater than 1.0, it would seem that the RIA method provides results that are greater than the GC method. Most probably, the RIA method detects either hydroxylated or conjugated methaqualone metabolites [*76*] not detected by the GC method. During methaqualone screening, two specimens repeatedly gave responses greater than the 0.1-mg/L methaqualone calibrator, but could not be confirmed by the GC method. The presence of methaqualone metabolites might also account for these findings.

Methaqualone is a nonspecific, centrally acting, central nervous system (CNS) depressant, sedative hypnotic drug. Marked sedative effects are produced by single oral doses (200 to 400 mg) of methaqualone hydrochloride [*76*]. Other common effects or side effects of methaqualone use include loss of motor control and coordination, drowsiness, dizziness, fatigue, torpor, ataxia, and mydriasis [*77-79*]. These properties make the use of this drug by drivers especially hazardous. The potentiation of the effects of methaqualone by other CNS depressant drugs, especially ethanol, is well-known [*77-79*]. Peak therapeutic concentrations of methaqualone were noted to be less than 5 mg/L in blood following a single oral 300-mg dose [*80*]. Lower therapeutic concentrations, 4 mg/L in blood [*78*] or 1 to 2 mg/L in serum or plasma [*77*] have been cited. Concentrations of methaqualone in blood are lower than serum or plasma concentrations because methaqualone is extensively bound to plasma albumin [*81*], and sequestered in the plasma fraction. Concentrations producing either toxic symptoms or death may not be significantly greater than therapeutic concentrations. A compendium [*76*] cites studies where toxic symptoms were produced in 20 chronic drug users at blood concentrations between 2 and 16 mg/L, and lethal blood concentrations were determined to be between 2 and 230 mg/L. Fifty-nine patients admitted to an emergency room with depressed levels of consciousness had serum methaqualone concentrations between 1 and 12 mg/L [*77*]. The mean serum concentration was 5 ± 3 mg/L (sd).

The 16 methaqualone-positive cases detected in this study represented 6.2% of the third-year specimens. This incidence rate is greater than rates determined in other studies of fatally injured drivers. Garriott et al [*66*] reported that methaqualone was detected at low concentrations (0.4 and 0.7 mg/L) in 2 of 127 dead drivers. The latter of these two drivers

had a BEC of 0.8 g/L. Cimbura et al [*46*] reported only 1 case where methaqualone was detected in 401 fatally injured drivers. The blood concentration determined (3.0 mg/L) was high enough to presume that adverse effects were experienced by the driver. Wetli [*78*] reported methaqualone blood concentrations in 58 fatally injured drivers. These concentrations ranged from 1.4 to 16 mg/L, and the mean concentration was 6.5 mg/L. Roughly 76% of these drivers had BECs less than 1.0 g/L. The incidence rate was not reported.

Much more information concerning methaqualone concentrations and incidence rates in drivers is available from studies that have determined drug concentrations in drivers arrested for impaired driving [*75,79,82-84*]. Most of these studies have used drivers with BECs less than 1.0 g/L as their study populations. Garriott et al [*82*] reported that 30 of 135 drivers (22.2%) arrested for driving under the influence of drugs had detectable concentrations of methaqualone in their bloods. The concentrations ranged from 0.4 to 8.6 mg/L, and the mean concentration was 4.0 mg/L. Lundberg et al [*75*] reported that 64 of the 877 drivers' bloods tested contained methaqualone at concentrations up to 14 mg/L. The average methaqualone concentration in drivers whose bloods contained no ethanol ($n = 34$) was 4.77 mg/L. Valentour et al [*83*] reported that 17 of the 788 blood specimens tested (2.2%) contained methaqualone at concentrations between 0.15 and 7.3 mg/L. The median concentration was 2 mg/L [*83*]. White et al [*84*] reported that 482 of 8116 blood specimens tested (5.9%) contained methaqualone. Concentrations were not reported. Finally, McCurdy et al [*79*] reported methaqualone concentrations in 974 impaired drivers. The 536 drivers (55%) with no detectable BECs had a mean blood methaqualone concentration of 4.1 mg/L. Drivers with BECs less than 0.5 g/L ($n = 138$, 14%) had a mean methaqualone concentration of 3.6 mg/L. Drivers with BECs greater than 0.5 g/L but less than or equal to 1.0 g/L had a mean methaqualone concentration of 3.1 mg/L. Other authors have also noted this general trend towards either decreasing incidence or decreasing mean methaqualone blood concentrations in drivers with increasing BECs [*78,84*].

