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Feasibility Assessment of Chemical Testing for Drug Impairment

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6 Abstract		
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FEASIBILITY ASSESSMENT OF CHEMICAL TESTING

FOR DRUG IMPAIRED DRIVING

- SUMMARY -

I. INTRODUCTION

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Can or do drugs other than alcohol cause sufficient impairment to lead to traffic crashes or result in a "driving-under-the influence" arrest? Numerous controlled studies suggest that drugs can cause impairment of various laboratory and real-world skills associated with driving. However, there are not sufficient data to establish to what extent drugs may be involved in those incidents. Several studies suggest that some drugs may be involved in traffic crashes or arrests, but there are not sufficient data to say whether these are over-represented compared to drug users driving but not involved in such incidents.

In spite of these uncertainties, responsible investigation of such incidents often leads to a finding of drug presence and frequently to prosecution for driving under the influence of a drug. This often occurs with little expert opinion on the scientific significance of such drug findings.

The feasibility assessment summarized in this report was undertaken in an attempt to establish preliminary guidelines on drug concentrations in body fluids that may be correlated with skill impairments that may, in turn, be associated with driving. Also, the study evaluated the feasibility of developing rapid and simple test methods that could be used on-site, such as in the stationhouse or emergency room that could serve to screen for drug-impaired individuals.

The study was prompted by recognition that there is little guidance on how to detect drug impaired drivers. Furthermore, drug-impaired drivers would not be detected if they provided a breath specimen alone. Some jurisdictions now require that blood specimens (when provided) be tested for drugs if they are found to contain little or no alcohol (e.g., California), or actually require blood specimens when breath testing for alcohol is negative (e.g., Wisconsin) or drugs are suspected. However. such sampling and/or testing are not customary. Therefore, one objective of this study was to explore the possibility of using drug and/or metabolite concentrations in more readily available body specimens, such as saliva and urine, as presumptive indicators of possible impairment or, more accurately, of drug concentrations in blood that would have stronger evidential value.

The initial task required a review of existing data regarding the possible relationship between impairment measured in the laboratory with drug concentrations in blood. This was necessary in order to determine whether there was any basis for establishing blood concentration standards similar to those accepted and recognized for alcohol. Fortunately, a recent study co-sponsored by the National Highway Traffic Safety Administration, Department of Transportation (NHTSA) and the National Institute on Drug Abuse (NIDA), designed for this purpose, provided much of the This study tested the effects of a single adminisinformation. tration of low to moderate doses of marijuana, diazepam, secobarbital, diphenhydramine, and methaqualone on various performance tasks in the laboratory. Although such tasks can give an indication that drugs may affect certain functions associated with they in themselves can not establish the relative risk driving, or involvement of drugs with traffic crashes or violations.

All five of the drugs covered in the earlier NHTSA/NIDA study and examined in the present study did cause varying degrees of impairment in the laboratory, even at the low to moderate single doses employed. Presumably, higher doses would cause greater impairment. However, the studies did not measure the mitigating role that tolerance may have on drug effects following repeated or frequent use. Therefore, it is extremely important to view the conclusions of the study described here as tentative and preliminary.

The review of correlations between drug concentrations in blood (the terms blood and plasma as used in this report are not interchangeable, since differences in drug concentrations in them occassionally exist) and the laboratory behavioral results revealed that satisfactory relationships could only be established for marijuana. It was possible to generate correlations between delta-9-tetrahydrocannabinol (THC) plasma levels and performance decrements in a few behavioral tasks. In the case of the other four drugs included, considerable inter- and intrasubject variability did not allow for correlations that were statistically valid. Therefore, results for those drugs in this study depend on data on the duration of the observed drug effects compared to well established drug blood concentrations over time. The main limitation imposed by this approach is that the two sets of data, i.e., behavioral effects of drugs and their blood levels, were generated from different people at different times and places. Thus the correlations are related only in a temporal sense rather than in any direct way.

The second major task of the study was to evaluate existing data that might relate concentrations of the study drugs and/or their metabolites in urine and saliva with those found in blood.

