

DRUGS AND DRIVING: INFORMATION NEEDS AND RESEARCH REQUIREMENTS

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16. Abstract This report presents the results of a comprehensive review and analysis of the relationship between drugs (other than alcohol alone) and highway safety. The report identifies research to define the problem of drugs and driving. Epidemiologic and experimental studies are examined in the review. Also reviewed is literature on approaches to countermeasures in this area of highway safety. Methodologic issues, problem areas, and information needs in drug and driving research are extensively discussed. Conclusions and recommendations for near-term research are developed, and a systematic program of research is suggested for implementing the recommendations.			
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Approximate Conversions to Metric Measures

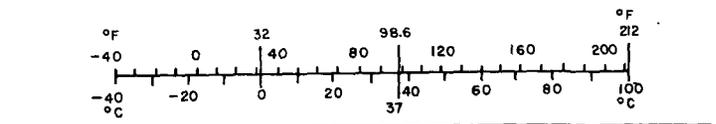
Symbol	When You Know	Multiply by	To Find	Symbol
LENGTH				
in	inches	*2.5	centimeters	cm
ft	feet	30	centimeters	cm
yd	yards	0.9	meters	m
mi	miles	1.6	kilometers	km
AREA				
in ²	square inches	6.5	square centimeters	cm ²
ft ²	square feet	0.09	square meters	m ²
yd ²	square yards	0.8	square meters	m ²
mi ²	square miles	2.6	square kilometers	km ²
	acres	0.4	hectares	ha
MASS (weight)				
oz	ounces	28	grams	g
lb	pounds	0.45	kilograms	kg
	short tons (2000 lb)	0.9	tonnes	t
VOLUME				
tsp	teaspoons	5	milliliters	ml
Tbsp	tablespoons	15	milliliters	ml
fl oz	fluid ounces	30	milliliters	ml
c	cups	0.24	liters	l
pt	pints	0.47	liters	l
qt	quarts	0.95	liters	l
gal	gallons	3.8	liters	l
ft ³	cubic feet	0.03	cubic meters	m ³
yd ³	cubic yards	0.76	cubic meters	m ³
TEMPERATURE (exact)				
°F	Fahrenheit temperature	5/9 (after subtracting 32)	Celsius temperature	°C

*1 in = 2.54 (exactly). For other exact conversions and more detailed tables, see NBS Misc. Publ. 286, Units of Weights and Measures, Price \$2.25, SD Catalog No. C13.10:286.



Approximate Conversions from Metric Measures

Symbol	When You Know	Multiply by	To Find	Symbol
LENGTH				
mm	millimeters	0.04	inches	in
cm	centimeters	0.4	inches	in
m	meters	3.3	feet	ft
m	meters	1.1	yards	yd
km	kilometers	0.6	miles	mi
AREA				
cm ²	square centimeters	0.16	square inches	in ²
m ²	square meters	1.2	square yards	yd ²
km ²	square kilometers	0.4	square miles	mi ²
ha	hectares (10,000 m ²)	2.5	acres	
MASS (weight)				
g	grams	0.035	ounces	oz
kg	kilograms	2.2	pounds	lb
t	tonnes (1000 kg)	1.1	short tons	
VOLUME				
ml	milliliters	0.03	fluid ounces	fl oz
l	liters	2.1	pints	pt
l	liters	1.06	quarts	qt
l	liters	0.26	gallons	gal
m ³	cubic meters	35	cubic feet	ft ³
m ³	cubic meters	1.3	cubic yards	yd ³
TEMPERATURE (exact)				
°C	Celsius temperature	9/5 (then add 32)	Fahrenheit temperature	°F



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The development of this report has been a multidisciplinary undertaking requiring contributions of many individuals. The principal investigators have been fortunate to have been assisted by many dedicated and capable colleagues, whom we thank.

The history of this project is interesting and unusual. The study design was developed and presented in response to a Request For Proposals issued by the National Highway Traffic Safety Administration (NHTSA) while the principal investigators--Kent B. Joscelyn, Ralph K. Jones, and Roger P. Maickel--were at Indiana University. Subsequently, each left Indiana University. Mr. Joscelyn joined the Highway Safety Research Institute of The University of Michigan to head the Policy Analysis Division. Mr. Jones formed his own company, Mid-America Research Institute, Inc. Dr. Maickel became Head of the Department of Pharmacology and Toxicology of the School of Pharmacy and Pharmacal Science of Purdue University.

The movement of the principal investigators required the transfer of the contract from Indiana University to The University of Michigan. This transition was accomplished because of the willingness of a number of individuals to devote additional effort to the identification of the proper procedures to accomplish the transfer. We thank the following individuals who were most helpful in the transition:

- Floyd W. Bird and Theodore E. Anderson of NHTSA;
- Harrison Shull and John T. Hatchett of Indiana University;
- and
- Lee D. Beatty and William E. McCormick of The University of Michigan.

The principal investigators continued to work together on this report and other workproducts of the study. They were joined in 1976 by Alan C. Donelson, who had completed his doctorate with Dr. Maickel at Indiana

University and then served as a postdoctoral scholar at The University of Michigan. Dr. Donelson played a principal role in the aspects of this project that focused on drugs other than alcohol, and in development of this report. In particular, he served as the primary writer for the drafts of this report.

The final text reflects the efforts of all authors as each reviewed and rewrote the work of the others. Dr. Maickel concentrated on technical issues related to pharmacology and drug analyses. Mr. Jones had primary responsibility for developing the companion reports on alcohol that were produced under this study. Thus he brought an understanding of the past work in alcohol and highway safety to the discussions of problem definitions and countermeasures. Mr. Joscelyn served as project director with responsibility for integration of the different disciplinary perspectives. The major findings, conclusions, and recommendations were jointly developed and are jointly made by all the authors.

The authors were assisted by reviewers who commented on early drafts of the report. These included Reginald G. Smart of the Addiction Research Foundation and Theodore E. Anderson, who also served as Contract Technical Manager for the study.

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We thank all who assisted.

Kent B. Joscelyn
Principal Investigator

Ralph K. Jones
Principal Investigator

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1.0 INTRODUCTION

This is a final technical report on drugs and highway safety. It contains:

- a review of recent research;
- an assessment of present knowledge; and
- recommendations for further research in this area.

The project reported on here included an assessment of research on alcohol and highway safety. These findings are reported in separate volumes (Jones and Joscelyn 1978a; Jones and Joscelyn 1978b).

This section provides an overview of this report. Subsections discuss four topics:

- the study objectives,
- the study approach,
- the literature search, and
- the organization of this report.

1.1 Objectives

The University of Michigan Highway Safety Research Institute (HSRI) received contract DOT-HS-5-01217 from the National Highway Traffic Safety Administration (NHTSA) to conduct a study of alcohol, other drugs, and highway safety. Entitled "State of Knowledge and Information Needs in Alcohol-Drugs and Highway Safety," this contract is one of a series that forms a comprehensive program for examination of these issues.

The study consisted of two parts, one concerned with alcohol and the other concerned with drugs other than alcohol alone. The first part of the study involved the review, evaluation, and summary of existing knowledge concerning the alcohol-crash problem. Its purpose was to update and extend the 1968 report of the Department of Transportation Alcohol and Highway Safety (U.S. Department of Transportation 1968). The final reports (Jones and Joscelyn 1978a; Jones and Joscelyn 1978b)

include recommendations for priority research likely to have a significant impact on transportation problems stemming from alcohol.

Concerned with drugs other than alcohol and highway safety, the second part of the study had as its objectives:

- to review critically, evaluate, and summarize existing knowledge concerning the relationship of drugs and highway safety; and
- to recommend priorities for further research in this area of drugs and highway safety--research likely to produce the most significant results.

This report is the product of that study. It describes problem areas, information needs, and research priorities in the field of drugs and highway safety.

Throughout this report, the word "drug" is used in its most general sense: any substance other than alcohol that alters biological functioning. We recognize that alcohol is a drug commonly used by drivers. As noted above, the other portion of this study extensively examined the relationship between alcohol and highway safety. Because we also recognize that alcohol is frequently used in combination with other drugs, this report includes topics on the combined use and effects of alcohol and other drugs.

1.2 Study Approach

Three basic facts increase concern about the role that drugs play in traffic crashes. First, many people use drugs that have the potential to affect behavior. Second, many of these people drive. Third, some people who use drugs are involved in traffic crashes.

Because only a limited number of investigations have established that drugs have played a causative role in specific traffic crashes, the information we now have does not support general statements about the role of drugs in traffic crashes. The evidence is sufficient to cause concern and to warrant further inquiry, but not to establish drugs and driving as a high-priority safety concern. Thus, for purposes of this study, the existence of a drug and driving problem has been a working

hypothesis. In fact, primary concern of the study has been to identify the research necessary to define the drug and driving problem adequately and to specify what information is needed to develop appropriate countermeasure programs to deal with any identified problem.

The following questions frame the scope of inquiry:

1. Given that the "drug-crash problem" is a research hypothesis, what research is required to define the problem? In other words, what are the research requirements in drugs and highway safety?
2. What is now known about the relationship between drugs and highway safety?
3. How reliable, and how useful, is the information now available?
4. What are the problem areas and information needs evident in drug and driving research?
5. What specific research is required before the relationship between drugs and highway safety is determined adequately?
6. Which research is a priority need and should now be conducted to improve the definition of the problem?

In this report we first attempt to define the field of drugs and highway safety, and specify research required to define the problem of drugs and driving (Question 1). Second, we examine research on drugs and highway safety. With past assessments in hand, we evaluate the state of knowledge (Questions 2 and 3). Third, we outline problem areas in drug and driving research and specify current information needs (Question 4). We provide in-depth reviews of several special topics of particular interest to current research. Lastly, we describe research needs in drugs and highway safety; we offer recommendations concerning future research priorities (Questions 5 and 6).

The scope of this inquiry was necessarily broad. It encompassed a range of disciplines and areas of applied research. Six major areas of concern were identified early in the study effort as focal points for inquiry:

- Identification of Drugs of Interest;
- Epidemiological Research to Estimate the Level of Drug Involvement in Accident and Non-Accident Driving Populations;
- Experimental Research to Determine the Effects of Drugs on Driver Performance;
- Analytical Methods for the Detection and Quantitation of Drugs in Biofluids of Drivers;
- Interpretation of Drug Levels in Biofluids as Related to Driver Performance; and
- Preventive Measures, or Countermeasures--Their Identification, Development, Demonstration, Implementation, and Evaluation.

These major topic areas served to organize the extensive body of literature that was examined to assess the state of current knowledge, specify information needs, and develop recommendations for research. These topics and the reason for their selection are described in greater detail in the next chapter.

1.3 Literature Search

To support the review and analysis of research on drugs and highway safety, literature was searched, both manually and with computers. The literature search actually supplemented an existing base of information supplied by a previous literature search and review and its bibliographic output (Joscelyn and Maickel 1977a; Joscelyn and Maickel 1977b). From this source we developed a list of journals that frequently contained material relevant to our needs. These and other journals were then searched for literature published since the cessation of the prior effort. Also searched were journals and other literature sources (e.g., Index Medicus) that serve areas of research not searched previously. Lists of authors and researchers active in their respective fields were used to identify recently published articles and reports. Bibliographies and selected abstract services supplied additional references.

Several computer-based information retrieval services supplemented this

effort. Data bases available to the research staff included the following systems:

- Social SciSearch (Institute for Scientific Information)
- NTIS (National Technical Information Service)
- BIOSIS (Biosciences Information Service)
- MEDLARS (State University of New York--National Library of Medicine)
- MEDLINE (Monthly Index Medicus Search)
- APA (Psychological Abstracts)

Other search methods and efforts contributed to the review of the state of knowledge. For example, the topic area **drugs and driving** is one of the search topics of the HSRI Information Center. The continuing surveillance of the literature by the Information Center staff included periodic computer searches of the relevant literature. Upon identification, all publications were collected and brought to the attention of research staff. The research staff also established communication with active researchers, who often provided current information in advance of publication.

1.4 Report Organization

This report consists of ten chapters arranged in three parts and a set of appendices.

PART ONE: A REVIEW OF RECENT RESEARCH ON DRUGS AND HIGHWAY SAFETY follows this introduction to the report. Its four sections describe what is now known about drugs and driving. Section 2.0 summarizes past efforts to discuss the state of knowledge. This section also presents a conceptual structure of drug and driving research. Sections 3.0 and 4.0 review research in two general categories, epidemiology and experimentation, respectively. Section 5.0 deals with the topic area of countermeasures in drugs and highway safety. It discusses concepts and constraints in the area of drug countermeasures.

PART TWO: PROBLEM AREAS AND INFORMATION NEEDS IN DRUGS AND HIGHWAY SAFETY discusses key issues in research to advance the state of knowledge. Again, separate sections (6.0 and 7.0) treat epidemiological and experimental branches of drug and driving research. Section 8.0 summarizes and evaluates research on drugs and highway safety.

PART THREE: CONCLUSIONS AND RECOMMENDATIONS presents the findings of this study. Section 9.0 describes strategies for future research, suggests priorities for required research, and lists recommendations for future research. The conclusions and recommendations are presented in summary form because Parts One and Two of the report describe in detail the research requirements, the problems, and the information needs pertaining to each major topic. Section 10.0 outlines a research program designed to implement the recommendations of this study.

A set of appendices examines in greater detail specific topic areas in drugs and highway safety. Appendix A contains two tables that summarize studies of drugs and their effects on driving-related skills. Appendix B reviews present knowledge about the relationship between levels of drugs in body fluids and their effects on human performance. Appendix C reviews the state of the art in drug analysis as it applies to highway safety.

1.5 Note to the Reader

To the extent possible this report was designed for use by the highway safety community at large. The subject, however, requires the use of pharmacological and other special terms and concepts, some of which may be unfamiliar to the general reader. The report also includes some detailed discussion of certain methodological issues of interest mainly to researchers in drugs and driving. The available time, funds, and space do not allow inclusion of background material on basic principles in pharmacology, drug nomenclature and classification, and analytical chemistry, but the resource documents listed below can assist the general

reader in understanding the technical portions of this report.

Brecher, E.M., and Editors of Consumer Reports. 1972. Licit and illicit drugs. In The Consumers Union report on narcotics, stimulants, depressants, inhalants, hallucinogens, and marijuana--including caffeine, nicotine, and alcohol. Mount Vernon, New York, Consumers Union.

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PART ONE

A REVIEW OF RECENT RESEARCH
ON
DRUGS AND HIGHWAY SAFETY

PREFACE

As indicated by its title, Part One of this report reviews recent research on the relationship between drugs and highway safety. It covers research efforts to identify the problem as well as to counter any problem identified. One purpose of Part One is to describe the base of information on which the findings of this study rest. Another purpose is to define the scope of research on drugs and highway safety. As the base of information is described and the scope of research is defined, the research required in this area and the information still needed become apparent.

Research both directly and indirectly related to drugs and driving is reviewed; for although drug and driving research per se is by no means nonexistent, it is scarce enough to warrant the inclusion of other studies which, though peripheral to the central issue, still provide valuable insight into the problem and its possible magnitude.

This report builds on earlier efforts to assess the state of knowledge in drugs and highway safety. Part One begins with a review of past reviews. Next, a conceptual framework for drugs and driving research is outlined. This scheme helped to organize the findings of recent research for evaluation. On this background, three sections review recent literature in drugs and driving and point out methodological and other issues in specific areas of research.

2.0 PAST AND PRESENT RESEARCH ON DRUGS AND HIGHWAY SAFETY

This section further describes the study approach outlined in the Introduction. It presents information on:

- Historical Perspectives on Drug and Driving Research;
- The Structure of Drug and Driving Research;
- Major Topics in Drug and Driving Research; and
- The Identification of Drugs of Interest.

These topics are discussed in greater detail here to provide common definitions, a better understanding of the scope of the study, and a framework that will assist the reader in his approach to subsequent sections of this report.

2.1 Historical Perspectives on Drug and Driving Research

The subject of drugs and driving has not been ignored in the past. Many researchers have examined various aspects of the problem and reported their results in the scientific literature. The subject has also been extensively discussed in the popular literature. Such discussions, however, are more rhetorical than factual.