The methaqualone concentrations presented in Table 10 are generally lower than those reported by Welti [*78*] in fatally injured drivers, and lower than those concentrations reported by various authors [*75,82-84*] in impaired drivers. The mean blood concentration ($n = 16$) was 1.59 $\pm$ 1.20 mg/L (sd), and the median concentration was between 1.6 and 1.7 mg/L. The mean ($n = 8$) and median methaqualone concentrations determined by the GC method were 1.31 $\pm$ 1.26 mg/L (sd) and between 1.1 and 1.6 mg/L, respectively, while the mean and median methaqualone concentrations ($n = 8$) determined by the RIA method were 1.86 $\pm$ 1.14 mg/L (sd) and between 1.7 and 1.8 mg/L, respectively. These two mean concentrations are not significantly different ($P < 0.40$). Ten of the drivers had BECs greater than or equal to 1.0 g/L. All of these drivers were probably impaired by ethanol whether or not they experienced any potentiating affects because of their methaqualone concentrations. Of these ten drivers, five had methaqualone blood concentrations greater than 1.0 mg/L, and probably did experience some degree of potentiated effects. Methaqualone-induced potentiation of impairment is certainly possible in any of the other five drivers, especially in the two drivers who had blood methaqualone concentrations of 0.9 mg/L, but not highly probable in the three drivers with blood methaqualone concentrations less than 0.5 mg/L. Therefore, seven drivers were impaired by ethanol, but probably experienced additional effects because of methaqualone (Table 10, Nos. 1 and 5-10). The two drivers who had BECs equal to 0.7 g/L were at least influenced by ethanol, and probably experienced some increase in impairment because of their methaqualone concentrations. The effects produced by the additional drugs found in these two drivers (Table 10, Nos. 11 and 12) probably increased the impairment produced by ethanol and methaqualone. One driver had a low BEC and probably was not significantly affected by ethanol (Table 10, No. 13). However the methaqualone concentration in this driver is high enough to have significant adverse effects. Two of the three drivers with no ethanol (Table 10, Nos. 14 and 15) were probably impaired by methaqualone. One of these two drivers had a very high THC blood concentration. Addi-

tional impairment may have occurred for this reason. Methaqualone induced effects in the driver who had no ethanol and only 0.5-mg/L methaqualone in his blood probably were not significant.

Therefore, a maximum of 16 drivers, and a minimum of 12 drivers (Table 10, Nos. 1 and 5-15) experienced some degree of impairment from methaqualone, or experienced some additional effects in the presence of ethanol. Although a significant number of drivers were to some extent adversely affected by the use of methaqualone, only three drivers could have been adversely affected by methaqualone in the absence of significant concentrations of ethanol (Table 10, Nos. 13-15). However one of these three drivers had a very high THC blood concentration. A majority of the drivers were either affected by or impaired by ethanol. Compared to the incidence of drivers affected by ethanol, the incidence of drivers affected by methaqualone was very low.

Barbiturates

Six-hundred blood specimens were tested for barbiturates using the RIA screening method. In 21 cases, the test response of a specimen was greater than that of the 0.1-mg/L secobarbital calibrator. The presence of a barbiturate was confirmed and its identity and concentration determined in 18 specimens, or in 3% of all cases accepted for study. Presumably the other three cases were not confirmed either because of a disparity between the sensitivities of the screening and confirmatory methods, or because the immunoassay also detects barbiturate metabolites. The identities and concentrations of the barbiturates detected are presented in Table 12.