Of the two fluids, saliva collection is the least intrusive and the more likely specimen to be accepted as a screening procedure which, if positive, would still require a blood specimen be taken and tested. In addition, available data revealed that in general, drug or metabolite concentrations in saliva more closely correlate to blood levels than is the case with urine. Sufficient data were available from several studies for diazepam, secobarbital, diphenhydramine and methaqualone to suggest approximate relationships between blood and saliva. The exception was in the case of marijuana. THC, the principle psychoactive drug in marijuana, is nearly completely bound to blood proteins, thereby preventing it from secretion into saliva. Thus, any THC found in saliva is present because it is trapped during smoking in tissue in the mouth, from which it slowly diffuses back into the saliva. Sufficient data are not presently available to associate saliva concentrations of THC with time of use, although it appears to be evidence that marijuana has been smoked in the recent past.

The situation with urine is more complicated. The direct secretion of drug (or metabolite) from blood into urine does not occur as it does for saliva. The complex physiological processes of urine formation tends to produce pronounced flucuations in urine drug concentrations. Nevertheless, there is an overall rate of excretion for many drugs that is still predictable. The approach used in this study made use of overall excretion rates and urinary output volumes for healthy adults to estimate drug concentrations in urine. As detailed below, this was only possible for the major urinary metabolite of THC but not for the other drugs included in this study.

The third phase of the study involved the correlation of saliva, and in the case of THC, urine concentrations, with time periods of demonstrated impairment. The results of this overall process, as detailed below, permitted the selection of concentrations of the drugs and/or metabolites in saliva and urine that may possibly serve as presumptive or threshold levels that could be used as a guide to further analysis or to justify the collection and testing of blood specimens. Blood tests are much more difficult to perform and are also more expensive. Positive saliva or urine tests could be used as a convenient and inexpensive screening procedure to identify those individuals whose blood specimens should be tested and to identify which specific drug to test for.

The last part of the study addressed the availability of, or ability to develop, test methods for saliva or urine specimens that could be performed in the stationhouse or emergency room. A available for the quick and inexpensive testing of method is total THC metabolites in urine. Based on the data available, this measurement may serve as a presumptive marker to select candidates for determining blood levels of THC. Additional data is necessary to further establish how well this assay predicts THC blood levels that may be associated with impairment. Unfortunately, such quick methods do not yet exist for detecting drugs in saliva, where lower drug concentrations are usually encountered. Conservative estimates indicate that saliva test methods could be developed perhaps within two years, since the required technology currently exists. However, it will take a sizeable developmental effort to apply it to the drugs of interest.

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II. PERFORMANCE AND PREVALENCE DATA

Much information on the effects of drugs on performance is available. Knowledge of the pharmacological properties of the five drugs included in this study shows that they all can depress the central nervous system. This alone makes them candidates for suspected involvement in the impairment of functions related to driving.

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A good source of information comes from published studies and reports on the incidence of drugs detected in drivers arrested, injured or killed. For example, a study in the State of California reported in 1983 revealed the presence of THC, at or above 5.5 ng/ml, in 14.4% of blood specimens collected from 1792 drivers arrested for a driving-under-the influence of drugs (DUID) offense. Of these, nearly half also contained alcohol in excess of 0.10%. It is not possible to establish a true incidence level from these data, since the 1792 specimens were selected from about 20,000 blood specimens collected over a period of one year. In addition, only about one-third of the DUID arrestees (for all reasons, not just accidents) during this period were said to have provided a blood specimen (Zimmerman et al., 1983).

A. similar study of data collected from all DUID cases in Georgia over the period of 1978 - 1981, revealed 974 blood specimens that were found positive for methaqualone, all in excess of 0.5 ug/ml. Of these, 536 (55%) contained methagualone alone in excess of 1.0 ug/ml (McCurdy et al., 1981). A study of 600 drivers killed in North Carolina over a four-year period indi-A study of 600 cated a low prevalence of drugs, e.g., with 7.8 % revealing THC levels over 3.0 ng/ml, although all but 6 also had varying levels of alcohol present as well (Mason and McBay, 1984). A study of 440 male drivers aged 15-34, killed in automobile crashes in California during 1982-83, showed two or more drugs present in 43%, cannabinoids in 37%, but alcohol in 70% (Williams et al., These and similar reports do not in themselves establish 1984). a strong basis as to the extent of drug involvement in crashes and fatalities. Unfortunately, all efforts to obtain drug incidence data from control groups of drivers not involved in accidents have been guite limited.