Perhaps one of the most important features of drug and driving research is that no unified body of literature addresses the full range of research issues in a research area that spans many disciplines. The breadth of the subject, the lack of a common body of literature, and the range of disciplines involved partially explain why past drug and driving research has been fragmented and relatively uncoordinated. Another factor is the complexity of the problem, which requires complex, large-scale research efforts for its definition. Only limited funding has been allocated to the study of the subject, and most research has been quite limited in scale. These limitations may have contributed to the methodological shortcomings found in many past studies.

At periodic intervals efforts have been made to review the research literature and summarize what was known about the relationship of drugs and traffic crashes. Some recent studies provide insight into the state of research in drugs and driving.

A 1968 Organization for Economic Cooperation and Development (O.E.C.D.) report drafted by Goldberg and Havard noted that very few studies had been carried out to establish the role of drugs in traffic accidents:

The situation can be compared to the one existing in the field of alcohol and road accidents forty years ago, before practicable methods to determine alcohol were introduced, before even the earliest legislation existed against alcohol impaired driving, and before any studies had been made on a comparison between the presence or absence of alcohol in accident-involved cases and in a control group of non-accident-involved cases, examined under similar conditions.

There is one difference, however, in that our experience in the alcohol field will make us aware that a problem does exist, even if we do not know its extent. (Goldberg and Havard 1968, p. 29.)

In 1972 a symposium held in Vermont under NHTSA sponsorship examined the extent of present knowledge on alcohol, drugs, and highway safety and recommended priorities for basic and applied research. In addition to general discussions of the subject areas, the participants--both researchers and practitioners--used a keyword rating system to develop forced-choice judgments. In reporting the process, Perrine (1974), cautioned that these judgments "should not be interpreted as being judgments about whole programs (whether of research or countermeasures)" (p. iv). Cost and time were excluded from consideration in making the ratings. Thus, the priorities developed were not intended to reflect a cost-effective allocation of limited resources for research or countermeasure programs.

Two sessions dealt with drugs other than alcohol and driving. R.G. Smart (1974) summarized keyword ratings for Session 6 ("Use of

Psychoactive and Hallucinogenic Drugs in Relation to Driving Risk"):

1. Knowledge levels in the area of drug use in relation to driving risk are lower than for almost all areas involving alcohol and driving.
2. Knowledge levels are seen as highest for countermeasures and lowest for risk contribution to accidents and accident histories of users.
3. Applied research priorities are rated highest for those areas where knowledge is low, i.e., the contribution of drug use to accident risk, extent of use of drugs by drivers, and accident histories of users. (pp. 334-5.)

In Session 7 ("Drug Influences Upon Driving-Related Behavior"), participants rated thirty-nine keywords representing a broad range of research areas and interests. According to Lubin (1974), the ratings indicated that present knowledge was inadequate, and that little differentiation existed between various research areas. Research **priorities** were rated more definitely. For example, cognitive functions, as opposed to perceptual or motor functions, were given higher priority for basic research. Complex cognitive and perceptual functions received higher priority ratings than less complex sensory and motor functions.

Perrine (1975) also summarized the results of the keyword rating of applied and basic drug research. While the basic research objectives were similar to those of research on alcohol, the applied research priorities differed:

Highest priorities for applied research on the **epidemiology of drugs** in highway safety were given to the incidence and prevalence studies necessary in the exploratory state of investigating a new problem (specifically, risk contribution of both hallucinogenic and psychoactive drugs to accidents, and extent of hallucinogenic drug use among drivers and pedestrians) . . .

Since none of the keywords concerning **drug countermeasures** received above-average priority ratings, it was concluded that more incidence and prevalence studies are

necessary to define the nature and scope of the drug and highway safety problem before any countermeasure programs can be undertaken. (Perrine 1975, p. 127).

Two and a half years later, in 1975, another symposium examined the state of the art in drugs and driving (Joscelyn and Maickel 1977c). Held in Bloomington, Indiana, the meeting was an integral part of a general research review for NHTSA. The review included an evaluation of epidemiological and experimental research, methodologies for measuring drug presence as well as drug effects, legal constraints on drug and driving research, and priorities for future research (Joscelyn and Maickel 1977a).

Although the Vermont and Bloomington symposia took place two and a half years apart, their conclusions and recommendations were nearly identical. In Bloomington, R.G. Smart, a participant in both symposia, discussed current research and future needs (Smart 1977). He ascribed the "prolonged infancy" of drugs and driving research to the large number of drugs to be considered and to the need for technological innovations in toxicology and biochemistry. Smart suggested that research be restricted somewhat to the major psychoactive and hallucinogenic drugs; that needed epidemiological and experimental studies should include quantitative determinations of drugs in body fluids; and that where analytical methods were required, e.g., for LSD and cannabis, the development of adequate methods should be pursued. Smart also recommended "experimentation with efforts to have physicians prescribe fewer psychoactive drugs or to give effective warnings about driving to their drug-using patients" (p. 230). He cited the need to determine why people require so many psychoactive drugs as well as what could be done to reduce their need for them.

The results of the symposium, the literature review, and an analysis of the literature were synthesized by the principal investigators, who authored a general report (Joscelyn and Maickel 1977a). They concluded that while research indicated the widespread use of drugs that could impair driving ability, existing research could **not** establish:

- the role that drug usage plays in traffic accident

causation;

- the nature and extent of drug usage by drivers involved in traffic crashes; and
- the nature and extent of drug usage by drivers at risk who are not involved in traffic crashes.

They attributed the deficient state of knowledge partly to the lack of sufficient funds for large-scale research efforts required for definitive examination of drugs and driving issues. The inconclusive findings of past research stemmed from the state of the art in drug analytical methodology and from the dearth of information relating the pharmacological effects of drugs to driver impairment. Legal constraints hampered data collection. The principal investigators also concluded that "a first priority should be to determine the nature and extent of the role of drugs in crash causation" and that "large-scale countermeasure programs focused on the drug/driving problem do not appear warranted at this time. The nature and extent of the problem must be better defined before a large-scale response can be developed or supported" (Joscelyn and Maickel 1977a, p. 8).

These recommendations, generally consistent with analyses of other researchers, led to the decision by NHTSA to undertake the present effort, which is intended to define more precisely the research necessary to define the role of drugs in traffic crash causation.

In 1976, during the course of the present study, the National Institute on Drug Abuse (NIDA) sponsored a critical review of literature relating drug use to driving. Intended to complement surveys and reports published by the U.S. Department of Transportation (DOT), the study reviewed the state of knowledge concerning drug effects on complex human behavior. The panel of experts who conducted the review and staff representatives from NIDA and DOT then participated in a conference that had two aims: first, to identify and order issues related to the study of drug effects on driving performance; second, to make recommendations for future initiatives by the government. In addition to reviewing studies of drug impairment, panelists prepared papers to guide the discussion of research issues during the conference. The 1977

monograph published by NIDA (Willette 1977) summarized this effort to review literature and to recommend research on drugs and highway safety.

The identified research issues fell into four major categories: epidemiology, laboratory studies, assay development, and legal questions.

Panelists developed three major categories of recommendations:

1. Levels of priority for study of specific drugs and drug groups. According to panel members, alcohol; cannabis, diazepam (Valium®), and their derivatives; and sedatives and hypnotics represent, in descending order, the three top levels of priority for further research.
2. Methodological issues. As topics for additional research, panel members noted methodological issues in epidemiology, experimentation, and drug analysis. They recommended a continued emphasis on **effective** epidemiological studies and suggested that laboratory studies should focus on the "chemical-behavioral component relationships," rather than attempt to link causally the relationship between drug dosage and the impairing of actual driving performance. They pointed out also the need to develop better methods to assess behavioral change and drug levels in the blood.
3. Prevention strategies. Several recommendations addressed measures to reduce the social liability of drugs and their use. The panelists suggested the study of unnecessary tranquilizer use, an increased focus on "erratic driving behavior" rather than "under the influence" at the enforcement level, and the expansion of labeling and education programs.

In 1978, the O.E.C.D. produced a report that reviews research findings on alcohol, other drugs, and traffic safety and examines countermeasure programs. The Road Research Group on "New Research on Alcohol and Drugs," created to follow-up earlier O.E.C.D. activities in this area (Goldberg and Havard 1968), finalized the report in a series of four

meetings held between July 1975 and March 1977. In many ways similar to the reports produced under the present contract, the objectives of the state of the art review were as follows:

- (a) review existing scientific literature and other available information on the role of alcohol and drugs in traffic accidents;
- (b) examine information related to impaired driving countermeasures and evaluate their effectiveness;
- (c) identify the research results obtained on current practices proven successful that can be recommended for general and immediate application in Member countries;
- (d) indicate priority needs for research in the fields of alcohol, drugs, and traffic safety and outline possible future international co-operative activities (O.E.C.D. 1978, p. 5).

The Research Group also developed a revised methodology for conducting roadside surveys of drinking-driver behavior, and prepared a list of analytical techniques for detection and quantitation of alcohol in drivers.

The report presented a series of recommendations for future activity in the area of alcohol, drugs, and highway safety. Because the role of alcohol in traffic accidents has been established, recommendations for alcohol and highway safety focused on the area of countermeasures. In assessing research findings for drugs other than alcohol and for drugs-plus-alcohol, the Research Group concluded that both experimental and epidemiologic studies had failed to define the nature and extent of the drug and driving problem. Despite the number of studies on drug effects, "experimental studies however remain unclear in defining what relationships exist between drug effects, test performance, driver performance, and traffic crash causation. Present experimental evidence has to conclude that a simple predictive measure of drug effects on human performance, which is important in driving, has not yet been obtained" (O.E.C.D. 1978, p. 111). Methodologic issues in epidemiologic studies, in particular analytical methods for determining the presence and

amount of drugs in drivers, have limited the validity of published research. The Research Group "recommended that valid research studies be designed to investigate the extent and nature of drug use among drivers and pedestrians involved in fatal and non-fatal traffic accidents with the most appropriate control groups selected from the general driving population" (O.E.C.D. 1978, p. 122). The most urgent need, according to the report, was the development of more sensitive, practical assay techniques for "all pharmacologically active forms of psychoactive drugs suspected or known to impair driving abilities" (O.E.C.D. 1978, p. 116).

Occasional scientific meetings have also addressed topics in drugs and driving. Noteworthy are the Sixth and Seventh International Conferences of Alcohol, Drugs, and Traffic Safety, held in Toronto, Canada, 1974 (Israelstam and Lambert 1975), and in Melbourne, Australia, 1977 (International Committee on Alcohol, Drugs, and Traffic Safety 1977), respectively. In addition to papers, the latter conference featured a series of workshops devoted to issues in alcohol, drugs, and highway safety. Unfortunately, the entire proceedings of that meeting and the results of its workshops were not published before the writing of this report.

2.2 Structure of Drug and Driving Research

The basic structure for this study is provided by the two kinds of research directly related to drugs and highway safety: **epidemiological** and **experimental**, as noted by Perrine (1976) for the alcohol-highway safety field.

Epidemiology is the science concerned with the incidence, distribution, and control of disease. Its methods, however, have been widely applied in the study of drug-related social problems (e.g., Rootman and Billard 1975). Observation of the real world is the hallmark of epidemiological research; studies using this approach focus on the involvement of drugs in traffic crashes. The aim of epidemiological research is associative; in highway safety, this approach (in drugs and driving) associates the presence of certain factors (e.g., kinds of drugs) with traffic crashes. Surveys attempt to demonstrate types of association based on statistics.

". . .The investigation of a relationship can be seen to progress from demonstration of statistical association to demonstration that the association is causal, and ultimately to ascertainment of its directness" (MacMahon, Pugh, and Ipsen 1960, p. 12).

Experimentation, of course, refers to research performed under controlled conditions, usually in a laboratory setting, indoors or out. Experimental research extracts factors (variables) from the real world for study. Studies using this approach examine the effects of drugs on behaviors believed related to actual driving performance. Experimental research attempts to establish that relationships between certain factors and the event under study are in fact **causal**.

Viewed in this way, epidemiologic and experimental approaches are complementary as MacMahon, Pugh, and Ipsen (1960) have pointed out:

The fact that the contributions of other disciplines are required in addition to those of epidemiology is implicit in the statement that the methods of epidemiology are predominantly observational. Since the most convincing test for causal relationship is usually through experiment, the methods of other disciplines are needed for more critical examination of suspected causal relationships and for the investigation of their mechanisms. (p. 10.)

Significant findings using one approach may be taken for further study with the other. (Later sections of this report elaborate this point to show the possibility for better coordination of research on drugs and highway safety.)

Undertaking research in these general areas in turn generates additional, more specific requirements for the study of drugs and driving. For example, how does one design and implement a sampling plan for a survey to collect information on the presence of drugs in drivers? How is the presence of drugs detected and quantified? How are drug effects best measured? Figure 2-1 illustrates the relationships between the general and specific research areas in drugs and highway safety. The specific research areas identified for epidemiological and experimental research and described below are not all-inclusive by any means. They

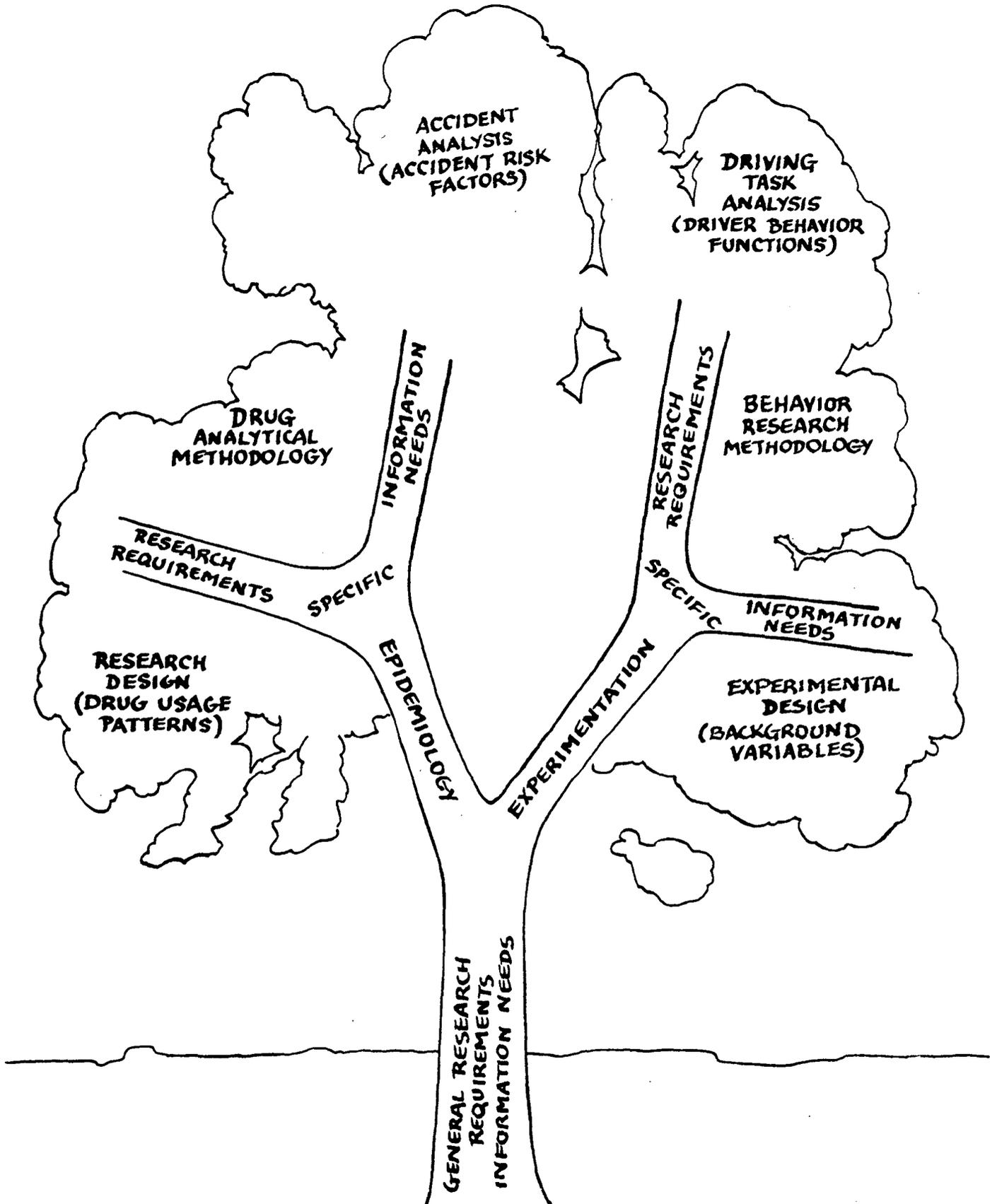


FIGURE 2-1. RESEARCH IN THE FIELD OF DRUGS AND HIGHWAY SAFETY

are, however, among the most important. Most issues in current research on drugs and highway safety involve these areas.