Drivers who had ingested barbiturates could not be differentiated from all drivers with regard to their sexual distribution. However barbiturate positive drivers were older, had lower BECs, and had a higher incidence of multiple drug use (Table 13). The hypothesis that

TABLE 12—*Barbiturate concentrations determined in 18 drivers classified by ethanol concentrations.*

No.	A/S[a]	BEC,[b] g/L	Barbiturate	Conc., mg/L	Other Drugs and Notes
1	42 M	2.5	phenobarbital	1.1	...
2	59 M	2.5	phenobarbital	1.0	...
3	45 M	2.1	phenobarbital	4.4	...
4	23 M	2.0	phenobarbital	10	phenytoin 8 mg/L
5	47 M	1.7	butalbital	2.3	fiorinal found on body
6	68 F	0.9	butalbital	1.1	...
7	22 M	0.7	phenobarbital	5.0	methaqualone 1.7 mg/L, THC 3.8 μg/L
8	17 M	0.4	butalbital	1.0	...
9	21 M	0.4	phenobarbital	1.0	...
10	27 M	0.4	butalbital	0.6	...
11	42 M	0.3	phenobarbital	2.6	...
12	56 M	N.D.	phenobarbital	39	phenytoin 11 mg/L, THC 3.5 μg/L
13	60 M	N.D.	phenobarbital, butalbital	17 2.2	...
14	31 M	N.D.	phenobarbital	9.0	...
15	24 M	N.D.	butabarbital	6.0	GC/MS confirmed
16	54 M	N.D.	phenobarbital	6.0	Hx epilepsy
17	70 M	N.D.	phenobarbital	5.0	...
18	68 M	N.D.	pentobarbital	1.1	...

[a]Age/sex.
[b]BEC = blood ethanol concentration and N.D. = none detected.

TABLE 13—*Statistical comparisons of population characteristics: barbiturate users.*

No.	Test Char. n (%)	Test Pop. n	versus	Test Char. n (%)	Ref. Pop. n	$P<$[a]
1	females	barb.		females	A.D.[b]	0.15
	1 (5.6)	18		80 (13.3)		
2	age > 31.2 yrs.[c]	barb.		age > 31.2 yrs.	A.D.	0.025
	11 (61.1)	18		212 (35.3)		
3	no EtOH	barb.		no EtOH	A.D.	0.11
	7 (38.9)	18		124 (20.7)		
4	EtOH	barb.		EtOH	A.D.	0.11
	11 (61.1)	18		476 (79.3)		
5	BEC 0.2-0.9[d]	barb.		BEC 0.2-0.9	A.D.	0.05
	6 (33.3)	18		69 (11.5)		
6	BEC ≥ 1.0	barb.		BEC ≥ 1.0	A.D.	0.0001
	5 (27.8)	18		407 (67.8)		
7	BEC ≥ 1.0	barb.+EtOH		BEC ≥ 1.0	EtOH	0.008
	5 (45.5)	11		407 (85.5)	476	
8	mult. drug use[e]	barb.		mult. drug use	A.D.	0.04
	4 (22.2)	18		9 (1.5)		

[a] $P < 0.05$ significance.
[b] All drivers, ($n = 600$).
[c] Mean age of all drivers.
[d] Blood ethanol concentration, g/L.
[e] Two or more drugs, ethanol discounted.

there was no association between the sex of a driver and the presence of barbiturates was not rejected ($P < 0.30$) when all drivers were classified accordingly. The mean and median ages of the barbiturate positive drivers were 43.1 ± 18.1 years (sd) and between 42 and 45 years, respectively. The mean age of these drivers is roughly 12 years greater than the mean age of all driver (31.2 years). The hypothesis that there was no association between driver's ages and the presence of barbiturates was rejected ($P < 0.025$) when the ages of all drivers were classified according to whether they were greater or less than the mean. Using all drivers as the tested population, the hypothesis that there was no association between the presence of a barbiturate and the presence of a BEC less than 1.0 g/L was rejected ($P < 0.0005$). The mean BEC in drivers who had used barbiturates ($n = 18$) was 0.77 ± 0.90 g/L (sd), and was 1.26 ± 0.90 g/L (sd) for drivers who had ingested ethanol and barbituates ($n = 11$). The latter of these two means is not significantly less than the mean BEC in all drivers who had ingested ethanol ($P < 0.82$), probably because of the small sample size, and because of the large variances around the mean BECs in both the sample and reference populations.