With the possible exception of the methaqualone study in Georgia, none of the incidence studies described above or reported provide any solid data on drug concentrations that might be associated with specific impairments related to the crash or arrest. For the purposes of the present study, it was therefore necessary to turn to laboratory measures of performance impairment. Although such studies provide the advantage of being able to control the doses of drugs and to measure performance in a controlled, accurate and reproducible manner, they have the major limitation of not directly reflecting actual on the road situations. In order to obtain a close approximation of "real life" driving conditions, several studies have employed driving simulators and driving on closed courses. Such studies have provided greater "face validity" to the impairments seen, but still are

not the same as routine driving situations. Furthermore, most of these studies use healthy volunteers, usually well rested, and with task learning and practice periods that can not fully duplicate the overlearned skills involved in actual driving. Nevertheless, such studies have consistently shown that many drugs do impair some of the skills associated with driving, and can thus provide a starting point both for guiding accident and arrest investigations and to plan further studies on the effects of drugs on driving.

Therefore, with all of the limitations stated above clearly in mind, the primary source of data used in the present study was the NHTSA and NIDA study of which the behavioral portion was performed by Moscowitz and Sharma (1979). They employed several performance tasks, such as critical tracking, tracking alone and with divided attention, reaction time alone and with divided attention, and in a driving simulator. These studies included the five drugs discussed above.

III. DRUG AND METABOLITE CONCENTRATIONS

Several sources of data on the concentrations of drugs and their metabolites in the body fluids of interest were used in this study. Of direct relevance were blood drug concentrations obtained from the same subjects used in the above mentioned performance studies of Moscowitz and Sharma. However, the blood samples could not be collected at the same time the performance measurements were made, as that would have interfered with the behavioral results. Nevertheless, the resultant blood concentrations versus time profiles were quite similar to those found in several independent studies. Thus, it was felt that the values used here were representative of those that may be randomly encountered following single dose use of the selected drugs.

It is important to again emphasize that these drug concentrations may not accurately reflect those seen following repeated or chronic administration of the drugs of interest. Little or no data are available on the relative roles that tolerance to drug effects and alterations in drug metabolism and/or excretion may play on the impairments measured in the cited studies. It is known, for example, that some of the behavioral effects of the drugs included here change with repeated drug use, but these have rarely been studied in connection with concurrent blood drug concentrations. However, in a series of studies, Ellinwood, Linoilla and associates have shown that normal therapeutic maintenance doses of diazepam can still cause specific impairments in laboratory tests performed by patients that were chronically dosed with the drug (Ellinwood et al., 1983).

A recent study compared blood concentrations of THC and metabolites for frequent smokers of marijuana (over 50 "joints" a month) to those of occassional users (no more than once a week). The blood concentrations versus time profiles for THC did not differ significantly between the two groups, although the initial

metabolite levels were considerable higher in the frequent smokers. Unfortunately, no behavioral measurements were made. Interestingly, urine concentrations were only slightly higher for some of the frequent smokers during the first 24 hours after their last marijuana cigarette (Jones and Peat, 1985). Nevertheless, even though these and related studies may or may not be representative of the population at large, they do provide additional guidance.

A most important aspect of the study reported here was the thorough evaluation of the pharmacokinetics of the drugs of interest. Pharmacokinetics is the study of the rate of absorption. distribution, and elimination of drugs in the body. Although this scientific discipline is over 30 years old, its detailed application to drug impairment is quite recent. Primarily focusing on the relationships between the concentrations of drugs in various body fluids and body tissues over time, pharmacokinetics allows us to mathematically fit actual data to theoretical models, which in turn may help in predicting new or unmeasured relationships. Good model fitting and reliable predictions require properly collected and measured data. Fortunately, adequate data are available for certain comparisons for the five drugs included in this study.

Of primary interest and concern are the widely used drug forms of the plant Cannabis. Often collectively called "marijuana", such preparations as hashish, hash oil, sensimilla, and "true" marijuana produce their pharmacological effects by virtue of their active ingredient THC. Literally hundreds of studies over the past 15 years has helped to characterize these _ effects. Amongst these studies are several on the absorption, distribution, metabolism and excretion of THC. Although there are several good studies of THC concentrations in blood, there are only a limited number on concentrations of THC metabolites in urine. There was an unfortunate preoccupation with blood levels in all the early studies. Now that it is recognized that urine tests are easier, faster, and cheaper to perform, studies on urine concentrations versus time are increasing in number. However, the results generated in the present study were based on only two well conducted studies, making it necessary to reemphasize the preliminary nature of the findings reported here.