Figure 2-2 also illustrates the structure of research in drugs and highway safety. The problem itself determines the general requirements for research. Two general approaches, epidemiology and experimentation, fulfill the general information and research needs. The efforts to meet the general requirements generate specific requirements for research. The specific information and research needs call on the methods and knowledge of many disciplines.

Both of the figures illustrate the multidisciplinary nature of research in this applied field. They show how necessary it is to specify a hierarchy of research requirements. For example, a discussion of epidemiologic research quickly leads to discussions of sampling theory, analytical methods for detection of drugs in body fluids, the interpretation of a drug's blood levels in terms of its influence on driving behavior, etc. This has led us to identify major topic areas for (1) general research and information needs directly related to drugs and driving and (2) specific research and information needs less directly related but required nonetheless to complete the general research.

The state of knowledge in each of these topic areas has been assessed. Identification of needed information establishes a requirement for research. As these requirements were identified through the analysis and review of the literature, they were expressed in the form of research questions or as research projects. The identified requirements were reviewed to establish priorities. A research program was then formulated to illustrate how projects could be implemented to develop the required information to determine the role of drugs in traffic crash causation.

2.3 Major Topics in Drug and Driving Research

This subsection briefly describes the major research topics discussed in detail in this report. Its objectives are to identify the major topics, to establish their importance, and to show their relevance to other topics.

Identification of Drugs of Interest. What researchers must first do is to select the drugs that are of interest for research in drugs and

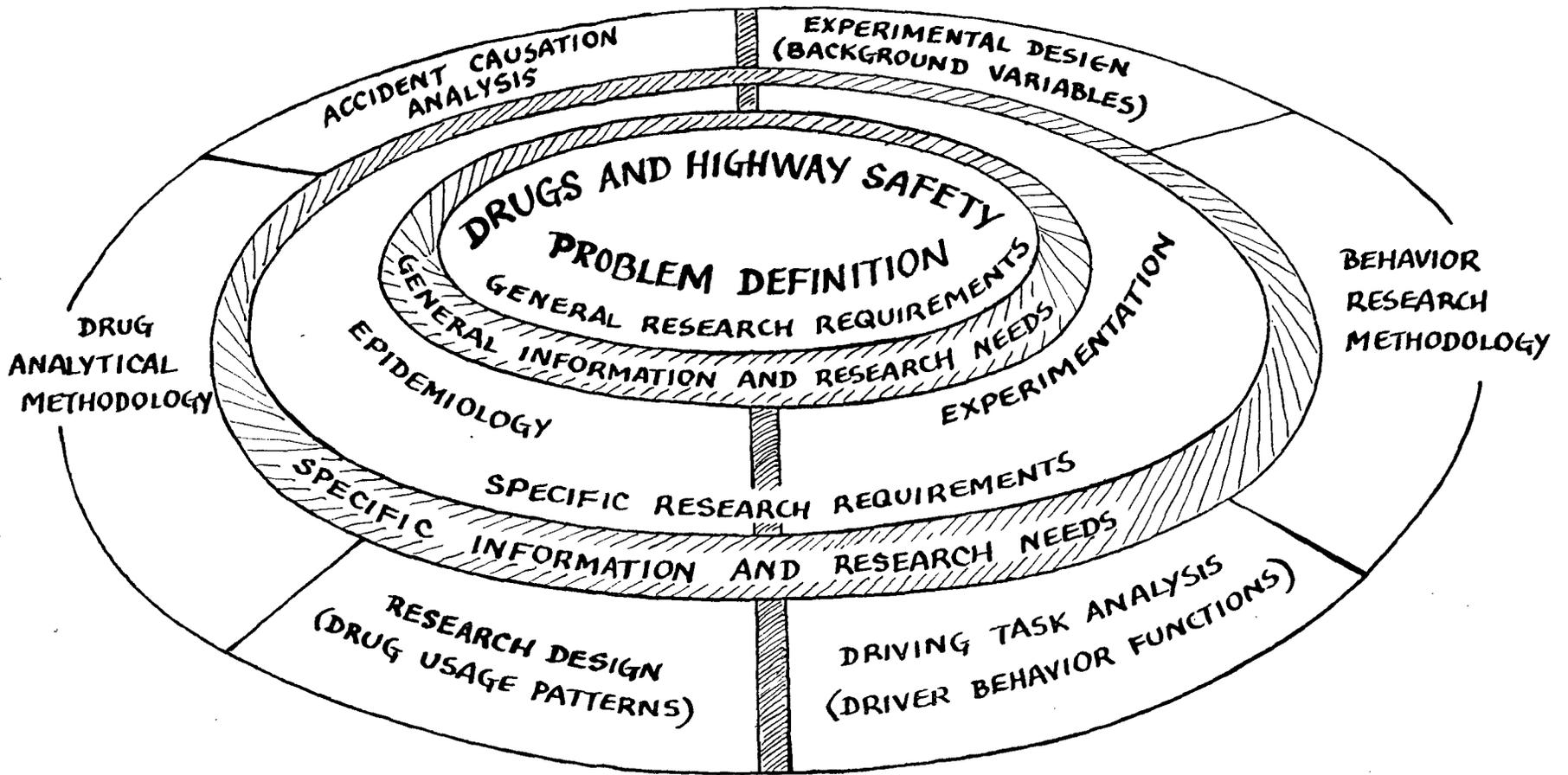


FIGURE 2-2. RESEARCH ON DRUGS AND HIGHWAY SAFETY: A STRUCTURAL CONCEPT

driving. Basically, almost every drug, if used to excess, has the potential to affect human behavior so adversely as to impair driving performance. Some therapeutic drugs even used as prescribed have this potential, too. But not all drugs, as they are commonly used, would be expected to impair driving. Drugs are so numerous, their effects and patterns of use so diverse, that some selection is a basic requirement for research in drugs and driving. Clearly, research should be focused on the drugs that are most likely to contribute to traffic accidents, which requires that the potential of drugs to increase risk to highway safety be assessed. Because it will narrow the focus of research to a set of drugs of interest, the process of risk assessment has great import for research on drugs and highway safety. Section 2.4 describes the information about drugs, their use and effects, that can be used in risk assessment.

Topics in Epidemiological Research. In addition to research aimed at selecting the drugs of interest in highway safety, epidemiological research is necessary to determine the prevalence of drugs in drivers--both accident- and nonaccident-involved. The frequency of drug use in the two populations indicate the nature and extent of the problem; over-representation of a drug or drug group in the accident population points to the necessity for further inquiry to define its role in crash causation.

As noted in Figures 2-1 and 2-2, three research areas are particularly important in the epidemiology of drugs and highway safety: research design, accident analysis, and drug analysis. As an area of research, the design of studies includes issues that range from plans for sampling different driving populations to the practical concerns of implementing such plans. Because many factors may interact with the drugs to increase crash risk, the analysis of such factors as driver and crash characteristics is also very important in drug and driving research. Screening techniques as well as proven methods to quantify the presence of drugs in the body are needed for surveys of driving populations. The mere presence of drugs **does not** establish driver impairment, but knowing the amount of drugs present makes some interpretation possible.

Section 3.0 reviews past and present epidemiological research on drugs

and highway safety. Section 6.0 describes information needs and requirements in this area of drug and driving research. Appendices B and C examine in detail the topics of the interpretation and analysis of drug concentrations in human biofluids.

Topics in Experimental Research. Although most research involves experimentation of some kind, experimental research includes controlled studies that examine some aspect of the drug and driving problem. Studies that measure the effects of drugs on human skills believed related to driving are common. Not as common but just as important are studies to describe the interaction of variables that pertain to the subjects and conditions of these experiments.

The specific research areas listed in Figures 2-1 and 2-2 are major topics in experimental research: driving task analysis, behavioral methodology, and experimental design. The analysis of driving as a task is required to determine which component skills are most important for the testing of drug effects. Behavioral methods for measuring the effects of drugs must also be analyzed--for their sensitivity and specificity as well as for their relation to actual performance of the driving task. In the design of valid experiments to assess the potential of drugs to impair driving, important questions concern the characteristics and rights of human subjects, the variability of drug effects, and variables of drug administration. The relation of experimental to epidemiological research in drugs and driving is perhaps best seen in the need for studies that correlate the behavioral effects of drugs with their concentrations in the biofluids of experimental subjects.

The sections of this report on experimental research parallel those on epidemiology. Section 4.0 reviews experimental research in drugs and highway safety. Section 7.0 describes information needs and requirements in this area of drug and driving research. Appendix A contains two tables that summarize studies on the effects of drugs and combinations of drugs on human behavior. As noted above, Appendices B and C deal with the interpretation and analysis of drug levels. While perhaps less important to experimental research, these topics overlap both general areas of drugs and highway safety.

Countermeasures. The introduction to this report (Section 1.2) emphasizes that the existence of a drug and driving problem was a working hypothesis for this study. The presumption of a problem is necessary simply because past research has not adequately described the relationship between drugs other than alcohol and highway safety. Consistent with this presumption is the review of literature on countermeasures in drugs and driving. The lack of basic information on the nature of the drug and driving problem, however, limits treatment of this topic.

Most experience with drugs in the field of highway safety comes from the study of one drug--alcohol. Alcohol is a unique drug in many respects. It can be easily detected and quantified in breath, blood, and urine. The relationship between its amount and its effects, if not perfectly linear, is at least grossly interpretable in terms of driver impairment. Other drugs do not behave so simply in the body; their presence is not so easily detected; and the meaning of their levels is not so certain. Countermeasures for alcohol reflect its chemical and pharmacological nature. Countermeasures for drugs other than alcohol must take into account these differences.

Section 5.0 deals with countermeasures in drugs and highway safety. The interpretation and analysis of drug levels in biofluids, two topics so important in the development of drug countermeasures, are the subjects of Appendices B and C, respectively.

2.4 The Identification of Drugs of Interest

This report deals indirectly with the first major topic described above, the identification of drugs of interest for drug and driving research. No attempt is made to select a set of drugs most likely to be involved in traffic crashes. (One purpose of an ongoing project, DOT-HS-7-01530, is to identify drugs whose potential to increase the likelihood of a traffic crash appears greatest.) Instead, this subsection outlines a number of criteria by which the potential highway safety risk of drugs may be assessed.

The very general definition of "drug" given in Section 1.1 perforce

raises the question: which drugs should be considered in research to define the relationship of drugs and highway safety? General criteria for estimating the traffic crash risk of drugs have been suggested in the literature (Smart 1977; Smart 1974; Waller 1975). For example, recognizing that all drugs, all users of drugs, and all circumstances of use are not equal in potential hazard, Waller (1975) proposed a "frequency quantity model" for the purpose of setting priorities for research and action:

I believe this question can be answered by means of a model of frequency and quantity of deviation behavior. In this case, deviant behavior is defined as behavior which has a high risk of initiating social problems. Now it is important to note that, with very rare exceptions, a perfect correlation does not exist, either with physical or biological phenomena, between the presence of a cause or causal set and the occurrence of an effect. However, the stronger the causal set the more likely it is that the effect will occur, and the greater it will be.

As applied to drugs and highway safety, the frequency-quantity model of deviancy, therefore, states the following:

- (a) the more frequently a drug is used in the highway setting the more often it is likely to be a problem.
- (b) the more impairing the effect of the drug, either because of its inherent nature or because of the [un]usual quantity consumed, the more likely there is to be a problem. (Waller 1975, p. 4.)

In general, then, a drug's potential risk to highway safety may be viewed as a composite picture of its **usage pattern** in the population at risk and its **effects**. Within these general categories are numerous, more specific factors that relate directly and indirectly to highway safety. A drug's usage pattern (or, more generally, exposure) is a comprehensive social profile that describes how, when, where, and by whom the drug is used. The frequency with which two or more drugs are combined is also an important factor. General categories of drug effects are

pharmacological, clinical, psychological, and behavioral. In both use and effects, the relevance of available data for risk assessment varies. We believe a broadly based assessment is required to select a set of drugs of interest for further research in drugs and driving.

Above all, a method or procedure is required to synthesize present knowledge for assessing a drug's potential risk to highway safety. Factors related directly and indirectly to highway safety should specify data needed for estimating the potential risk of drugs. Because of limited knowledge in this research area, initial methods developed will necessarily be heuristic. (As noted above, an attempt to develop a paradigm for risk-assessment is being made under contract DOT-HS-7-01530.)

In Section 3.0 and 4.0, the review of research was expanded to include information on factors that may be of use in assessing the potential highway safety risk of drugs. For example, in the epidemiology of drugs and highway safety, the literature on general patterns of drug use was reviewed. Included in experimental research were studies not explicitly done to estimate impairment of driving. We hope that this approach, in addition to updating the review of literature on drugs and driving, will indicate the information available for the risk assessment of drugs.

2.5 Summary

This section has explained the approach used to conduct the study and to present the report. First, a summary of past reviews presented earlier assessments of research on the drug and driving problem. Second, a conceptual framework of drug and driving research described the scope of the field and its constituent areas of research. Third, major topics in drugs and highway safety were identified. Fourth, one major topic, the identification of drugs of interest, was discussed. Factors in the risk assessment of drugs were cited to indicate the scope of the review effort presented in later sections.

The following parts of this report evaluate the research literature associated with each of the major topics. The results of this review and evaluation are summarized as conclusions and recommendations. A research program is proposed to integrate the recommendations for

further study of the drug and driving problem.

3.0 EPIDEMIOLOGY IN DRUGS AND HIGHWAY SAFETY

This section is a review of literature on the use of drugs by drivers as well as by other populations. Its purpose is twofold. First, by including reports on patterns of drug use by other than driving populations, we wish to assess their value for showing the potential impact of drug-taking behavior on traffic safety. Second, by reviewing the more specialized studies in drugs and driving, we update past reviews. We also point out methodological and other issues in this research and then evaluate the current state of knowledge. The overall objective is to present background information for the later section on problem areas and information needs in the epidemiology of drugs and highway safety.

3.1 Patterns of Drug Use

The use of drugs, or "drug-taking," has been termed a behavior (Ray 1978, p. 9). Like any behavior, it can be described. Patterns of drug use are many and varied, and include information on where, when, how often, how much, why, and by whom a drug is used. They range from self-medication with home remedies to inpatient treatment with restricted drugs; from the use of socially accepted drugs, like alcohol and caffeine, to the use of socially nonaccepted, illicit drugs, like marijuana and cocaine; from the self-administration of prescribed pharmaceuticals to the self-prescribed, nontherapeutic use of these medicaments. Certain drugs may have but a single use in a limited setting; others may be used for very different reasons in various situations. So the pattern of use for a drug in a population may be simple or complex.

Unfortunately, the use of most drugs by the general population is difficult to describe. The amount of drugs (total sales, dosage units) available for use in the general population is only approximately known, if at all. The statistics of drug use have been described as "largely inadequate and inaccurate" (Milner 1976). The frequency and manner of

drug use by individuals in the population is all but unknown. Prescription data are "either poorly compiled or not freely available" (Hemminki 1976). Therefore, information about the personal characteristics of the consumers of drugs (age, sex, occupation, driving frequency) is rarely obtained without special study. The illicit use of drugs is, of necessity, clandestine and subject to assessment only by confidential survey (Kandel 1977). Even here, the true contents of street-drug samples often differ from their alleged contents (Siegal 1978), and the subjects of these surveys may not know themselves which drugs they've actually taken.