Barbiturate users did not have a significantly lower incidence of ethanol use than was found for all drivers. However the proportion of drivers with low BECs (0.2 to 0.9 g/L) was significantly greater, while the proportion of barbiturate positive drivers with high BECs (greater than or equal to 1.0 g/L) was significantly lower than the respective incidences determined for all drivers (Table 13). The incidence of multiple drug use in drivers who had used barbiturates (4 of 18, 22.2%) was significantly greater than the incidence of multiple drug use in all drivers ($P < 0.04$).

The tendencies of barbiturate positive drivers to be older and to have lower BECs than the rest of the population should be expected. Intermediate acting and long acting barbiturates are most commonly prescribed for use as sedatives and hypnotics [*85*], and, in addition, in the case of phenobarbital, as an antiepileptic drug [*85*]. Conditions requiring the use of sedative or hypnotic drugs would be expected to occur with increased frequency in older persons. The additive or synergistic interaction of concurrently administered ethanol and

barbiturates [*85-87*] would cause increased impairment of performance at lower BECs. In effect, the presence of the barbiturate may have decreased the BEC required to produce impaired performance versus that required in drivers who had not ingested barbiturates. Although barbiturate positive drivers had a significantly greater incidence of multiple drug use, one of the blood specimens contained both phenobarbital and phenytoin (Table 12, No. 4), a commonly prescribed drug combination used in antiepileptic therapy. (The case records did not indicate a history of epilepsy.) If this case is eliminated from consideration, the incidence of multiple drug use in barbiturate positive drivers would not have been significantly greater than the incidence in all drivers ($P < 0.08$).

Barbiturates are general, nonspecifically acting, CNS depressant drugs. Moderate doses of barbiturates that produce blood concentrations within normal therapeutic limits, also produce significant CNS depression, drowsiness, loss of emotional control, loss of motor control, and impaired abilities to concentrate and make critical judgements [*87*]. These effects are produced with the greatest magnitudes in naive individuals. Chronic barbiturate users or barbiturate dependent individuals may acquire pharmacodynamic tolerance. They exhibit decreased susceptability to the hypnotic or sedative effects of barbiturates, and of other CNS depressants, including ethanol [*85*]. Naturally, resistance to the performance impairing effects of barbiturates is less likely to be expressed in barbiturate tolerant drivers who had ingested both barbiturates and ethanol.

The effects of barbiturates make their use by drivers especially hazardous. Laboratory studies and driving or driving simulator studies have shown that moderate doses of barbiturates severely degrade performance of critical driving skills. Performance of psychomotor skills such as vehicle handling and reaction time, perceptual skills, tracking abilities, oculomotor functions, and information processing skills were all impaired by barbiturates [*87*]. The incidence of barbiturate use in drivers involved in traffic accidents has been reported to range from 2 to 9%, depending on the at-risk population being studied [*87*]. Whether or not these incidence rates are significant is not determinable. Very few studies have been completed that have determined the incidences of barbiturates in appropriate reference populations for comparison [*87*].

Studies to determine the incidence of barbiturates in blood specimens from fatally injured drivers have shown that this incidence is usually low (0 to 3%), and that phenobarbital was detected with greater frequency than intermediate acting barbiturates. Garriott et al [*66*] detected barbiturates in only 4 of 127 blood specimens (3.1%) taken from fatally injured drivers in Dallas County, Texas. Three of these specimens contained phenobarbital at subtherapeutic concentrations, and two of them also contained ethanol at concentrations greater than or equal to 2.0 g/L [*66*]. The fourth specimen contained a high concentration of secobarbital (5.3 mg/L) [*66*]. Turk et al [*65*] detected barbiturates in only 3 of 171 blood specimens (1.8%) taken from fatally injured drivers. All three specimens contained phenobarbital at subtherapeutic concentrations [*65*]. One of the specimens contained phenytoin (5 mg/L) and a high concentration of ethanol (1.7 g/L) besides the phenobarbital (8 mg/L) [*65*]. Cimbura et al [*46*] did not detect barbiturates in any of the blood specimens taken from 401 fatally injured drivers killed in Ontario, Canada. Krantz et al [*88*] did not detect barbiturates in any of the blood specimens taken from 122 drivers killed in southern Sweden.