Several suitable studies were available on blood and saliva concentrations of the other four drugs of interest, which permitted adequate pharmacokinetic evaluations to be carried out as part of this study.

IV. RESULTS

A. Marijuana

Marijuana and other forms of Cannabis are more widely used than any other illicit drug. It is the most prevalent drug in all driving studies in which adequate tests were performed to find it. Therefore, it is of great interest that the role of marijuana in traffic safety be better established, and that convenient methods for detecting its use and enforcing sanctions, when appropriate, be developed.

Several studies have measured the behavioral effects of mardemonstrating that it impairs some functions associated ijuana, with driving. For example, Klonoff et al. (1976), Reeve et al. (1980), and Reeve (1983) have observed impairment in actual automobile driving on closed courses and, in the Klonoff study, on city streets by drivers following the smoking of marijuana. Although blood concentrations of THC were not determined or reported, the time courses for adverse behavioral effects were similar following equivalent doses. The first blood levels reported were those cited earlier in connection with fatalitites, injured and arrested drivers.

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The earliest studies on the correlation of blood levels of THC with pharmacological effects made use of self-reported intoxication ("high") and the increased heart rate caused by marijuana. Some investigators, e.g. Hollister et al. (1979), questioned the ability to use blood levels to predict intoxication, whereas others demonstrated that correlations do exist, if timedependence is taken into consideration (Coccetto et al., 1981; Barnett et al., 1982; Chiang and Barnett, 1984; Domino et al., 1984), within 45 to 60 minutes following the smoking of marijuana and in about 3 hours after oral consumption of THC (Hollister et al., 1979; Wall et al., 1981, 1984).

The most definitive correlation to date has been that made on the laboratory measures of Moscowitz and Sharma (1979) and blood concentrations measured in the same individuals (vide supra). Barnett et al. (1985) have shown a highly statistically significant correlation between performance on a critical tracking task and plasma levels of THC for average data on reight subjects for about seven hours (and a weaker correlation for 12 hours) with smoked doses of THC up to 20 mg (equivalent to about two half-gram marijuana joints of 2% THC). Although such tasks indicate the potential for impairment, the direct relationship to real driving is not established, as cautioned earlier. Nevertheless, this constitutes a significant step forward in beginning to understand the complex relationships between driving and marijuana use.

THC concentrations in blood rise and fall Unfortunately, very capidly during the smoking of marijuana, largely due to the rapid distribution of THC throughout the body. Concommitantly, THC is rapidly metabolized to numerous metabolites, two-thirds of which are excreted into feces and the other third into the urine. Thus, even when demonstrable impairment still exists, blood concentrations of THC have fallen to 1 to 2 ng/ml. Often, such low levels are reached within 3 to 4 hours after smoking, depending on the potency and quantity of the material smoked and the efficiency of the smoker (Chiang and Barnett, 1985). This has made it difficult to detect and measure THC concentrations in the blood of arrested drivers. Although a few jurisdictions are attempting to analyze blood samples from drivers (Wade et al., 1983), most jurisdictions have been discouraged from doing so because of the above mentioned difficulties and the expense involved. It was for these reasons that the present study was initiated. It was projected that, with the recent availability of blood concentration data that have been correlated to intoxication and impairment and properly collected and measured urine concentrations of the major THC metabolite (THC-9-acid), it may be possible to establish a temporal relationship between urine concentrations and blood levels and thus, indirectly, to impairment.

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The THC blood concentrations were taken from the NHTSA/NIDA study. From that study, it was observed that THC plasma levels in excess of 1 to 2 ng/ml were associated with impairment of the various laboratory tasks, the longest lasting being significant for about 7 hours after smoking. This set a time frame for which it would be desirable to establish a urine concentration that was predictive of such THC blood levels.

The urine concentrations came from two carefully controlled studies in which known amounts of marijuana were smoked by healthy volunteers. In the Perez-Reyes et al. (1982) study, nine volunteers smoked a single marijuana cigarette containing 2.8% THC. In the Jones and Peat (1985) study, five subjects were frequent users (more than 50 "joints" a month) and five were infrequent users (no more than one "joint" a week).

By applying standard pharmacokinetic analysis to the THC blood concentration versus time data, theoretical urine concentration profiles were generated. This required assigning certain assumptions to some of the factors involved in the disposition of THC in the body. Then by using the actual urinary concentrations for specimens collected at the different time intervals, the critical factors were varied until the theoretical model most closely simulated the actual curve. This approach gave a preliminary indication that one can possibly predict THC blood levels from THC-9-acid metabolite levels in urine.