As Robins has pointed out, "Drug use is a function not only of the predisposition of the individual to use but also of his opportunities to do so" (Robins 1975, p. 14). This applies not only to street drug supplies, which are variable, but also to the prescribing habits of physicians and the policies of drug maintenance centers. The use of different types of drugs may be linked to variations in supply. For example, fluctuations in the sale of over-the-counter (OTC) drugs containing psychoactive compounds may reflect availability of street drugs in some areas. The sources of information on such matters are limited indeed.

Aside from the formidable task of obtaining information on the use of drugs generally, the existing literature is limited specifically in its application to the subpopulation of interest here, namely, the driving population. The limitations have been described previously (Joscelyn and Maickel 1977a; Cooperstock 1975):

- published studies range from carefully designed and reported efforts to popular "guesstimations";
- even well-done research includes only a limited set of drugs, often grouped by classes rather than identified separately;
- the data are often old and difficult to apply to the driving population;
- the data on "average use" or per capita usage data do not allow study of individual variations in use of a drug;
- the total sales of manufactured units do not reflect any distributional inhomogeneity within a general population;

and

- the prescription data do not yield information on the quantity of drug, number or refills permitted or obtained, or how the drug was consumed.

Table 3-1 summarizes the sources and types of data used to describe drug usage patterns and presents a listing of their main limitations. Note that such information is limited generally by the fact that the driving population itself is included nonspecifically. Thus, the relationship between the use of drugs and driving remains unknown with these data.

On the other hand, in the absence of research on drug use by the driving population, information about drug use by the whole population at least provides an estimate of "how much" and "by whom." It is true that general information on drug use says nothing at all about driving while using drugs. But as one author has characterized self-reporting in general, direct information from drivers is also "notoriously unreliable" (Hurst 1976). But short of extended studies to determine the actual prevalence of drugs in driving populations, indirect information on patterns of drug use would seem to indicate what the driving population may be using while driving. For the purpose of identifying drugs of interest, known patterns of drug use, in conjunction with behavioral and pharmacological data, should supplement what little epidemiologic data may be available.

The classification of different kinds of drug use presents some difficulty. Not even the definitions of terms used to study drug use have been standardized (Elinson and Nurco 1975; Elinson 1977). Both general and specific categories related to the type and use of drugs have been used. For example, drug usage may be discussed in terms of:

- the purpose of drug ingestion (e.g., medical or nonmedical);
 - the legal status of drugs (e.g., licit or illicit, controlled or uncontrolled);
 - the mode of drug acquisition (e.g., prescribed, over-the-counter, or street-bought);
- the medical condition being treated (e.g., depression, anxiety, etc.);

TABLE 3-1

SOURCES AND LIMITATIONS OF DRUG USE INFORMATION

<u>Type of Data</u>	<u>Main Limitations</u>
Production	<ul style="list-style-type: none"> ● Gross amounts reported unrelated to dose, use. ● Uncertain distribution among individuals. ● Changes in use over time difficult to estimate.
Total Sales	<ul style="list-style-type: none"> ● Uncertain distribution among individuals. ● Far removed from actual consumption patterns.
Prescription Sales	<ul style="list-style-type: none"> ● User characteristics unspecified. ● Unknown variations in type and duration of prescription. ● Amount of drug used often concealed.
Commercial Market Research	<ul style="list-style-type: none"> ● Most comprehensive source of information, but usually unavailable to nonindustry researchers.
Institutional Use and Dispensing	<ul style="list-style-type: none"> ● Small percentage of total use represented. ● Different patterns of drug use compared to general population.
Household Interview Studies	<ul style="list-style-type: none"> ● Limited set of drugs, usually reported as general classes. ● Data old. ● Validity problems, especially underreporting.
Independent Prescription Research	<ul style="list-style-type: none"> ● Only approximate actual consumption patterns. ● Often involve select (localized or special) populations.

TABLE 3-1 (Continued)

<u>Type of Data</u>	<u>Main Limitations</u>
Emergency Room Drug Incidence Studies	<ul style="list-style-type: none"> ● Analytical methods insufficient. ● Largely uncharacterized population with unknown relation to general population. ● Selection of a "typical" population possibly due to type of admission (drug overdosages, serious drug side effects) or type of accident. ● Cases involving "street drugs" dependent on changes in strength of available drug. ● Multiple drug use complicates analysis and interpretation.
Street Drug Analysis	<ul style="list-style-type: none"> ● Uncertain distribution throughout population. ● Volatile patterns of availability to user.
Studies of Nonmedical Drug Use	<ul style="list-style-type: none"> ● Data not current. ● Populations surveyed are not representative of the driving population.
Drug Confiscation Reports	<ul style="list-style-type: none"> ● Gross indication of drug use trends only. ● Uncertain levels of police activity over time.
Drug Treatment Center	<ul style="list-style-type: none"> ● Data dependent on such variables as drug availability, client acceptance policies, and police or court referral rates.
Arrest Statistics	<ul style="list-style-type: none"> ● Must assume police activity and criminal justice system activity remains constant over time. ● Selective enforcement of drug laws.
Conviction Statistics	<ul style="list-style-type: none"> ● Data dependent upon arrest statistics and levels of police activity. ● Unknown number of cases dropped or lesser charges granted.

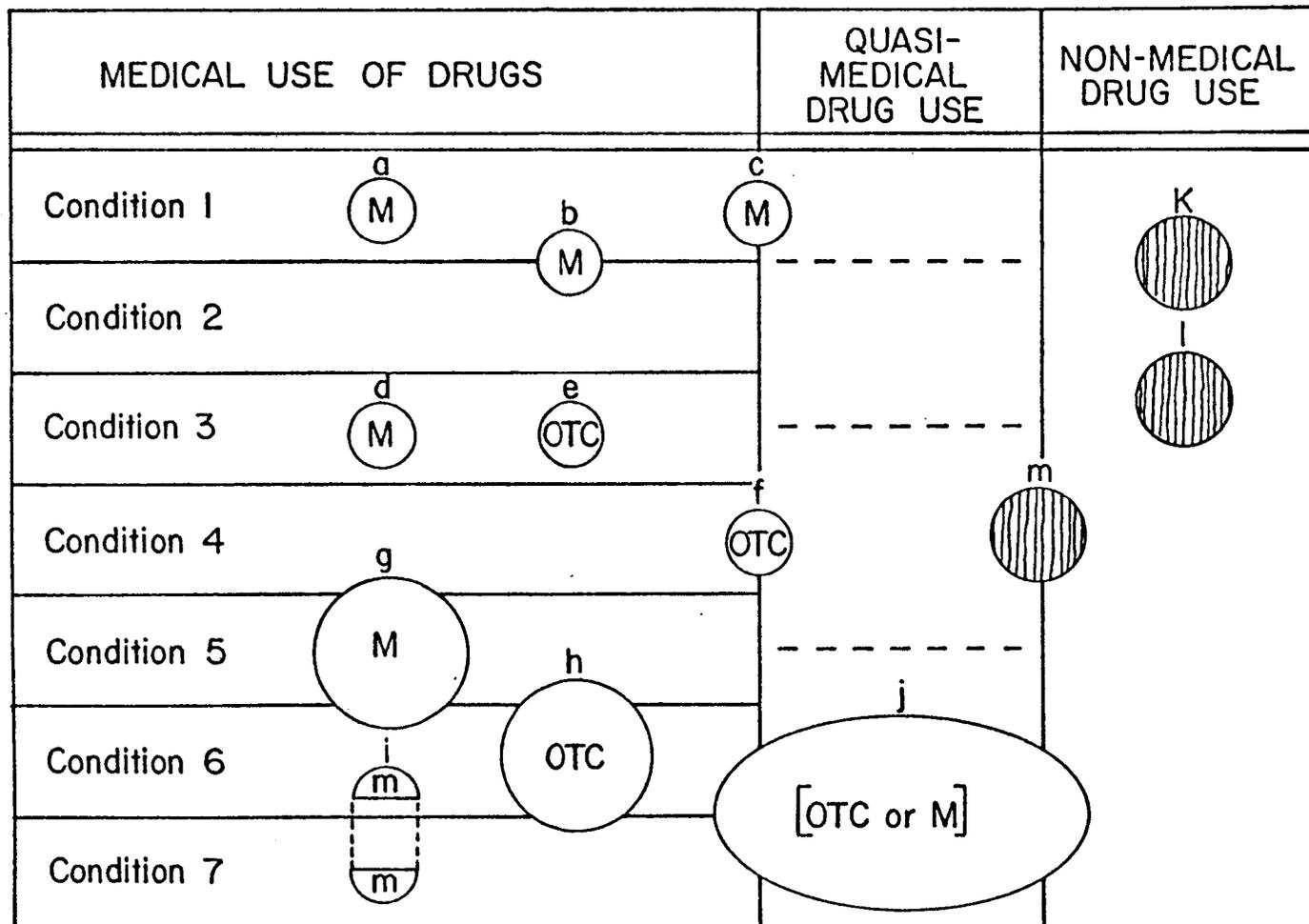
- the drug class, based on pharmacologic action or chemical structure; or
- the individual drugs themselves.

The more general of these categories touch on different aspects of drug usage: medical, legal, and commercial. But many drugs or drug classes have multiple uses. As a result, complicated patterns of use involving several general categories may be described.

A categorization of drug usage patterns is illustrated in Figure 3-1. Quite general are categories that indicate the purpose of drug use. The "medical" use of drugs refers to the rational, medically sanctioned use of therapeutic agents for the treatment of conditions and the alleviations of disease symptoms. The "nonmedical" use of drugs includes all use of drugs for other than therapeutic reasons (e.g., curiosity, intoxication, enjoyment). A third, less well-defined category has been recognized (O'Donnell et al. 1976): "quasi-medical" drug use. It involves self-diagnosis and self-medication with drugs. The drugs may be bought through established medical channels or obtained from other sources (e.g., friends). Nonconformance to traditional medical practice places this type of drug use outside medically accepted drug use. However, since the drugs are used for the rational treatment of specific conditions, this usage pattern hardly constitutes "drug abuse" in the popular sense. (In fact, Richards [1977] uses the term "drug abuse" to include all nonmedical use of drugs, recognizing that not all such use has "adverse consequences.")

The medical use of drugs may be categorized according to the medical condition being treated (therapeutic classification), according to the properties of the drug (pharmacologic classification), according to chemical grouping of drugs (structural classification), or according to source (e.g., prescription or over-the-counter). The patterns of drug use usually require the specification of two or more of these classifications. In Figure 3-1, seven hypothetical medical conditions represent possible therapeutic classifications (e.g., depression: antidepressants). Two types of therapeutic agents—prescribed and over-the-counter (OTC) drugs—are indicated by circles. For condition 1, different drugs or drug classes may be prescribed (a,b,c). Both prescribed and OTC drugs (d,e) may be used

FIGURE 3-1. CATEGORIZATION OF DRUG USAGE PATTERNS



- Recognized therapeutic agent or drug class available through prescription.
- Recognized therapeutic agent or drug class available over-the-counter.
- Drug or drug class with no recognized or established medical use, whose use is generally proscribed by law or social precedent.

for the same medical condition. Broader use of prescribed and OTC drugs is possible, so that a drug may have several therapeutic classifications (b,g,h). Drug classes, especially those characterized by chemical structure (e.g., the barbiturates), may have five or more members. Usage patterns for large drug classes may reflect the application of different members to two or more types of medical condition (i).

The nonmedical use of drugs may involve prescription (j), OTC (j), or controlled drugs (k,l,m). Even uncontrolled, natural substances are used in this manner (Siegal 1978). In this category, drug usage is often better described by quantity and frequency than by reasons given for drug use (i.e., intoxication, recreation, boredom, etc.). The quasi-medical use of drugs lies somewhere between the opposite poles of medical and nonmedical drug use. In this category, the use of drugs—prescription, OTC, or other—is more or less tied to self-diagnosed conditions. Self-treatment is the rule, and some drugs may be used nonspecifically.

For the purpose of this review, two general categories are used. **Medical drug use** includes all uses of therapeutic substances in a health care context. **Nonmedical drug use** includes all uses of drugs for purposes unrelated to personal health care. These categories reflect two main reasons for drug use: (1) to alleviate a medical condition or relieve the symptoms arising therefrom; and (2) to produce a condition or state of intoxication. They also raise two questions about drugs and highway safety:

- Do patients needing psychotherapeutic drugs drive better while under treatment for their condition or do the impairing effects of the drugs outweigh possible benefits to their driving ability?
- Is the recreational use of drugs hazardous to driving safety?

Quasi-medical use of drugs remains ill defined. Although potentially important to our understanding of some patterns of drug use, little research has been performed in this area.

Some difficulty in the discussion of drug usage patterns remains, of

course. Although conceptually distinct, medical and nonmedical drug usage patterns probably overlap in practice. For example, if the frequency and quantity of ingested drugs form the basis for comparison, the excessive use of prescribed drugs should be similar to the nonmedical use of these agents. Only the source of drugs may differ. **Drug misuse** within the context of medical drug use may represent a usage pattern closely related to nonmedical drug use. For the purposes of highway safety, little difference would be evident, and in this report, therefore, the deliberate or unwitting misuses of prescribed or OTC drugs are discussed under nonmedical use of drugs.

3.2 The Medical Use of Drugs

The medical use of drugs, the first of the two categories of drug usage considered in this report, includes the rational, therapeutic use of drugs in a health care context. For highway safety, the concern is mainly with drugs that are psychoactive, that contain psychoactive components, or that have psychoactive side effects. The extent of psychotherapeutic drug use and known characteristics of the user population have been reviewed previously (Joscelyn and Maickel 1977a; Brecher 1972; Kibrick and Smart 1970). Both prescription and over-the-counter drugs are used widely and frequently. Long regarded as the most important type of drugs affecting highway safety, prescription psychoactive drugs include barbiturates, nonbarbiturate sedative and hypnotic agents, minor tranquilizers (also called ataractics or antianxiety agents), stimulants (including amphetamines), antidepressant drugs, and antipsychotic drugs. The sustained and recent increases in psychotherapeutic drug use reported in the literature are largely due to the rise in consumption of antianxiety agents. Physicians in private practice prescribe over seventy percent of these drugs, two-thirds of them to women.

The different classes of psychotropic drugs show different usage patterns according to the age of the user. For example, the elderly, constituting only ten percent of the population, receive about twenty-five percent of all prescriptions and probably consume the same proportion of

over-the-counter drugs (Task Force on Prescription Drugs 1968; Peterson and Whittington 1977). Among the classes of drugs most prescribed to older age groups are tranquilizers and sedative hypnotics. What little data are available suggest that misuse of these drugs and adverse drug reactions are not a great problem among the elderly (Petersen and Whittington 1977; Guttman 1977).

From total sales data available in the United States, one may appreciate the magnitude of prescription volume. Retail pharmacies in 1975 filled an estimated 1.5 billion prescriptions, half of them refills (Pharmacy Times 1976). In 1971, hospital pharmacies filled 1,972 million outpatient and 699 million inpatient prescriptions (Social Security Administration 1972). The total financial outlay for prescriptions was reported to be \$11 billion in 1974 (Knoben 1976). Even if drug utilization in medical care were not to increase as predicted, drug usage as it stands now may be considered of sufficient magnitude to warrant immediate concern in traffic safety.

A summary of data from the National Prescription Audit (NPA) lists the 200 most prescribed drugs in retail pharmacies (Pharmacy Times 1976). In all, these drugs accounted for 69% of all prescriptions in 1975, and the first 100 most prescribed drugs accounted for 54% of all prescriptions. Among the most frequently prescribed drugs, a considerable number of psychoactive agents are listed either alone or in combination with other drugs, including benzodiazepines (first, seventh, seventeenth ranked), propoxyphene (sixth ranked), diphenhydramine (nineteenth ranked), and phenobarbital (twenty-fifth ranked).