The incidence of detection of barbiturates in drivers in populations of impaired drivers is often much greater than the incidence determined in fatally injured drivers. Furthermore, unlike fatally injured driver populations, impaired drivers used intermediate acting barbiturates (secobarbital, amobarbital, pentobarbital, butabarbital, butalbital, and others) at a greater frequency than they used phenobarbital. Lundberg et al [*75*] detected 370 barbiturates (74 barbiturate-barbiturate combinations, 76 barbiturate-other drug combinations, and 172 barbiturate-ethanol combinations) in 736 drivers who had been arrested for impaired driving, and whose bloods contained one or more psychoactive drugs other than or in addition to ethanol. The majority of the barbiturates detected ($n = 265$) were intermediate

acting. Secobarbital alone comprised the largest single group ($n = 177$), while phenobarbital comprised the second largest group ($n = 105$). For the 28 cases where phenobarbital was detected in the absence of other drugs (excluding ethanol), the blood concentrations ranged from 2.0 to 68 mg/L and the mean concentration was 21.0 ± 21.1 mg/L (sd) [*75*]. One driver had a phenobarbital blood concentration (not included in mean) of 110 mg/L [*75*].

Garriott et al [*82*] detected barbiturates, either alone or in combination with other barbiturates or other drugs in 55 or 135 drivers (40.7%) arrested for driving under the influence of drugs in Dallas County, Texas. The large majority of the barbiturates detected were intermediate acting. Phenobarbital was detected in only six cases (4.4% of all drivers, 9.5% of all barbiturates detected). Of the barbiturates detected ($n = 63$), secobarbital/amobarbital combinations ($n = 23$) and secobarbital alone ($n = 16$) comprised the majority. Cole [*89*] detected barbiturates in 141 alcohol negative blood or urine specimens submitted for analysis from 707 drivers (20.0%) arrested for driving under the influence (DUI) in San Diego, CA. Barbiturate identities and concentrations were not reported. White et al [*84*] detected barbiturates in 1276 of the 8116 blood specimens analyzed (15.7%) that were submitted by drivers arrested for DUI in California who had BECs less than 1.0 g/L. Secobarbital ($n = 394$, 30.9% of barbiturates, 4.8% of all drivers) and secobarbital/amobarbital combinations ($n = 165$, 12.9%, 2.0%) comprised the majority of the barbiturates detected [*84*]. Robinson [*90*] determined that 17 of 372 blood specimens (4.6%) from drivers who had been arrested for DUI in Northern Ireland and who had BECs less than 0.8 g/L contained barbiturates, either alone or in combination with other barbiturates, other drugs, or alcohol. Again, the majority of the barbiturates detected were short or intermediate acting. Only three specimens containing phenobarbital were noted.

Valentour et al [*83*] detected barbiturates in blood specimens from 28 of 788 drivers (3.5%) arrested for DUI who had BECs less than 1.0 g/L. In contrast to other studies the most commonly detected barbiturate was phenobarbital ($n = 16$), with short and intermediate acting barbiturates comprising the remainder. Phenobarbital concentrations ranged from 1 to 110 mg/L [*83*], and the median concentrations was 11 mg/L. Finally, Honkanen et al [*91*] did not detect barbiturates in any of the 201 serum specimens submitted from drivers in Finland who were admitted to emergency rooms for treatment within 6 h following motor vehicle accidents. No barbiturates were found in a control population ($n = 325$) of randomly selected volunteer drivers who submitted serum specimens at gas stations.