The other approach involved comparing the number of urine specimens at or over certain concentrations against the time of collection. Thus, in the study involving nine subjects, 86% (6/7) of the specimens containing over 100 ng/ml of the metabolite THC-9-acid were provided within eight hours of smoking. Similar results were seen in the infrequent users in the second study (7/8), but the frequent users only provided 69% (11/16) of their specimens with concentrations greater than 100 ng/ml during that same 8-hour time period. Five of the specimens over 100 ng/ml in the latter study were collected at 24 hours after smoking and one at 48 hours. The last specimen came from a frequent user whose THC-9-acid concentration was over 700 ng/ml at the start of smoking, thus illustrating the inherent difficulty of predicting the time of smoking or blood drug concentrations, especially with frequent smokers of marijuana.

In the study by Jones and Peat (1985) concurrent blood and concentrations were measured. It was thus possible to urine assess the utility of the urine threshold concentration of 100 ng/ml identified above to predict the plasma levels in the same None of the infrequent users would have been found to subjects. have THC plasma concentrations at or over 5 ng/ml. However, 37% of these users did have concentrations that were over (3/8) 1 ng/ml of THC. In the frequent user group, 17% (3/18) were predicted to have 5 ng/ml or more and 67% (12/18) to be over 1 ng/ml of THC. Taking the ten users together, the use of the 100 ng/ml urine threshold would have only predicted correctly 58% (15/26)of the plasma concentrations found to contain over 1 ng/ml of THC. This was due in large measure to the fact that the infrequent user group dropped below 1 ng/ml of THC in plasma between 2 to 4 hours after smoking, which was the same time frame wherein urine concentrations were rising to 100 ng/ml for THC-9-acid. On the other hand, the frequent users, who generally started with urine concentrations above 100 ng/ml, dropped below 1 ng/ml of THC in plasma over a period of 3 to 48 hours. The use of a lower urine threshold, such as 80 ng/ml of THC-9-acid, did not substantially change the correlation.

These data suggest that urine concentrations exceeding a threshold such as 100 ng/ml of the major THC metabolite will have some limited predictive value of blood levels associated with impairment for a mixed population of marijuana users who smoke at widely varying frequencies. Therefore, it would seem prudent to recommend collecting and testing blood specimens from any driver that is found to have a urine specimen positive for cannabinoids above a certain level, e.g., 100 ng/ml of total metabolites. This would provide for detection of infrequent users during the first few hours following smoking, a period during which they would more likely be impaired. This could be accomplished using the existing EMIT (Enzyme Multiplied Immunoassay Technique) urine assays for cannabinoids, which have a detection cut-off of 100 ng/ml of total cross-reacting THC metabolites and take only a few minutes to perform.

B. Secobarbital

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Secobarbital was selected for the NHTSA/NIDA study as a representative example of a fast-acting and short duration barbiturate. It has been well studied, thus much data were available for the present study. Unfortunately, relatively low doses (approximately 70 mg and 130 mg; the usual dose prescribed for sleep is 100 to 200 mg) were used in the NHTSA/NIDA study, and the behavioral measures were highly variable. Thus, there were no significant correlations between blood drug levels and measures of impairment. However, time intervals for duration of impairment on a variety of laboratory tasks from several studies were used to help select blood barbiturate concentrations that might serve as a threshold for identifying a level of barbiturate use that might impair performance.

As noted earlier, secobarbital and the other drugs included except marijuana, are not excreted into urine in in this study. sufficient amounts to make a suitable specimen for predicting blood levels. However, much data does exist on the secretion of secobarbital into saliva. It was found experimentally that secobarbital appears in saliva in a ratio of approximately 0.3 to for doses of 50 mg and 100 mg. Standard pharmacokinetic plasma. calculations were employed to regenerate the experimental plasma versus time curves at three dose levels, using the data from the NHTSA/NIDA study. From these curves, theoretical saliva concentration profiles were then computed using the 0.3 saliva/plasma ratio. A saliva concentration of 0.5 ug/ml, corresponding to a plasma level of 1.67 ug/ml, was selected as a possible threshold level for predicting impairing effects based on the NHTSA/NIDA laboratory studies. Drug concentrations remain above this level during the first 12 to 15 hours after administration of usual doses of secobarbital.