The widespread use of certain psychoactive prescription drugs is best illustrated by some examples. Diazepam (Valium [®]), a benzodiazepine used as an antianxiety agent is the most frequently prescribed drug in the United States. It accounts for over 50 million prescriptions (Greenblatt and Shader 1974). It has been estimated that 2 million persons take diazepam continuously (Jick 1974). Linnoila calculates that the "average American" ingests 40 tablets of diazepam annually (Linnoila 1976). Barbiturates, among the most widely used drugs, are dispensed at upwards of 2.6 billion 100 mg dosage units through prescriptions and other medical

uses; 4.4% of the population between 18 and 74 years was found to be using barbiturates in 1970 (McGlothlin 1973).

Knoben and Wertheimer (1976) provided a more detailed account of physicians' prescribing patterns by reporting data derived from a special tabulation of unpublished figures by the National Disease and Therapeutic Index, from the National Prescription Audit conducted by IMS America Ltd. With respect to the volume of prescriptions as related to age, they reported that the "average total number of prescriptions per year of age declines sharply after the first few years of life, then gradually increases to a level approximating the use of medication by infants" (p. 400). In the 20-39 and 40-59 year age groups, psychotropic agents (antidepressants, antiobesity, sedative-hypnotics, and tranquilizers) accounted for 20% of the prescriptions. Drug use was found to differ quantitatively and qualitatively according to patient age. Heavy users of prescription drugs (eight or more different prescription drugs during a three-month period) tended to be women, older, and Caucasian; heavy drug use was associated with greater use of other medical care and was usually a persistent characteristic (Lech, Friedman, and Ury 1975).

Patterns in the use of two or more groups of drugs may be linked. For example, drugs from several chemical classes may be used to induce sleep and maintain it. The sedative-hypnotics, as these drugs are commonly called, compete in the market for prescriptions. The rise in popularity of one drug or drug class may lead to a decline in the use of another. Cohen and Blutt (1978) have reviewed current practices in therapy with hypnotic drugs, and they find that benzodiazepines (in the U.S., flurazepam) are displacing barbiturates:

Flurazepam, the only benzodiazepine with an indication for hypnosis available in the United States, was introduced in 1970. By 1974 the annual prescription rate was 4.45 million, and by 1976 it was 6.76 million. All barbiturates prescribed for hypnosis equalled 8.29 million in 1974 and fell to 5.32 million in 1976.

While new flurazepam prescriptions have been increasing by over a million a year during the 1974-1976 period, all

barbiturate prescriptions have fallen about 1.5 million a year. In 1974 the barbiturate to benzodiazepine ratio was 1.27:1. By 1976 it was 0.62:1. It is also important to note that all hypnotic prescriptions are decreasing at the rate of 1 million a year. (p. 6.)

In summary, prescription drug data indicate that psychotropic drug use is widespread, well established, and, in general, increasing. The patterns of drug usage depend on the drug, as well as the age and sex of the patient. Sedative-hypnotic and antianxiety agents are the most frequently prescribed. Both kinds of drugs have been identified previously as of interest in highway safety.

It has been recognized that drugs obtainable without prescription (over the counter, OTC) are used even more widely than prescription drugs (Brecher 1972; National Committee on Uniform Traffic Laws and Ordinances 1965). These include the so-called "nondrugs": alcohol, caffeine, and nicotine, in addition to the OTC medications. Therapeutic OTC drugs are considered safe for unsupervised self-administration by the public because their relatively weak pharmacological activity results in lesser effects. Nevertheless, some of the effects are those sought after by users of prescription medications: sedation, stimulation, tranquilization. If other commonly used substances, such as caffeine (in beverages) and nicotine (in tobacco products) are also considered (Ray 1978; Brecher 1972), even the OTC drugs may be of concern, depending on how they are used.

The history, present scope, nature, and social acceptance of self-medication in societies such as the United States has been reviewed (Council of Europe 1976a). In terms of sales, excluding alcohol, nicotine, and beverages containing caffeine, nonprescribed medicines comprise 20-25% of the total medicine sales. Yet, in treating symptoms of illness, most people (up to 66%) apparently turn to OTC remedies, many of which have psychoactive components or drugs with psychotropic side effects (Joscelyn and Maickel 1977a; National Committee on Uniform Traffic Laws and Ordinances 1965). This pattern of drug usage is further confirmed by studies that have shown ready acceptance of certain home remedies, such

as cough and cold preparations, and their prevalence in home medicine chests (Council of Europe 1976a).

Other patterns of over-the-counter drug use have been defined and summarized (Council of Europe 1976a). Lower income groups may purchase these lower priced, freely available drugs more frequently to avoid the costs of professional medical care. Higher income groups have more drugs of both types, prescribed and nonprescribed, in the home. Age, sex, education, and other personal variables may influence the use of OTC drugs. Also, those in urban areas tend to use more of these drugs than rural dwellers. "There is unfortunately too little documentation available on most of these matters to enable one to establish clear correlations" (Council of Europe 1976a, p. 24).

3.3 The Nonmedical Use of Drugs

The second major category of drug use, the nonmedical use, seems a very minor phenomenon compared with the medical use of drugs. So disparate are such measures as "numbers of users" and "doses consumed" that the present level of social and political concern appears disproportionate. After all, one argument goes, the practice of using drugs nonmedically emerged from prehistory and extends far beyond the transcultural use of fermented drink. Nonetheless, the sudden increase in this pattern of drug use, perhaps coupled with a social awareness born of our experience with alcohol, has caused a great reaction which is yet to subside.

Some fears have been confirmed, of course. One illicit drug—marijuana—has attained a high level of acceptance among younger adults. As with alcohol, the nonmedical use of drugs commonly results in impaired states, both physiological and psychological, depressed and stimulated. Because of the much publicized adverse effects of such drug use, much attention has been given to what has been termed "drug abuse," a vague term laden with negative connotations and now falling into disuse. In the Department of Health, Education, and Welfare, the National Institute on Drug Abuse has focused efforts to study and deal with the problem.

With the rising national interest in the use and misuse of drugs, the highway safety community has begun to look beyond alcohol to see if other drugs might increase traffic crashes. After all, one reason for using drugs nonmedically is to produce altered states of awareness, states likely to impair the ability to drive safely. Moreover, this kind of drug use appears most concentrated in groups of driving ages with poorer driving records than most. Thus, information on the nonmedical use of drugs becomes one indicator of the nature and extent of the drug and driving problem.

The sources of information on the nonmedical use of drugs are diverse and depend on how the data are gathered. The surveys employed in the study of the nonmedical use of drugs have been categorized as follows:

- surveys of both household and special populations;
- analysis of indirect indicators, including arrest and conviction statistics, hospital admission data, drug screening ("urinalysis"), seizure records, etc.;
- case-finding and other anthropological techniques; and
- information-gathering from knowledgeable people.

(Blackwell 1975, p. 113.)

These sources are subject to the limitations summarized in Table 3-1. A more detailed discussion of these surveys is contained in the edited transcripts of a recent conference on the epidemiology of nonmedical drug use and dependence. The purpose of the conference was to review the state of research at the time, identify major problems and gaps, and recommend new directions that should be taken. The transcripts have been published as a monograph by the National Institute on Drug Abuse (Richards and Blevens 1977).

Several national surveys of the nonmedical or illicit use of drugs have also been reported. (Abelson and Fishburne 1976; Abelson, Fishburne, and Cisin 1978; Johnston, Bachman, and O'Malley 1977). Each of the cited studies produced more data than can be reproduced in this report. The surveys dealt with **classes** of drugs that seem of interest to highway safety: cannabis, inhalants, hallucinogens, cocaine, heroin and other drugs with morphine-like pharmacological actions (narcotic analgesics),

stimulants, sedatives, and tranquilizers. With the exception of the more popular illicit drugs, the use of drugs within classes (e.g., diazepam (Valium®) in the class tranquilizers) was not specified.

Siegal reviewed the recent literature on "street drugs" (1978). In addition to a summary of specific patterns and trends of drug use, he provided a brief description of his sources of data. These included DAWN (Drug Abuse Warning Network), a project with federal support that samples hospital emergency rooms, medical examiners and coroners, and crisis intervention centers for reports of drug problems; laboratories engaged in the analysis of drugs from the street; the so-called "alternative press"; and medical-scientific literature. He presented examples of data available and discussed their limitations.

The remainder of this subsection reviews current knowledge of the nonmedical use of marijuana and other "controlled" substances (see Swinyard 1975, pp. 1615-5), as well as the excessive use of licit drugs. Findings from the national surveys and other sources will be included as appropriate for each drug or class of drugs discussed.

Marijuana, once a symbol for social change, now appears established as a recreational drug in American society, albeit illicitly. The literature concerning marijuana is voluminous. Extensive studies of marijuana use have been reported and reviewed (McGlothlin 1977; O'Donnell et al. 1976; U.S. Department of Health, Education, and Welfare 1973; U.S. Department of Health, Education, and Welfare 1974; U.S. Department of Health, Education, and Welfare 1975; Petersen 1977; Johnston 1973; Michigan Department of Public Health 1975). Patterns of marijuana use have been studied in Canada (LeDain et al. 1972) and Great Britain as well (Edwards 1974).

In the United States, the use of marijuana has increased since the late 1960s, mainly among persons under thirty, although some indicators point to decreased rates of incidence in the general population. Survey data, including household, student, and age-related studies, have been summarized in recent reports to Congress by the Secretary of Health, Education, and Welfare (U.S. Department of Health, Education, and Welfare 1975) and by McGlothlin (1977). In general, the surveys show the

following.

- Current use of marijuana has increased in recent years, especially among those under eighteen years.
- There are indicators that marijuana use is stabilizing, especially among older subgroups.
- Marijuana use, despite increases, continues to involve mostly those under thirty.
- Characteristics of use patterns have altered; use has been broadened to groups considered more conservative and established in society.
- Regional differences in national use data are present, but diminished somewhat over the years.
- Patterns of use are nonhomogeneous, with localities evidencing wide deviations from national survey data.
- National trends and predictions for marijuana use remain tentative, due to volatile nature of the patterns observed.

In one of these reports (U.S. Department of Health, Education, and Welfare 1975), user characteristics were summarized from recent surveys.

Marijuana use is more likely and more frequent:

- among men than women;
- among those less traditionally oriented in society;
- among the unemployed;
- among those who have had contact with the criminal justice system; and
- among those under thirty and living in urban settings.

Marijuana use tends to be a part of a larger pattern of nonconformity, however, and the inference of causal relationships between use and other user characteristics (criminal record, living arrangements) has been discouraged. While marijuana use has in the past been positively correlated with higher education attainment, income level, race, and demographic characteristics, recent surveys indicate that differences are diminishing across many if not all of these categories (O'Donnell et al. 1976; U.S. Department of Health, Education, and Welfare 1975; Michigan Department of Public Health 1975). Nevertheless, one hopeful trend,

summarized in the latest report to Congress, has been observed.

As was emphasized in earlier reports, many users stop or markedly diminish their use of marihuana as they take on various adult responsibilities such as new marital, parental and work roles. Thus, while the future patterns of use of marijuana in our society are in doubt, there is reason for believing that a variety of considerations, including negative attitudes of many potential users toward regular drug use, serve to moderate and discourage more extensive use even when the drug is widely available. (Secretary of U.S. Department of Health, Education, and Welfare 1976, p. 10.)

Other illicit substances, often called "street drugs," include:

- substances that have restricted or limited application in medicine, or that have no use whatsoever, and that are available to users via the "street market"; and
- drugs available through prescription but which are illegally channelled to the street market for sale.

Since these drugs are for the most part illegal and are used illicitly, information regarding usage patterns is quite limited. The following sources provide most if not all the data available:

- household surveys;
- special studies of age or education subgroups;
- street drug identification programs;
- drug analyses in emergency cases resulting from drug overdose;
- forensic toxicological analyses in drug-related deaths; and
- DAWN (Drug Abuse Warning Network) (Siegal 1978).

Psychedelic drugs include LSD, mescaline and peyote, psilocybin, and substituted phenethylamines (STP, MDA, DOM). Unlike most other drug groups, the prevalence of psychedelic drugs appears to be declining (O'Donnell et al. 1976). In the national survey of young men 20-30, 22% (est. 4,180,000 persons) had tried this type of drug; of these, less than a third (1,370,000) currently used psychedelic agents. In this sample, more men who used these drugs quit using than continued to use them.

However, the extent of use was positively correlated with current use. In another national survey (LeDain et al. 1972), 4.6% of the adults and 4.8% of the youths surveyed had tried psychedelics. In Michigan, 5.3% of the sample had used them (Michigan Department of Public Health 1975).

Psychedelic drugs are less available than other drugs (O'Donnell et al. 1976; Wright 1976), but only 1% in a sample of patients and volunteers who had discontinued use after LSD therapy gave unavailability as a primary reason. The continued and considerable presence of LSD and other psychedelics in the street market has been indicated by analyses of illicit drug samples (Siegal 1978; Gupta and Lundberg 1976). The well-known problem of falsely represented street drugs complicates surveys on the availability and usage patterns of these and other drugs. Users of psychedelics are more likely to have tried marijuana than not and their characteristics tend to follow those of users of marijuana. Among young adults, 18-34, an even distribution of psychedelic use was seen across education, race, and place of habitation (O'Donnell et al. 1976; Johnston 1973). Abelson, Fishburne, and Cisin (1978) found current use rates of hallucinogens (not including PCP) to be unchanged since 1976. Johnston, Bachman, and O'Malley (1977) report a decline in their use among high school seniors since 1975. These investigators included PCP with the hallucinogens.

Phencyclidine (PCP), although often classed with hallucinogenic or psychedelic drugs (e.g., Michigan Department of Public Health 1975), is an arylecycloalkylamine which produces "dissociative anesthesia," with side effects which include hallucinations (Reher 1971). Unlike the feeling of "oneness" produced by psychedelic agents, PCP produces feelings of dissociation from the user's environment (Ray 1978, pp. 386-7). Its toxic effects are quite different and considerably longer lasting than the most psychedelic agents. Unfortunately, PCP is often sold under the name of THC or some preferred psychedelic, e.g., psilocybin and mescaline (Siegal 1978). This complicates any assessment of its prevalence. It has been legally used only by veterinarians, and most of the drug is "home made" (Gupta and Lundberg 1976). It is widely available on the streets, and is responsible for many drug overdose cases nationally (Tong et al. 1975;

Liden, Lovejoy, and Costello 1975). In contrast to the trend for hallucinogens, the trend in PCP use is for increased prevalence rates (Abelson, Fishburne, and Cisin 1978; Siegal 1978).

Opioids are natural or synthetic drugs related to morphine pharmacologically. They are represented on the street primarily by heroin, methadone, and codeine. Other related substances of interest include propoxyphene, meperidine (pethidine), opium, and morphine. The epidemiology of narcotic-related problems has been reviewed and sources of information identified (Blackwell 1975). National surveys report little change in the low levels of opioid use (Abelson, Fishburne, and Cisin 1978; Johnston, Bachman, and O'Malley 1977).

Gordon (1976) reviewed the relationship of narcotic drugs and highway safety and cited estimates of 350,000 users in the United States. Those maintained on methadone were estimated to number 100,000, or one-third of the total number of opioid drug users. Among young people, heroin was disapproved of most and used the least (Johnston 1973). Yet, even by 1971, there were indications that the traditional dividing line between heroin and other drugs had been broken (Brecher 1972). Heroin use at any time among young men 20-30 was 6%, the lowest of any drug type. While 31% had used opiates other than heroin, up to one-third of their use was considered quasi-medical: "Only 20 percent of the sample can be said to have used opiates in a way that could reasonably be seen as abuse of opiates, and in only eight percent of the sample was this use more than experimental" (O'Donnell et al. 1976, p. 30). The current use (1974-75) of heroin and opiates in this survey was 1.8% and 10.2%, respectively, with most probable figures nationally placed at 340,000 and 1,900,000, respectively (O'Donnell et al. 1976). Abelson, Fishburne, and Cisin (1978) reported lower figures (.5% and 1%), but these figures may not be directly comparable. These investigators and others recognize that, of all drugs, heroin use is most likely to be underreported. Whatever the absolute number of users in the United States, other indicators point to a leveling of the prevalence rates for heroin use. Tennant and Ruckle (1976) discussed trends in heroin use in Los Angeles County, population over seven million in 1979. They based their report on

data adjusted for population changes over a fifteen year period—including heroin-related deaths, arrest rates, serum hepatitis cases, visits to emergency rooms, referrals to civil commitment and probation, admissions to heroin detoxification, and year of self-reported onset of heroin use. They concluded that, while the prevalence of heroin use has increased over the past fifteen years, since 1973 it may have stabilized or even slightly decreased.