As in other studies of fatally injured drivers, the overall incidence of barbiturate use in the at-risk population was low (3%). Whether or not this incidence rate is significant is not determinable, as the incidences of barbiturate use in appropriate reference populations are unknown. Identifications of the barbiturates were based on relative GC retention times, which were equivalent for butabarbital and butalbital. Further qualitative procedures were not necessary because of their similar activities. These barbiturates were nominally identified as being butalbital because of the comparitive rarity with which butabarbital is prescribed. However, in one case tablets containing butalbital were found on the body of a driver, and in another case butabarbital was identified by GC/MS during a forensic science investigation outside the scope of this study. Therefore, in the barbiturate positive drivers, phenobarbital was detected twelve times, butalbital five times, and butabarbital and pentobarbital one time each. There were four cases where barbiturates and other drugs were noted, and phenobarbital was detected in all four. Phenytoin and THC were detected in two cases each, and methaqualone in one. The preponderance of long acting barbiturates detected in this study corroborates findings in earlier studies of barbiturate incidences in fatally injured drivers. The low number of intermediate acting barbiturates detected reflects both their decreased availability, and the increased availability of other sedative-hypnotic drugs such as methaqualone.

It is possible, but not probable, that all 18 drivers who had used barbiturates experienced some effects that either impaired the driver's abilities, or added to an impairment caused by

other factors. However, interpretations of the effects experienced by drivers based on barbiturate concentrations in blood or serum are hindered by an apparent lack of data concerning correlations of barbiturate concentrations and associated effects. Therefore, these interpretations are mainly speculative.

There were eight cases (Table 12) where phenobarbital was detected either alone, or only in the presence of ethanol. All of the phenobarbital concentrations determined in these eight cases were below the commonly accepted therapeutic range for anticonvusant therapy (10 to 30 mg/L) [*76*]. Because medical records for these drivers were not available, we were unable to determine the proportion of phenobarbital positive drivers that had a medical history of epilepsy or other convulsive disorders. However, it might be more dangerous for epileptic drivers to drive without using appropriate medications, thereby risking having a seizure while driving. Three of the phenobarbital positive drivers had BECs greater than 1.0 g/L (Table 12, Nos. 1-3) and relatively low phenobarbital blood concentrations. These drivers were impaired by ethanol, and probably experienced little additional barbiturate-induced impairment. There were two drivers (Table 12, Nos. 9 and 11) with very low BECs and very low phenobarbital blood concentrations. It is unlikely that these two drivers were impaired significantly by these drugs at these low concentrations. If any of the five drivers above were epileptics, then they should not have had detectable BECs, as ethanol is contraindicated in epileptics [*86*]. There were three drivers (Table 12, Nos. 14, 16, and 17) who had no detectable BECs and who had low phenobarbital blood concentrations. It cannot be inferred with any great certainty that these drivers were impaired by phenobarbital alone. Therefore, none of the eight drivers who had ingested phenobarbital and no other drugs besides alcohol would have been significantly impaired by the phenobarbital alone. The three alcohol impaired drivers probably experienced no increase in effects caused by phenobarbital.

Another four drivers had ingested butalbital, and all four had detectable BECs. In only one case (Table 12, No. 5) was the butalbital concentration high enough (2.3 mg/L) that the driver could possibly have been significantly impaired. However, this driver also had a BEC of 1.7 g/L, and would have been impaired by ethanol alone. The combination of ethanol and butalbital in one elderly driver (Table 12, No. 6) may also have caused significant impairment. One driver had a high blood concentration of butabarbital (Table 12, No. 15) and no ethanol. The concentration detected is probably high enough to cause significant impairment. A similar argument can be proposed for the driver who had ingested pentobarbital (Table 12, No. 18).

All of the four drivers who had ingested phenobarbital in combination with other drugs were impaired by the combined effects of those drugs. The driver who had ingested phenobarbital, phenytoin, and ethanol (Table 12, No. 4) would have been impaired by ethanol alone. No doubt the phenobarbital and phenytoin increased the effects. The driver who had ingested phenobarbital, methaqualone, THC, and ethanol probably would have not been impaired by any one of the drugs at the concentrations detected. However, the combination of all four drugs could have produced significant impairment. Interactive effects have been noted to occur not only between barbiturates and other CNS depressants such as ethanol and methaqualone, and between ethanol and THC, but also between THC and CNS depressants [*92*]. The driver with the phenobarbital blood concentration in the high therapeutic range (Table 12, No. 12) may have seen significantly impaired by the phenobarbital alone. The addition of phenytoin and THC probably increased the effects that were experienced. Finally, one driver had ingested both a long acting and a short acting barbiturate (Table 12, No. 13). This is not consistent with normal antiepileptic therapy. Both drugs were detected at therapeutic concentrations, and in combination may have produced significant impairment.