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It is necessary to point out again that the use of higher or more frequent doses will lead to higher plasma and saliva concentrations for longer periods of time than found for the doses employed in the studies referred to here. This illustrates the continuing necessity to evaluate any plasma or blood level found in the context of the person's drug history in order to fully diagnose drug-related impairment. The saliva level may only be used to determine whether or not to collect the blood specimen.

C. Diazepam

Diazepam has been the most widely used prescription drug of all time. Not surprisingly, it appears with great frequency in most studies looking at drug-related highway acccidents. In laboratory studies, high doses (up to 160 mg) have shown impairing effects for up to 24 hours. However, in the NHTSA/NIDA study the single low doses of 5 mg and 10 mg, which are the usual single dose repeated 2 to 4 times a day as prescribed for anxiety, produced significant impairments from 3 to 8 hours, depending on the task.

Since urinary levels do not relate well to blood concentrations, saliva concentration versus time profiles were generated as before. Unfortunately, diazepam and its active metabolite, desmethyldiazepam, have low plasma levels and very low saliva/ plasma ratios, being 0.013 and 0.018, respectively. Nevertheless, an examination of the curves suggested that a saliva concentration of 2 ng/ml of diazepam would predict an 8 hour time period following a single dose of 10 mg. However, this level would detect a dose of 40 mg for greater than 48 hours. A level of 7 ng/ml would detect the 40 mg dose for its impairing period It would therefore seem advisable to use a saliva 12 hours. of assay that could detect diazepam and its metabolite at some concentration that was intermediate between these, for example 5 ng/ml, in order to identify those individuals that had used the drug and were still impaired. A positive saliva test would then

provide sufficient grounds to take a blood sample in order to better assess the possibility of drug impairment. Such interpretations would have to take in to account the possibilities of chronic use, which is common for this drug, and the development of tolerance.

D. Diphenhydramine

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As a major example of an antihistamine, diphenhydramine has been widely used for more than 20 years and is now available in many over-the-counter preparations. Well known for its sedating effects, it has been used as a night-time sedative. Therefore, it should not be surprising that some performance impairments in a wide variety of laboratory tasks have been found when testing this drug. Using single doses of 50 mg, the usual antihistamine and sedating dose, the time course for significant effects has been limited to about 2 to 4 hours after an oral dose, although careful analysis of the reaction time and tracking results from the NHTSA/NIDA study suggests effects out to 8 hours (Licko, 1981).

Diphenhydramine is secreted in high amounts into saliva, giving a saliva/plasma ratio of approximately 3 at 2 to 4 hours after taking a 50 or 100 mg dose. Thus, a threshold concentration of 180 ng/ml of diphenhydramine in saliva would correlate to plasma levels seen up to 3 hours following a single oral dose of 50 mg or greater. Again, it is important to restrict the saliva test only for the purpose of screening for the drug, thereby helping to decide whether a blood specimen should be obtained. Only the blood test will allow a more definitive evaluation of possible drug impairment.

E. Methaqualone

Most frequently known by one of its trade names, Quaaludes, methaqualone became a major drug problem during the 1970s and into the the 1980s. It was for this reason that it was included in the NHTSA/NIDA study. However, its abuse had reached such proportions that its manufacture in the United States was totally prohibited. Only sporatic and small amounts are now reported in the illicit drug trade.

The NHTSA/NIDA study as well as others found demonstrable impairment in the laboratory measures employed for only 3 hours following single doses of 50 to 200 mg.

Methaqualone is extensively metabolized and its metabolites are excreted in urine over extremely long periods of time, thus making this an unsuitable specimen for detecting possible impairment. Studies on plasma and saliva concentrations of metaqualone have established a saliva/plasma ratio of 0.1. Doses of 200 mg to 300 mg, which is the usual dose prescribed for sleep, would produce plasma levels of 1.5 to 2.0 ug/ml through the 3 hour period of experimentally measured impairment. This is the same concentration level that was found associated with obvious intoxication in the 536 DUID cases described earlier in which methaqualone alone was present (McCurdy et al., 1981). Thus, a saliva concentration of 150 ng/ml would be a reasonable threshold level to set for obtaining and analyzing a blood specimen.