Estimates of the availability and use of stimulants such as amphetamine, methamphetamine, and cocaine exist. Supplies diverted from legitimate production, illegal synthesis and distribution, and smuggling operations provide the street scene with stimulants. These drugs frequently vary in quantity and quality, making exact usage patterns difficult to determine. Siegal (1978), reviewing the literature on street drugs, does note that samples of supposed amphetamine have decreased in quality, one sign of decreased availability. Two national surveys (Abelson, Fishburne, and Cisin 1978; Johnston, Bachman, and O'Malley 1977) report slight or no changes in the prevalence rates for stimulants. Estimates of current use of stimulants ranged from about 1% for youth and adults to about 9% for high school seniors. In the national survey of young men aged twenty to thirty, current use (1974-75) estimates for "stimulants" and cocaine were 2,180,000 and 1,310,000 respectively (O'Donnell et al. 1976). Increased seizures of cocaine by federal authorities, as well as local statistics regarding cocaine use, point to increasing use of this drug nationally (Gay et al. 1975).

The term "sedative-hypnotics" includes both the barbiturates, perhaps the best known, and the nonbarbiturates. Cohen and Blutt (1978) summarized data from the National Prescription Audit on new hypnotic prescriptions. While decreasing at the rate of one million a year, still over twenty million new prescriptions were written in 1976. Sharma (1976) reviewed the relationship between barbiturates and driving. He cited estimates in 1970 of 1.6 billion 100-milligram dosage units (160,000 kilograms) for illegal sales alone. Current nonmedical use of sedatives (drug used in past month) reported in national surveys ranged from about 1% to 5.1%, depending on the age group; among young adults, the

prevalence rates have increased significantly (Abelson, Fishburne, and Cisin 1978; Johnston, Bachman, and O'Malley 1977). The use of sedatives was slightly less among young men aged twenty to thirty than the use of stimulants (O'Donnell et al. 1976). Wesson and Smith (1977) discuss a full range of topics about the use, misuse, and abuse of barbiturates in their book.

The use of "inhalants," meaning glue, organic solvents, nitrous oxide, amyl nitrite, and the like, has also received attention. Both recent national surveys included questions on their use. The national household survey found greater lifetime prevalence among youth aged twelve to seventeen than among adults, with current use of these drugs less than one percent (Abelson, Fishburne, and Cisin 1978). The survey of high school seniors found a slightly higher current use rate of 1.3%, representing about 39,000 persons (Johnston, Bachman, and O'Malley 1977).

A final note on the nonmedical use of drugs concerns a miscellaneous group of substances. Almost unnoticed has been the recent increase in the sale and use of herbal products for purposes similar to the nonmedical use of drugs (Siegal 1976; Seigal 1978). A trend toward use of "natural" drugs, uncontrolled and not illegal, may be possible.

The misuse of prescription medicines has been the subject of a recently published report (Council of Europe 1976b). The patterns of use deviating from therapeutic and medical standards were related to the prescriber, patient, manufacturer, and distributor. Six types of patient-oriented misuse were identified:

- failure to take a prescribed medicine as intended;
- consultation of more than one physician;
- combination of prescription treatment with self-medication;
- use of prescribed medicines for nontherapeutic purposes;
- self-medication with prescription medicines; and
- suicide and deliberate self-injury with medicines.

Self-medication with prescription drugs takes several forms, including the stockpiling of prescription drugs in the home medicine chest for future needs. Aside from the misunderstanding of physicians' instructions, patients who disregarded instructions did so because they thought they

need an extra dose (the "more is better" syndrome) (Latiolais and Berry 1969). The use of prescription drugs in lieu of preferred but unavailable intoxicants is also known. In a survey of alcohol and other drug use in Michigan, it was found that the nonprescribed use of prescribed drugs was generally low. When it did occur, however, "fun, enjoyment, and celebration," experimentation, and group activity were most commonly cited as reasons, depending on the type of drug (Michigan Department of Public Health 1975).

In the Michigan study (Michigan Department of Public Health 1975), users of prescribed drugs for nonprescribed purposes were predominantly young (less than thirty-four years), and were slightly more likely to be male. Users were more likely to live in central cities, and the higher use rate was associated with use of amphetamines and depressants. It was suggested that the college population, concentrated to a large extent in these areas, was responsible for the higher use rate.

Other than these studies, very little factual information is available to indicate the extent to which prescribed drugs are misused in the United States. The best sources of such information at present seem to be drug overdose studies. These are reports of emergency room cases and toxicological analyses made after discovery of fatalities due to drug overdose. For example, the most frequently prescribed drug in the United States, diazepam, was also the most commonly reported drug other than alcohol in 2,500 patients suspected to be drug overdose victims. The levels of drug found were indicative of "acute ingestion of more than the normal therapeutic amount of the drug..." (Rejent and Wahl 1976, p. 891). Similarly, in deaths involving psychoactive drugs, prescription medicines were commonly found (Dinovo et al. 1976).

Even less is known concerning the misuse of over-the-counter preparations. However, the sheer volume of sales and prevailing habits of self-medication seem to indicate a potential hazard to highway safety. The types of "home remedy" most commonly associated with potential misuse include antitussives, antiasthma preparations, stimulants, sedatives, antihistamines, and nasal decongestants. In a report concerning the abuse of medicines, it was concluded that, while certain self-medication

practices using over-the-counter drugs presented a clear health hazard, information was required in the following areas before national policies could be formulated:

- motivation (of user),
- manner of use of home remedies,
- extent of use of home remedies,
- extent of abuse of home remedies, and
- adverse effects of home remedies for the individual and the community. (Council of Europe 1976a, p. 25.)

3.4 Multiple Drug Use

Multiple drug use, also called polydrug use, may be defined as the concurrent, if not simultaneous, use of two or more drugs such that their respective effects overlap in time (Teo 1975). Of greatest concern is the possibility of "drug interactions," where the combined effects of two or more drugs differ qualitatively or quantitatively from the effects of the individual agents (National Committee on Uniform Traffic Laws and Ordinances 1965; Teo 1975; Hussar 1976). In some cases, this may mean the intensification or diminution of the therapeutic action of a prescribed drug. Often the two drugs may act similarly to produce a greater than expected effect; this is especially the case with central nervous system depressants, including alcohol.

Drug usage patterns alone indicate the prevalence of potential drug interactions in the general population:

- frequent use of alcohol by broad segments of the general population;
- the common practice of prescribing psychoactive drugs, especially antianxiety agents;
- the patterns of self-medication with preparations containing drugs that can interact with alcohol, e.g., antihistamines, dextromethorphan (a common OTC cough medicament);
- the widespread ignorance and disregard of the dangers of multiple drug use; and

- the deliberate mixing of drugs to achieve states of intoxication.

Surveys have confirmed the prevalence of multiple drug use (O'Donnell et al. 1976; Johnston 1973; Michigan Department of Public Health 1975). The use of marijuana was associated strongly with multiple drug use in the national study of men, 20-30 years (O'Donnell et al. 1976). In a Michigan drug-use survey of those who used alcohol, 20% and 10.7% had also used one or more prescribed or illicit drugs, respectively (Michigan Department of Public Health 1975). Toxicological examinations, forensic and medical, consistently result in the finding of two or more drugs (Rejent and Wahl 1976; Dinovo et al. 1976; Finkle et al. 1976). Thus, while patterns of multiple drug use are not well characterized, they may be presumed to be widespread, and a potential factor in highway safety (Milner 1972).

3.5 The Study of Drug Use in Driving Populations

The use of drugs by the general population indicates the potential for drug involvement in accident causation. But it is more desirable to know directly the extent of drug use by the driving population itself. Of most value, of course, would be complete information on the number, kind, and amount of drugs in drivers:

- who have committed moving traffic violations,
- who have been injured in accidents, and
- who have been fatally injured in accidents,

compared with similar information from appropriate control populations. Of critical importance in this type of study is the selection of a suitable control sample of drivers for comparison purposes.

Basically, three approaches have been used in the epidemiology of drugs and highway safety. First, the direct analysis of driver body fluids has been attempted. Studies involving drinking drivers, "driving under the influence of drugs" cases, and accident-involved and fatally injured drivers have been reported. Second, surveys and questionnaires have been used to investigate self-reported drug use and driver frequency. Third, the driving records of drug user groups have been used to assess, indirectly, the

effect of certain types of drug use on driving performance.

In published reviews of literature on drugs and driving, significant methodological issues have been raised concerning past epidemiological efforts (Joscelyn and Maickel 1977a; Kibrick and Smart 1970; Nichols 1971; California Highway Patrol 1974; Ashworth 1975). These are summarized in Table 3-2. The most serious criticisms involve questions of reliability and validity. The methods employed in population sampling, data collection, and drug analysis are most often mentioned in this regard. For example, the analytical methods used for detecting drugs in body fluids have been considered inadequate (Joscelyn and Maickel 1977a; California Highway Patrol 1974; Kapur 1975; Silverstone 1974). They have lacked the required sensitivity or have not detected the active form of the drug or have been limited to a restricted set of drugs. Moreover, no comparisons among studies are possible, since different methods were chosen. Since only a few studies have been performed, the results available are fragmentary.

The present state of knowledge does not result only from issues stemming from methodology. The problem under study is demanding and the conditions for research are less than ideal. One reason for the lack of valid data and the limited efforts to date may be a lack of adequate research funding in this area. The dilemma is circular, of course. The area of drugs and driving is not a priority concern in highway safety because present data do not show that drugs other than alcohol are overrepresented in traffic crashes. Lacking priority, drug and driving research has not received the level of funding required for definitive studies.

Other reasons have been offered: screening for drugs in the blood and urine is complex and costly. Advanced, ultrasensitive techniques, which are needed to detect and quantitate some drugs of interest, were still in the developmental stage or limited to a few centers at the time surveys were conducted. In the past, the requirements of drug analysis in highway safety research have extended beyond the limits of the state of the art. Early studies of drugs in drivers, for example, lacked methods to detect marijuana and diazepam (Valium[®]) e.g., Finkle, 1969). Still five years later, in a study of drugs in fatally injured drivers, methods

TABLE 3-2
METHODOLOGICAL ISSUES IN EPIDEMIOLOGICAL RESEARCH
ON DRUGS AND HIGHWAY SAFETY

PREVALENCE OF DRUGS IN DRIVERS' BODY FLUIDS

- deficiencies in general experimental design;
- invalid sampling procedures, including samples of convenience and nonrandom sampling;
- lack of control samples from living or non-accident-involved drivers;
- invalid comparisons between accident-involved and general driving populations, use of inappropriate statistical methods;
- studies are of limited geographical scope;
- lack of accurate information about the frequency of drug use in the appropriate geographical location;
- random sampling procedures detect few cases for any given drug;
- substantial missing data rates with introduction of selection bias;
- sample collection and handling procedures not standardized, a potential source of error;
- drug analytical methodology inadequate, insensitive, or unavailable;
- limited range of drugs detected or screened; and
- data analysis and interpretation lack rigor.

QUESTIONNAIRE TECHNIQUES

- samples of convenience often chosen;
- reliability of studies based on self-reporting by subjects is unknown;
- study results rarely verified by drug analysis; and
- low estimates due to demonstrable underreporting.

TABLE 3-2 (Continued)

STUDIES OF DRUG USERS' DRIVING RECORDS

- only indirectly related to drug use while driving;
- methods of selection result in inappropriate comparison populations;
- samples of convenience often used; unreflective of general driving population (e.g., the survey of college students);
- uncertain reliability in age-, mileage-, and driving frequency-matched populations; and
- poor driving records may result from causes underlying both drug use and accident-involvement.

incapable of reliably detecting these and other drugs were employed (e.g., Woodhouse 1975; Turk et al. 1975). But adequate methods, based on gas chromatographic and immunochemical techniques, have since moved from the research laboratory into the field, making this much less of a problem today (Forney and Sunshine 1975; Finkle 1975).

Compounding the analytical task are the very large number of drugs in common use. Moreover, compared to alcohol, any given drug probably would appear infrequently. For some drugs, active metabolites must also be detected. But the set of drugs of interest can be reduced to a manageable size simply by selecting those with the greatest apparent potential for increasing the risk of a traffic crash. One panel, for example, suggested cannabis, diazepam, and the sedative-hypnotics (Willette 1977). For a study to compare the prevalence of particular drugs in different driving populations, large sample sizes would appear necessary.

The problem of interpreting the findings of such studies remains. Drug levels in the blood, which is the preferred body fluid for interpreting drug effects, have uncertain meaning at best. The presence of active metabolites, or two or more drugs, including alcohol, complicate an already complex problem. Small wonder no great commitment to define the role of drugs in traffic crashes has been made. Nevertheless, less ambitious studies might still have been done, to establish the relative frequency of occurrence and to indicate the magnitude of the drug and driving problem.

The above-mentioned problems in epidemiologic research have occasioned a note of caution in the analysis of results stemming from studies done to date. Strictly on the basis of data available, most authors have concluded that no evidence has been produced to show that any drug (other than alcohol) is overrepresented in the accident-involved driving population (Kibrick and Smart 1970; Nichols 1971; California Highway Patrol 1974; Silverstone 1974; Colburn and Garland 1974; Waller 1971). Yet, few are willing to state categorically that drugs do not present a problem. At a 1974 traffic safety conference, Colburn and Garland made this point:

traffic fatalities in six counties of North Carolina. No comparison group of drivers was studied.

Garriott and Latman (1976) reported the analyses of blood samples of drivers arrested in Dallas County, Texas, for "driving under the influence of drugs" (DUID). The period covered was July 1, 1973, through December 1974, and involved 199 cases. Drivers were selected after arrest if breath analysis for alcohol resulted in lower than expected values considering the degree of intoxication observed. Drivers arrested for driving under the influence were also selected when there was evidence of drug use by questioning, symptoms, or drug samples in the person's possession. Blood samples totaling 24 ml were usually obtained. Further, the arresting officer completed an arrest report that included a questionnaire asking for information concerning circumstances of arrest and the individual's behavior.

Drugs, including alcohol, were screened using gas chromatography and ultraviolet spectrophotometry. Sedative-hypnotic drugs along with diazepam, an antianxiety agent, accounted for almost all of the drugs detected. The most frequently detected drugs were ethanol, methaqualone, diazepam, the barbiturate mixture amobarbital and secobarbital, secobarbital, and pentobarbital. In 1974, diazepam became the most frequently detected drug other than ethanol (22.5% of 71 cases), replacing methaqualone (28.2% of 64 cases in 1973, 17% of 71 cases in 1974). Barbiturates as a class accounted for 42.2% of all cases in 1973, and 39.4% of all 1974 cases. The incidence of multiple drug detection was large, occurring in over one-third of the cases; in most of these cases, alcohol was involved. The investigators noted that certain drug categories would have gone undetected. These included volatile substances not detected in the ethanol procedure, hard narcotics, cannabis constituents, and psychedelic drugs. However, other evidence indicated the use of some of these substances as well. For example, marijuana was noted by the arresting officer in 12.7% of the 1974 case reports, and in 14% of the cases in 1973. Indications of the inhalation of paint fumes or paint thinner were also observed in 1974.