In summary, the overall incidence of barbiturate use was low (3%). While it is possible that all 18 drivers were either impaired by, or experienced increased impairment because of barbiturates, it is not highly probable. Three drivers experienced significant impairing ef-

fects produced by barbiturates alone (Table 12, Nos. 13, 15, and 18). Another driver (Table 12, No. 6) was impaired by the combination of a barbiturate and alcohol. Five drivers were impaired by ethanol, but only two drivers (Table 12, Nos. 4 and 5) experienced additional barbiturate-produced effects. Two drivers were impaired by barbiturate-other drug combinations (Table 12, Nos. 7 and 12). Therefore, only 8 of the 18 drivers probably experienced significant barbiturate induced effects. Compared to the number of drivers impaired by ethanol, the number of drivers potentially impaired by barbiturates was very low.

Other Drugs

Amphetamines were not detected in any of the 340 specimens tested. Cocaine and benzoylecgonine, opiates, phencyclidine (PCP), and volatile substances besides ethanol were detected only rarely (Table 14). For this reason, their presence was not confirmed by nonimmunological methods. Three drivers were positive for PCP, and all were impaired by ethanol. THC was detected in two of these drivers. Interactions between PCP and ethanol, ethanol and THC, and THC and PCP [*92*] probably increased the effects experienced by all three drivers, and especially in the driver with the high THC blood concentration. The bloods of three drivers were positive for opiates. One of these three drivers was impaired by ethanol. The opiate concentrations in these drivers were estimated by semiquantitative RIA to be near 40 μg/L. The effects produced by opiates at this concentration cannot be estimated. Two drivers were positive for cocaine and benzoylecgonine, one with a high BEC. Cocaine induced effects, if any, cannot be estimated. One ethanol impaired driver also had detectable concentrations of two other volatile substances in his blood. The low frequencies with which all these drugs were detected indicates that their use was not a significantly large detrimental factor affecting traffic and highway safety.

Summary and Conclusions

An inclusive population of blood specimens was collected from drivers that satisfied the primary study requirements, and a majority of the specimens satisfied all secondary study requirements. The driver population was predominantly composed of young white males who died during the evening or night hours, who exceeded posted speed limits, and who did not use restraint systems. Ethanol was present in 79.3% of all drivers, while drugs were present in 13.8% of all drivers. Drugs and alcohol were used by 11.0% of all drivers, while 2.8% used drugs alone. Drug and ethanol use was not associated. Drug users were not dif-

TABLE 14—*Other drugs detected in drivers.*

No.	A/S[a]	BEC,[b] g/L	Drug	Conc.	Other Drugs and Notes
1	32 M	2.7	phencyclidine	...	THC 37 μg/L
2	33 M	1.9	phencyclidine	...	...
3	36 M	1.3	phencyclidine	...	THC 3.5 μg/L
1	19 M	1.0	opiate	...	...
2	68 M	N.D.	opiate	...	...
3	25 M	N.D.	opiate	...	...
1	18 F	1.1	cocaine and benzoylecgonine	...	...
2	19 F	N.D.	cocaine and benzoylecgonine	...	...
1	44 M	2.9	acetone	0.1 g/L	...
			isopropanol	0.1 g/L	

[a]Age/sex.
[b]BEC = blood ethanol concentration and N.D. = none detected.

ferentiable from all drivers by either age or sexual distribution, or by any aspect of ethanol use.