V. FEASIBILITY OF DETECTING THRESHOLD CONCENTRATIONS

One of the objectives of the present study was to assess the feasibility of detecting the drugs described above in saliva and, in the case of marijuana, in urine in the stationhouse or emergency room. Furthermore, the tests would have to be sufficiently specific and sensitive in order to properly identify the drug or drugs present and at the concentrations indicated above.

If the approach suggested above for detecting the presence of total THC metabolites in urine as a means of identifying individuals for blood collection was adopted, the methodology for testing urine specimens on-site, such as in the stationhouse or emergency room, already exists. In fact, many emergency rooms currently use the method to provide a rapid, qualitative test for the presence of suspected drugs. The method is based on an immunoassay that provides a detectable signal within one minute, the enzyme multiplied immunoassay technique, EMIT, marketed by the Syva Company. It is available in a portable single test format and also as a more elaborate tabletop version. It is calibrated against standard concentrations of THC-9-acid, usually at 100 ng/ml, although a kit is available to detect down to 20 ng/ml of total metabolites. For the purpose of detecting candidates to provide blood specimens, the 100 ng/ml cut-off would be recommended.

The assay described above is based on the principle of using antibodies that have a "recognition" for specific molecules. In practice, this is often a small group of closely related molecules. Thus, the EMIT cannabinoid immunoassay detects not only the major metabolite, THC-9-acid, but other minor metabolites as well. Nevertheless, it does not detect other types of molecules and may be used as an assay specific for THC metabolites. It would not be useful for attempting to measure the concentration of THC-9-acid itself. In fact, the prospects for developing such an assay are quite remote due to the close similarity between many of the THC metabolites.

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The other four drugs included in this study would require assays that could be applied to saliva. The concentrations range from 5 ng/ml for diazepam to 500 ng/ml for secobarbital. No such saliva screening tests currently exist. Inqueries were made with several investigators that suggested possible assay techniques, but only those that would make use of an antibody reaction appear to offer the necessary specificity. In fact, only one manufacturer was identified that had developed a technology that would

be amenable to applying antibody-based assays to use on-site. Although not exactly a "dip-stick," it could be equally simple. Unfortunately, conservative estimates place the development time for a saliva assay for the drugs included in this study at two years at a cost of about one million dollars. In order to initiate such a project it would be necessary to convincingly demonstrate that the approach proposed here would be widely used. In other words, there would have to be broad appeal for the idea of using quick screening tests to screen for possible drug-impaired individuals, and providing the justification for obtaining a blood specimen for more definitive testing.

VI. CONCLUSIONS AND CAVEATS

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It is important to reiterate the limitations and underlying assumptions utilized in the present study. Because of the 'lack of adequate epidemiological data that would best characterize the role that drugs may play in traffic crashes or arrests, it was necessary to use measures of impairment based on laboratory As noted above, this may not correspond perfectly to the tests. type of impairment involved in actual traffic conditions. Thus, the calculations and drug concentration thresholds presented here can only serve as preliminary indicators of possible relationships between impairment and drug levels. Furthermore, most if not all of the data employed for these calculations were based on controlled administration of low to moderate single doses of the drugs. No data are available assessing the role that frequent or chronic use of the drugs may play, either with respect to the development of tolerance or alterations in drug pharmacokinetics. It would be expected that chronic users that have become tolerant to some of the effects of these drugs would produce significantly higher body fluid concentrations while possibly demonstrating It is therefore important to view in this reduced impairment. context the results of the study and conclusions presented here. The suggested threshold levels were arrived at in a very indirect manner and cannot be considered as direct evidence of impaired driving performance.

This preliminary assessment suggested that the measurement of THC-9-acid concentrations in urine might provide a better than even chance to predict blood levels of THC that could be associated with impairment. When single doses were followed in infrequent users of marijuana, the probability improved but at the risk of missing high blood levels shortly after smoking. Therefore, it was concluded that it may be more prudent to use a simple urine test at an appropriately high cut-off to identify indiviuals that may be impaired by marijuana.

Saliva was judged to be a more appropriate specimen for the possible detection of the presence of impairing blood levels of secobarbital, diazepam, diphenhydramine and methaqualone. Although the saliva threshold levels selected are primarily related to single doses, they may serve as a preliminary guide to further testing. The point here is that unless all persons arrested on

suspected DUID offenses or injured or killed in a vehicular crash have blood specimens screened for drugs, there will be no means of identifying drug-impaired drivers. This study suggests that it may be possible to narrow down the number of drug possibilities and blood specimens requiring testing to a level that is economically feasible.