Persons arrested for DUID ranged in age from seventeen to fifty-six

The effects of other drugs do not appear to challenge those of alcohol as a contributor to highway injuries and death, but there seems to be good reason for concern about them. The most urgent need is studies of the amounts of various drugs in the fluids and tissues of persons injured or killed in highway crashes compared to those of persons using the highways under the same conditions and at the same times but not involved in accidents. (Colburn and Garland 1974, p. 16.)

In the following sections recently published studies that report drug use by drivers are reviewed to integrate their results with past evaluations of the epidemiological literature.

3.6 Recent Literature in the Epidemiology of Drugs and Driving

Recent studies using the most direct approach to assessing drug involvement in traffic crashes--that is, by determining the identity and amounts of drugs in driver body fluids--are reviewed in the following section.

3.6.1 Incidence of Drugs in Drivers. Since the last major review of field surveys (Joscelyn and Maickel 1977a), several studies have been published.

Turk et al. (1975) reported the involvement of alcohol, carbon monoxide, and other drugs for 233 traffic deaths in North Carolina (171 drivers, 62 pedestrians). Several methods were used to analyze specimens of blood, liver, and urine. Limitations of the methods included the inability to detect d-lysergic acid diethylamide (LSD) and marijuana as well as therapeutic concentrations of benzodiazepines (e.g., Valium® and Librium®). In drivers involved in single-car crashes, the major drug detected was alcohol. Alcohol alone was detected in forty-six cases; alcohol plus drugs in four cases; but in no case were drugs alone detected. In drivers involved in multiple-car crashes, alcohol again was found most often (eighteen cases). Three cases where drugs alone were detected involved the sedative-hypnotic phenobarbital, the cardiovascular drug quinidine, and quinine. This report represents a three-year study of

years, with an average of 26.6; average age for "driving while intoxicated" (DWI) was thirty-seven years. The ratio of females to males in the DUID group was twice that for DWI. The blood concentrations of drugs indicated that in most cases the drugs taken appeared in greater than therapeutic doses, and, if obtained by legitimate prescription, were not taken as prescribed. Although DUID arrests amounted to only 1% of the DWI arrests, the authors believed that the prevalence of drugs among drivers was higher. Infrequent detection was blamed on difficulties in implementing and enforcing a DUID program.

Garriott and co-workers also completed a study of drugs and alcohol in fatally injured motor vehicle drivers (Garriott et al. 1977). Using a drug screening system similar to the one described above, 207 cases were found. The results of this study are summarized below:

- In the total sample (drivers, passengers, and pedestrians) one or more drugs were detected in 15% of all individuals; alcohol appeared in 62%.
- In the 127 drivers, drugs were detected in 9%, alcohol alone was found in 52%, drugs plus alcohol in 9%.
- Only 30% of the drivers had no drug or alcohol in the blood; only four of twenty-two pedestrians had no drug or alcohol detected.
- With the exception of three cases, central nervous system depressants were the only drugs detected.
- Diazepam, or its metabolite, nordiazepam, were detected in thirteen (56.5%) of the twenty-three drug-positive drivers.
- Of the 105 drivers presumed to be at fault, eighty (76%) had drugs, alcohol, or both in their blood.

The authors concluded that the results of their study indicated that psychoactive drugs, alone and with alcohol, contribute significantly to motor vehicle accidents. In the absence of alcohol, the drug concentrations suggested the use of excessive amounts of drug; when alcohol was also present, the majority of such drivers had therapeutic concentrations of drugs in their blood.

Lundberg (1976) presented a study in California by the California Association of Toxicologists (CAT). Data on 836 cases from thirteen laboratories were collected between May 1973, and December 1975, on a comprehensive form developed by the CAT. The 375 elements of information tabulated on each case included driver characteristics, acute or chronic drug use, suspected or possessed drugs, field sobriety test, nineteen different states of subject, eight problems of driving behavior, forty-eight drugs from three sources, and information about the analysis of specimens. The majority of cases came from Orange County. In 97.5% of the cases, the specimen was blood; in the rest, urine.

The CAT study produced a veritable mountain of data, of which only a portion will be summarized here. A suspected drug was listed in 36% of the cases; a drug was found in the possession of the person in 26% of the cases. In the 260 cases where some drug was suspected and a drug was found, in 53% of the cases the drug suspected was found. In 175 cases a drug was found in possession of the subject and a drug was detected in blood or urine. But in only 54% of the cases were they the same drug.

Forty different drugs were identified, alone and in combination. The number of drugs found per case ranged from none to nine, with a mean of three. Most frequently found were barbiturates (400 times), followed by alcohol in combination with other drugs (257 times), and diazepam (171 times). A single drug occurred in 357 cases; two drugs (including alcohol) appeared in 369 cases.

Among the conclusions drawn from this "incomplete study," as the authors described it, are the following:

- The presence of psychoactive drugs other than, or in addition to, alcohol in persons with driving behavior problems is common in California.
- Impairment of both driving performance and sensory-motor capabilities are commonly observed in drivers whose blood contains such drugs.
- The psychoactive drugs (other than alcohol) most likely to be involved in a driving behavior problem in this study were various barbiturates, diazepam, methaqualone,

chlordiazepoxide, meprobamate, and ethchlorvynol.

- More than half the time, two or more drugs, including alcohol, were found.
- In general, the correlation of blood levels of the various drugs and driving behavior problems, including accidents and fatalities, is not yet possible.

Lundberg, White, and Hoffman (1979) also report the results and conclusions of this collaborative study by the California Association of Toxicologists.

Blackburn and Woodhouse (1977) reported a study sponsored by the U.S. Department of Transportation, National Highway Traffic Safety Administration. Specimens and collateral data were collected from 900 fatally injured drivers by medical examiners in 22 areas of the country. Drivers from the at-risk population were interviewed at times and places of recent fatal crashes in Dallas, Texas, and Memphis, Tennessee. Of 1,196 drivers in this sample, 91.6% cooperated with the interview. Of those interviewed, "nearly all" gave a breath specimen, but only 67.2% were able to give a urine specimen (about 62% of the total sample). About 65% of the total sample provided a specimen of blood.

Specimens were analyzed for forty-three drugs in seven groups: sedative-hypnotics; tranquilizers; stimulants and antidepressants; antihistamines and decongestants; narcotic analgesics; hallucinogens; and miscellaneous. Quantitative tests for LSD were done only on urine specimens from fatally injured drivers using a radioimmunoassay. The general analytical scheme involved preparation of the specimens, including hydrolysis of possible drug metabolites; extraction of hydrolyzed specimens with a nonionic resin; qualitative detection of drugs by thin-layer chromatography; and quantitative confirmation by gas chromatography. Marijuana and the benzodiazepines diazepam and chlordiazepoxide were not detected by the methods employed.

In 587 fatally injured drivers for whom both blood and urine specimens were available, antihistamines/decongestants (thirty-one cases) were found most often, followed by sedative-hypnotics (thirty cases), and narcotic analgesics (fifteen cases). The incidence of one or more drugs was 12%

(with a 95% confidence interval of $\pm 8.4\%$) in this group of drivers. Among 897 living drivers, for whom both blood and urine specimens were analyzed, the incidence of one or more drugs was about 7.9%, only fifty-nine drivers. The distribution of drugs among the groups as defined was similar to the sample of fatally injured drivers.

In addition to these studies, all of which relate to drivers in the United States, several reports concerning drivers elsewhere have been published. Because some patterns of drug use appear similar between the United States and other countries, e.g., use of sedative-hypnotics (Cohen and Blutt 1978), these reports are briefly summarized here.

Kaye (1975) described a study of 508 out of 577 traffic deaths occurring in Puerto Rico during 1973. The sample included 126 drivers (25%). Alcohol was found in 60% of the 110 drivers analyzed. Only three cases involving drugs were found; in each case the drug was phenobarbital, but in only one case was it present in a driver. Not reported were the methods used to detect the drugs, their sensitivity, or the range of drugs included in the screen.

Bo et al. (1975) compared the incidence of ethanol and diazepam in seventy-four injured drivers with a group of 204 nonaccident drivers randomly selected during routine medical check-ups. In the former group, 6.8% were female and 72% were thirty years old or younger; in the latter group 10% were female and only 24% were thirty years old or younger. Ethanol alone was found in thirty-one injured drivers (41.8%), twenty-six of whom were over the legal limit of 50 mg/100 g blood. Diazepam alone was found in seven injured drivers, six of whom (8.1%) had levels that might impair their driving ability. Eight drivers had a combination of ethanol and diazepam. In the reference group, three had ethanol (1.5%), four had diazepam (2.0%), while none had the combination. The investigators concluded that "regular or intermittent use of diazepam and other psychotropic drugs may significantly add to the problem of traffic safety, but ethanol is still the major, and presumably also an underestimated, causative factor in serious road traffic accidents in Norway" (Bo et al. 1975, p. 447).

Alha and colleagues (1977) reported the prevalence of drugs among

drivers arrested for drinking while driving in Finland. Qualitative and quantitative analyses of drugs were performed with a combined thin-layer and gas chromatographic system. Two percent of all drivers suspected of drinking were also suspected of using other drugs. Of 100 such drivers, twenty-four had no detectable alcohol in their blood; eighteen of these twenty-four drivers were positive for drugs. Of the seventy-six drivers with detectable levels of alcohol, twenty-five also had drugs in their specimens. Of 100 randomly chosen drivers suspected of drinking, five had drugs in their specimens and four of the five also had alcohol. The benzodiazepines were most commonly found; no stimulants were detected.

Simpson et al. (1977) examined coroners' records and toxicology reports on 721 fatally injured drivers in British Columbia, Canada. The incidence of alcohol and barbiturates was studied for 594 drivers who died within six hours of the crash. The frequency of testing for these drugs was 85% for alcohol (46% of the drivers impaired with an excess of 80 mg%), and about 33% for barbiturates (only five cases found). None of the five cases involved alcohol, and each was a single-car crash. The authors concluded that "despite the relatively high rate of testing for barbiturates among deceased drivers in British Columbia, the frequency of positives is very small" (Simpson et al. 1977, p. 224).

Ojerskog et al. (1978) delivered a preliminary report on a Swedish study of alcohol and drugs in traffic injuries. Cases were obtained at the County Hospital of Varberg, Sweden, during three four-month periods. The subjects, seventy in number, were responsible for the accidents. Only nine persons had measurable levels of alcohol in their blood, and only six persons reported being on continuous drug therapy. No consistent analyses for drugs had been performed, however, to determine the incidence of drugs in this group of drivers.

In the following subsection, surveys using indirect means of assessing drug use by drivers are reviewed.

3.6.2 Self-Reported Drug Use and Driving Frequency Studies. In a series of reports by the Traffic Accident Research Project of Boston University School of Law (Sterling-Smith 1976; Boston University 1976;

Sterling-Smith and Graham 1976), the historical and focal human factors variables associated with drivers "most responsible" for an accident fatality were studied. The involvement of alcohol and other drugs was also investigated. The Boston team attempted to collect information concerning the use of marijuana and other drugs by the driver during the two hours immediately preceding the accident. Sterling-Smith (1976) reported that 16% of the fatal accidents investigated were evaluated to have been marijuana-related. Other drugs noted were predominantly central nervous system depressants, such as barbiturates. Of the total number of accident-related operators, 45% were determined to be regular marijuana smokers (at least three to eight occasions in the year prior to contact). It was concluded that marijuana smokers were overrepresented in the accident sample (Sterling-Smith and Graham 1976). The findings of this study are summarized by Sterling-Smith (1975).

Note that the marijuana study did not involve the detection of cannabis constituents in the body fluids of drivers. Marijuana use prior to driving was indirectly assessed and, within the reliability of the collected reports, only approximates the actual usage rates. Further, the number of cases studied was quite small. Definitive studies concerning the overrepresentation of marijuana in the traffic crash population remain to be performed.

In a study designed to investigate the incidence of drug use and driving by the population of South Carolina (Jaeger, Fleming, and Appenzeller 1975), licensed drivers were selected at random from among visitors to licensing bureaus throughout the state. The age group from sixteen to forty-nine was emphasized particularly. Drug use and driving information was elicited during an interview and covered the twelve-month period prior to the interview. Some of its major findings are summarized below:

- Of 488 drivers, 16-49 years, 292 (59.8%) had used psychoactive drugs during the previous year, and 190 (38.9%) had driven afterwards.
- Of the 351 (71.9%) who had consumed alcohol, 255 (52.3%) had driven afterwards.

- Illicit drugs had been used by 121 (24.8%) of the sample and 88 (18.0%) had driven afterwards.
- Substantial percentages of those drivers who had used over-the-counter, prescription, or illicit drugs in conjunction with alcohol had driven after using those combinations (about 70% for each combination).
- Self-reported driving behavior of persons who drove after using psychoactive drugs was poorer than persons who did not drive, especially as measured by traffic tickets.
- Drug use patterns were nonhomogeneous regionally in the state, and were highest in large cities and suburbs.

The study group recommended that certain countermeasures be implemented, including the training of law enforcement officers for apprehending persons driving under the influence of drugs, and public information and education campaigns to reduce driving after the consumption of alcohol and other drugs.

Maki and Linnoila (1976) recently reported a questionnaire study of Finnish outpatients. Subjects included 765 rheumatoid arthritic, 715 tuberculous, and 1,050 psychiatric outpatients, along with 587 persons in a control group matched for age and living district. With traffic exposure controlled, the non-drug-treated patients were not involved in accidents more often than the controls. However, in the psychiatric outpatient group, drug use was linked with an increased accident rate. The combined use of alcohol and drugs also increased accident-involvement.

Rouse and Ewing (1974) conducted a questionnaire study of student drug use, risk-taking, and alienation. A proportionate random sample, stratified on the basis of sex and year in school, was drawn from the total undergraduate enrollment at a large southeastern coeducational university. One aspect of risk-taking, i.e., driving after using drugs, was examined. Here, since most women did not own a car or did not drive, only men were considered. Of the total number of men, 70% drove after drinking alcoholic beverages, 26% after smoking marijuana, 20% after using both alcohol and marijuana, and 5% after using alcohol and amphetamines. Marijuana users were most likely to drive after using

alcohol or any drug combination.

Smart and Fejer (1976) investigated drug use and driving risk among high school students. They attempted to determine the frequency of accidents and the frequency of drug-related accidents, comparing driving exposure under various drug effects. Anonymous questionnaires were given to 1,538 upper-level high school students in a classroom situation. Of the total sample, 710 had driven in the year prior to the survey. About 15% reported an accident and 20% a driving offense. Users of all drugs more often reported accidents than nonusers, but the results were statistically significant for tobacco, marijuana, opiates, "speed," LSD, and other hallucinogens. Only 2.7% had an alcohol-influenced accident and 2.0% a drug-influenced accident. Exposure to drinking and driving (56% of sample) was far more common than drug use and driving (1 to 6%, depending on the drug). When exposure to drug-related driving occasions was considered, LSD, tranquilizers, and stimulants were the most dangerous drugs. These drugs appeared more dangerous than alcohol. However, the infrequent use of drugs made their total effect on accidents small compared to alcohol.

Mortimer (1976) conducted a survey of the frequency and kind of drug use at the University of Illinois in 1975. Data collected with the same survey instrument at Eastern Michigan University (EMU) in 1971 were used for comparison. Alcohol, caffeine, nicotine, and marijuana were most frequently used. Compared to the earlier survey, an increased use of nearly all drugs listed was noted. In addition, analyses of the EMU data were performed to determine biographical and drug usage variables most associated with accident and violation rates. The results showed that those who had high violation rates had a different profile of drug use than those with high accident rates. Alcohol users-while-driving had high violation rates, while female marijuana, female alcohol, and male alcohol users were identified as having high accident rates. Interestingly, the concurrent use of caffeine and nicotine was associated with a reduction of the effects of other drugs on both violation and accident rates.

Finally, in a study that relates to a potential problem in the United States, Nix-James (1977) has presented a paper dealing with self-reported

alcohol and amphetamine use by long-distance drivers of heavy vehicles in New South Wales, Australia. Over forty percent of a total of 615 drivers reported using amphetamines "sometimes" or "often." Although the use of drugs was not directly related to self-reported involvement in accidents when exposure was controlled, relationships between drug use and other variables suggested hazardous driving behavior resulted. Nix-James concluded that any publicity about the possible adverse affects of stimulants "will have to be worded carefully to be effective against the firm conviction, of many amphetamine users, that the drug is essential insurance against falling asleep at the wheel" (p. 17).