The ethanol concentrations detected were very high; 67.8% of all drivers and 85.5% of all drivers positive for ethanol had BECs greater than or equal to 1.0 g/L. BECs in ethanol positive drivers ($n = 476$) were normally distributed with a mean of 1.81 ± 0.74 g/L (sd). The large number of drivers who had ingested ethanol and the high BECs that were detected indicate that ethanol use has a severely detrimental effect on driving safety. By comparison to ethanol, other drug use was detected only rarely. THC was detected in 7.8%, methaqualone in 6.2% (of 260), and barbiturates were detected in only 3% of all drivers. Multiple drug use was detected very rarely. Discounting ethanol, only nine drivers (1.5%) used two or more drugs in combinations.

THC positive drivers were generally younger and had a greater incidence of multiple drug use than all drivers in the study population, but did not differ with regard to sexual distribution or any aspect of ethanol use. THC concentrations ranged from 3.1 to 37 μg/L, and were heavily skewed towards lower concentrations. The mean THC concentration detected was 8.7 ± 8.25 μg/L (sd), and the median concentration was 5.4 μg/L. 9-Carboxy-THC was detected in 44 of the THC positive drivers. 9-Carboxy-THC concentrations were higher than THC concentrations, and were distributed in the nonnormal platykurtic manner from 0 to 157 μg/L. The mean concentration detected was 39.8 ± 38.0 μg/L (sd), and the median concentration was 30.0 μg/L. THC and 9-carboxy-THC concentrations were used to estimate potential impairment. A maximum of 28 drivers and a minimum of 9 drivers could have experienced some marijuana-induced effects, or experienced increased effects after using both ethanol and marijuana. There was probably only one driver who could have been significantly impaired by marijuana use alone.

EMIT responses were, as expected, more dependent on 9-carboxy-THC concentrations than on THC concentrations. Following the 1:3 dilution during the methanolic protein precipitation-extraction, 8.8% of the 260 blood specimens tested were EMIT positive. All EMIT positive specimens contained greater than 25-μg/L 9-carboxy-THC. Therefore, there were no false positive EMIT results. All specimens containing greater than 38 μg/L of 9-carboxy-THC were positive by EMIT. Of the 30 specimens that contained greater than 20 μg/L of 9-carboxy-THC, 7 (23.3%) were falsely negative. The EMIT assay could have been successfully used to screen out THC negative (less than 3.0 μg/L of THC) specimens. The sample population would have been reduced in size by about 90%, and only 3.4% of all EMIT negative specimens contained greater than 2.9 μg/L of THC. Roughly 70% of all EMIT positive specimens were positive for THC.

Methaqualone was detected in 16 specimens (6.2% of 260). Methaqualone positive drivers did not differ from third-year drivers with respect to any aspect of ethanol use. However, they were generally younger than other third-year drivers. Drivers in the third-year population were not differentiable from drivers accepted for study during the first two years, except that a significantly lower fraction of the third-year drivers were females. The majority of the methaqualone concentrations detected were within the commonly cited therapeutic ranges. The majority of the methaqualone positive drivers had high BECs. Probably twelve of these drivers could have experienced some effects or experienced methaqualone induced increases in impairment in the presence of ethanol. Probably only three drivers were impaired by methaqualone in the absence of significant concentrations of ethanol. However, one of these three drivers had a high blood concentration of THC.

Barbiturates were detected in 18 (3%) drivers. These drivers were generally older, used less ethanol, and had a higher incidence of multiple drug use than drivers in the study population. Phenobarbital was the predominant barbiturate detected. Most of the barbiturate concentrations detected were within, or were below their accepted therapeutic ranges. A maximum of eight drivers could have been impaired by barbiturates or could have experienced increased barbiturate induced effects in the presence of ethanol or other drugs. Only three drivers could have been impaired by barbiturates alone.

A high incidence of ethanol use was noted in these drivers. The incidences of detection of THC, methaqualone, and barbiturates were comparatively much smaller. Other drugs were detected rarely, or were not detected. Drug concentrations were usually within or were below commonly accepted therapeutic or active ranges. Therefore, only a small number of drivers could have been influenced by drugs, and most of them had high BECs. The number of drivers potentially influenced by drugs alone was very small. Ethanol was the only drug tested for that appears be a significantly detrimental factor affecting driving safety. "Diverting attention from the many alcohol influenced drivers to the few who might be influenced by other drugs most probably would be counterproductive to highway safety" [*48*].

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