VII. REFERENCES

G. Barnett, C. N. Chiang, M. Perez-Reyes, and S. M. Owens, Kinetic study of smoking marijuana, J. Pharmacokinet. Biopharm. 10, 495-506 (1982).

G. Barnett, V. Licko, and T. Thompson, Behavioral pharmacokinetics of marijuana, Psychopharmacology **85**, 51-56 (1985).

C. N. Chiang and G. Barnett, Marijuana effect and delta-9-tetrahydrocannabinol plasma level, Clin. Pharmacol. Therap. **36**, 234-238 (1984).

C. N. Chiang and G. Barnett, personal communication (1985).

D. M. Cocchetto, S. M. Owens, M. Perez-Reyes, S. DiGuiseppi, and L. L. Miller, Relationship between plasma delta-9-tetrahydrocannabinol concentration and pharmacologic effects in man, Psychopharmacology **75**, 158-164 (1981).

L. E. Domino, S. E. Domino, and E. F. Domino, Relation of plasma delta-9-THC concentrations to subjective "high" in marijuana users: a review and reanalysis, in "The Cannabinoids: Chemical, Pharmacologic, and Therapeutic Aspects" (S. Agurell, W. L. Dewey, and R. E. Willette, eds.), Academic Press, Inc., New York, 1984, pp. 245-262.

E. H. Ellinwood Jr., M. Linnoila, M. E. Easler, and D. W. Molter, Profile of acute tolerance to three sedative anxiolytics, Psychopharmacology **79**, 137-141 (1983).

L. E. Hollister, H. K. Gillespie, A. Ohlsson, J.-E. Lindgren, A. Wahlen, and S. Agurell, Do plasma concentrations of delta-9tetrahydrocannabinol reflect the degree of intoxication? J. Clin. Pharmacol. 21, 1715-1775 (1981).

R. Jones and M. Peat, Comparison of plasma levels and pharmacokinetics of THC following smoking in frequent and infrequent users, submitted for publication (1985).

H. Klonoff, Marijuana and driving in real-life situations, Science 186, 317-324 (1974).

V. Licko, Contract report to the National Institute on Drug Abuse, 1981. H. Moscowitz and S. Sharma, Contract Technical Reports to the National Institute on Drug Abuse (1979).

A. P. Mason and A. J. McBay, Ethanol, marijuana, and other drug use in 600 drivers killed in single-vehicle cráshes in North Carolina, 1978-1981, J. Forensic Sci. **29**, 987-1026 (1984).

H. H. McCurdy, E. T. Solomons, and J. M. Holbrook, Incidence of methaqualone in driving-under-the-influence (DUI) cases in the State of Georgia, J. Anal. Toxicol. 5, 270-274 (1981).

M. Perez-Reyes, T. S. Baker, and R. L. Myers, personal communication (1982).

V. C. Reeve, Marijuana and impairment: a closed-course study, presented at the 9th International Conference on Alcohol, Drugs, and Traffic Safety, San Juan, 1983.

V. C. Reeve, W. B. Robertson, J. Grant, J. R. Soares, E. G. Zimmerman, H. K. Gillespie, and L. E. Hollister, Hemolyzed blood and serum levels of delta-9-THC: effects on performance of radside sobriety tests, J. Forensic Sci. **28**, 963-971 (1983).

N. Wade, Incidence of drugs in blood from DUID arrests, presented at the 9th International Conference on Alcohol, Drugs, and Traffic Safety, San Juan, 1983.

M. E. Wall, B. Sadler, D. Brine, H. Taylor, and M. Perez-Reyes, Metabolism, disposition, and pharmacokinetics of delta-9-tetrahydrocannabinol in male and female subjects, in "The Cannabinoids: Chemical, Pharmacologic, and Therapeutic Aspects" (S. Agurell, W. L. Dewey, and R. E. Willette, eds.), Academic Press, Inc., New York, 1984, pp. 185-210.

A. F. Williams, M. A. Peat, D. J. Crouch, J. K. Wells, B. S. Finkle, Drugs in fatally injured young male drivers, submitted for publication (1984).

E. G. Zimmerman, E. P. Yeager, J. R. Soares, L. E. Hollister, and V. C. Reeve, Measurement of delta-9-tetrahydrocannabinol (THC) in whole blood samples from impaired motorists, J. Forensic Sci. 28, 957-962 (1983).

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