3.6.3 Investigations of Driving Records of Drug User Groups. In addition to those studies reviewed elsewhere (Joscelyn and Maickel 1977a; Perrine 1974), two investigations of driving records were identified in the review of literature on drugs and driving. Smart (1973) reported the accident and violation rates for young persons convicted of marijuana possession or dealing in 1968 and 1969. The main purpose of the study was to determine how accidents and violations varied over the year prior to and subsequent to conviction. From the total sample of 1,546 male drivers, 245 held a driver's license during the periods of study and were between the ages of seventeen and twenty-three. This group was compared to all experienced male drivers and young experienced male drivers. Both collision and driving conviction rates for the marijuana group were in general much higher (1.5 to 2 times) than the rates for young experienced male drivers. Reductions in the rates of collisions and driving convictions appeared to be associated with the marijuana conviction. The countermeasure effectiveness of drug conviction was temporary for collisions while more long-lasting for driving convictions.

Maddux, Williamson, and Ziegler (1975) studied the driving records of 174 former heroin users maintained on methadone in San Antonio, Texas. Driving record changes during three periods--before heroin use, during heroin use, and during methadone maintenance--were described. Nearly all the subjects were male, Mexican-American, and with less than a high school education. In all driving categories (speeding, negligent collision,

other moving violations, driving without license, accidents), rates decreased from the period before heroin use to the period during heroin use, but increased from the period of heroin use to the period of methadone maintenance. This pattern was the same for self-reported and driving record data. When compared to the accident rate for all Texas drivers, the methadone group exceeded the average expected rate.

3.7 Summary

It is evident that the general population of the United States consumes large quantities of drugs each year. Yet production data, total prescription sales, over-the-counter sales volume, and other gross measures do little more than indicate per capita consumption. Few studies have been done to elucidate general drug usage patterns; with the one exception of marijuana, no studies are available to describe the use of specific drugs over broad segments of the population. Multiple drug use, while suspected, remains largely uncharacterized.

Despite an absence of detail, some characteristics of drug use have emerged from surveys. Users of illicit drugs, including marijuana, are primarily young adults eighteen to thirty-four years and, perhaps by example, younger adolescents. Although use of alcohol is relatively ubiquitous, the use of other drugs is nonhomogeneous with respect to region of the country, and perhaps within localities as well.

Total prescription sales indicate that central nervous system depressants within classes of antianxiety and sedative-hypnotic agents are very widely and quite frequently used. Among illicit drugs, marijuana stands out as the most frequently used by the greatest number of people. Over-the-counter antitussives, cold remedies, sedatives, and stimulants enjoy huge sales. However, none of these drugs are used more frequently than alcohol.

The data presently available do not give clear indication of:

- how and for what purpose the drugs are used,
- how often the drugs are used,
- in what combinations the drugs are taken,

- by whom the drugs are used, and
- where the drugs are used.

Closely associated with these questions are information needs concerning the availability of drugs nationally, regionally, and locally--in short, wherever drug usage patterns are to be characterized.

Three approaches to determining the influence of drugs on accident rates have been reviewed. They vary considerably in their ability to associate drug use with driving exposure. Further, each is limited by methodological problems peculiar to the chosen approach. On the other hand, the information derived from this body of literature does provide some data for assessing the contribution of drugs to problems in highway safety.

Clearly, the analysis of body fluids for drugs is the most direct and surest means for determining their incidence in drivers. Unfortunately, many barriers remain before this approach can yield its potential. First, and foremost, adequate analytical methods for screening of a wide range of drugs must be available and applied. Investigations to date have been limited by the insensitivity of their methods or by the unavailability of methods to detect, for example, the constituents of marijuana.

A second difficulty arises in the direct, analytical determination of drug prevalence in the driving population: that of obtaining a suitable control sample. Obtaining the voluntary cooperation of living, non-accident-involved drivers becomes crucial. A high refusal rate may invalidate any comparisons. Unfortunately, since local drug usage patterns for the driving population are almost completely unknown, there is no way to ascertain if the control sample is indeed representative. Thus, the validity of any large-scale field survey may be called into question.

Other issues are associated with the conduct of field surveys. The multifactorial nature of accident causation requires that the relative significance of each contributing factor be assessed. No ready reference yet exists for the interpretation of drug levels in terms of driver impairment. The presence of two or more drugs in driver body fluids presents an added degree of uncertainty. The possibility exists that several accident factors are interactive. Drugs may act to increase the

susceptibility of drivers to other causal factors. Until these limits to field research are addressed and removed, studies involving the measurement of drugs in drivers will remain exploratory and indicative only of the existence of a problem. Definitive research must involve the comprehensive analysis of accidents involving drugs.

By use of the questionnaire technique, both the type and frequency of drug use may be associated directly with driving exposure. Accident and violation rates both for drug and nondrug driving trips can be established. A major problem with questionnaire studies is the doubtful reliability of self-reporting. It has been established that underreporting occurs. Aside from the low estimates obtained, errors in reporting due to faulty memory or difficulty in recalling details may also reduce the value of findings obtained by this approach.

On the other hand, questionnaire studies elicit information quite useful in assessing the extent of the drug problem in traffic safety, for they yield data on the attitudes of drivers toward the use of drugs concurrent with driving. The prevalence of drivers who may drink or use drugs before driving may be estimated from these studies. Estimates of the public's awareness of the effects of drugs on driving performance may also be obtained. Questionnaire studies remain, however, a crude indicator of the prevalence of drugs in drivers. While more indicative than drug usage patterns in the general population, these studies cannot reliably determine the frequency with which drugs contribute to driver impairment or accident involvement.

Studies of driving records remain the least useful and the most indirect measure of the effects of drugs on the violation and accident rates of users. The relevance of such investigations varies directly with how closely the user group corresponds to the general population. In the methadone maintenance study reviewed above, the subjects were nearly all young, Mexican-American, ex-heroin addicts. It is questionable whether the results of that study could be used to predict the effects of methadone or heroin on the driving performance of other user groups. In other studies of a similar nature, when user groups are matched carefully for age, driving exposure, and types of accidents, differences that might

be attributed to drug use have diminished to insignificance (Waller 1965; Waller and Goo 1969).

Other complications in the analyses of driving records have been pointed out. When the use of a particular drug, for example, marijuana, is correlated with violation or accident rates derived from driving records, little attention is directed to the fact that marijuana users also use alcohol, frequently at the same time. Multiple drug use is more prevalent still among users of other drugs, such as heroin. Also, within a group defined by the use of a single drug, meaningful differentiations have been made on the extent of drug use. Thus, **how** the drug is used may have more bearing on a user's driving performance than the simple fact of its use. As reviewed by Nichols (1971), several research groups have suggested that personality problems that underlie the use of drugs may also contribute to poor driving records. As in the case of alcohol users, it may well be that a certain subgroup of drug users contributes disproportionately to accident causation. In this regard, other demographic and personal characteristics may correlate better with driving records than drug use per se.

The value of driving record investigations may rest in the identification and characterization of various subgroups of drivers who, by reason of their use of drugs, evidence a clear danger to themselves and others when behind the wheel. In this regard, great care must be taken to assure that the variable under study, the use of drugs, is not confounded by other user characteristics. Nevertheless, the problem of multiple drug use and the difficulty in estimating drug use and driving frequency would seem to relegate this type of study to a minor role.

In sum, the reported studies have thus far shown that drugs do appear in accident-involved drivers, that drugs are used just before driving, and that many drug users have poorer than average driving records. As Clayton recently wrote, "the role of [psychotropic] drugs in the causation of driving accidents, however, remains unclear and will remain so until carefully controlled large-scale field studies are undertaken" (Clayton 1976, p. 241).

4.0 EXPERIMENTATION IN DRUGS AND HIGHWAY SAFETY

The preceding section reviewed epidemiological efforts to describe the involvement of drugs in motor vehicle accidents. In this section, the other major approach used to define the drug and driving problem is reviewed, namely, the experimental study of the effects of drugs on driving performance. The first subsection outlines the methods of behavioral studies and notes briefly theoretical and practical limits of the experimental approach. The second subsection reviews research whose findings relate to the effects of drugs on driving performance for the purpose of updating previous reviews in this area of drug and driving research. In the last subsection, current knowledge is assessed by comparing what is known with what is yet to be learned about the effects of drugs on driving performance.

4.1 Background

Reviews of literature on patterns of drug use in general and driving populations have indicated a lack of precise information. It is not known, for example, how and in what situations individuals in the general population use widely prescribed drugs such as the barbiturates and benzodiazepines. Also, the analytical methods employed in epidemiological studies of accident-involved or fatally injured drivers were not capable of detecting such drugs as amphetamine or marijuana. It is not surprising, therefore, to have greater reliance placed upon experimental findings of drug effects on human performance (Ashworth 1975; Clayton 1976; Moskowitz 1976b). As Moskowitz (1976b) points out for marijuana:

Until studies capable of determining marijuana presence in accidents are performed, the major source of information regarding the accident potential of marijuana must come from experimental studies of driving-related performance

while under the influence of administered marihuana. (p. 22.)

Many reviewers have been concerned about the limitations of experimental research as applied to highway safety (Joscelyn and Maickel 1977a; Kibrick and Smart 1970; Waller 1971; Joscelyn and Maickel 1976; Silverstone 1974). In general, however, the criticisms offered are tendered with the realization that such complete epidemiological studies as the one Borkenstein et al. (1964) performed for alcohol have not been performed for any other drug, and may not be for some time. Experimental studies of drug effects, therefore, are very much needed to indicate the potential magnitude of the problem.

To identify drugs whose effects may impair driving performance, preliminary considerations often focus on known pharmacological properties of therapeutic and nontherapeutic agents (National Committee on Uniform Traffic Laws and Ordinances 1975; Colburn and Garland 1974; Waller 1971). For example, use of sedative-hypnotic drugs results in drowsiness, and hallucinogens have powerful sensory-perceptual effects. Both types of drug effects would prove hazardous for any driver. In the same manner, some drugs whose action would not be expected to impair driving ability, such as antacids and some antibiotics, can most likely be quickly eliminated from potential study.

However, it is a basic principle in pharmacology that a drug's effect is related to its concentration at the site of action. Thus, any drug taken in sufficient quantity may be expected to affect human performance significantly. For highway safety concerns, it is more appropriate to know if a drug's effects in commonly used dosages would impair driving performance. The effects of drugs are most often assessed by laboratory test systems designed to measure some aspect of human behavior. These methods may then be used to measure the behavioral consequences of therapeutic doses of drugs, as well as the effects of drugs used nonmedically, e.g., marijuana.

Experimental studies of drug effects occur in several settings, apply

numerous behavioral methods, and measure a host of variables. The relation of a behavioral method to the variable under study may not be simple. Different tests of human performance may measure the same variable, and behavioral variables may be measured directly or indirectly. For example, from measurements of eye movements may be inferred changes in the rate of information processing. General classification schemes exist for behavioral methodologies and specific tests, but concepts of human skills and psychological functions remain imprecise and subject to debate. Moreover, as Clayton (1976) noted, "most tasks involve elements of sensory, cognitive, and motor skills. Further, it is not always clear which element(s) is/are being measured by the task performance scores" (Clayton 1976, p. 243). Even within a group of tasks having a common behavioral measure, the differences in task requirements may significantly alter the results obtained. This has been shown for reaction time (response latency) tests by Perrine (1976). In addition, different methods have varying degrees of sensitivity, depending on the type of drug and drug effect under study.

It is difficult, therefore, to summarize both succinctly and accurately the experimental approaches that have been used to study drug effects on driving performance and on human skills believed related to driving. Nevertheless, in an attempt to give the reader some idea of behavioral research methodology applied to the study of drug effects, Table 4-1 presents an outline of experimental methods and specific tests. This table was developed in conjunction with the review of experimental literature, which follows. In Table 4-1, experimental methods are listed in five general categories. The methods range from those closely related to real-world driving, i.e., actual driving in traffic, to those less directly related to actual driving performance, e.g., physiological measures such as galvanic skin response or the EEG. Methods that measure psychophysical, psychological, and physiological functions or skills might be more generally termed "laboratory tests." Specific behavioral variables (e.g., vigilance) and specific response variables (e.g., number of performance errors in a test of vigilance) may also be measured in driving simulators or actual

TABLE 4-1

AN OUTLINE OF BEHAVIORAL RESEARCH METHODOLOGY AS APPLIED IN STUDIES
OF DRUG EFFECTS ON DRIVING PERFORMANCE AND ON HUMAN SKILLS BELIEVED RELATED TO DRIVING

TYPE OF METHODOLOGY	EXPERIMENTAL SETTING	EXAMPLES OF TESTS, TASKS, AND BEHAVIORAL OR RESPONSE VARIABLES
ACTUAL DRIVING (subject drives vehicle)	Open Road	Lane Position, Steering Wheel Reversals, Velocity (speed), Changes in Velocity, Car Following Distance, Gap Acceptance
	Closed Course	Driving Maneuvers, Including Fender Judgment (e.g., parallel parking, gap acceptance), Chassis Set (e.g., vehicle handling), Curve Management, Obstacle Avoidance, Controlled Braking
SIMULATED DRIVING (subject operates driving simulator)	Behavioral Laboratory:	
	Simple Driving Simulator	Tracking Task, Others (can measure visual perception, vigilance)
	Complex Driving Simulator (secondary tasks included)	Tracking and Search and Recognition Tasks, Measuring Visual Perception, Vigilance, and Rate of Information Processing
METHODS TO ASSESS HUMAN PSYCHOPHYSICAL FUNCTION	Behavioral Laboratory:	
Sensory-Perceptual		Kinetic Visual Acuity; Static Visual Acuity; Critical Flicker Fusion Frequency
Sensory-Motor		Simple Reaction Time (e.g., responses to visual or auditory stimuli)
Perceptual		Depth Perception; Sustained Attention (Vigilance)
Perceptual-Motor		Choice Reaction Time; Complex Function Tracking; Eye Movements
Motor Skills		Hand, Body Steadiness; Ocular Motor Control; Tapping
METHODS TO ASSESS HUMAN PSYCHOLOGICAL FUNCTION	Behavioral Laboratory:	
Cognitive Skills		Digit Symbol Substitution Test, Mental Arithmetic; Digit Span; Stroop Test
Mental Functions		Memory; Learning; Rate of Information Processing
Other		Motivation; Personality; Intelligence
METHODS TO ASSESS HUMAN PHYSIOLOGICAL FUNCTION		
Physical Parameters		Electroencephalogram (EEG); Electrocardiogram (EKG); Galvanic Skin Response; Hormone Levels and Cycles; Motor Nerve Impulse Conduction

driving tasks. For more detailed accounts of behavioral research methodology the reader is referred to the literature pertaining to that subject area. Zabik (1977) and Orzack (1977) reviewed various testing methods and research issues associated with their use at a symposium on drugs and driving in 1975.

As an important part of this report, reports on studies of drug effects were collected and reviewed. Our survey, a continuation of a previous effort (Joscelyn and Maickel 1977a), revealed a great variety of approaches in the experimental literature. Table 4-1 indicates the great diversity in methods employed to measure the effects of drugs on man. In addition, research on the effects of drugs is performed for a variety of reasons. Experiments have been conducted in order to determine:

- the effects of drugs on actual driving performance,
- the effects of drugs on other human behavior,
- the nature of drug effects in man, and
- the type and severity of drug effects in animals.

Of greatest interest here are studies that describe the effect of drugs on driving performance. In this group of studies, the sophistication of the methods employed varies considerably. Some have employed methods carefully designed to reproduce the driving task, at least in part. Others have used tests of such simple functions as reaction time or motor coordination. These latter tasks, while obviously part of the real-world driving task, have an uncertain relation to driving performance as a whole. Thus, while significant drug effects might be found, the drug's influence on driver behavior would remain unclear. It is possible that some laboratory tests may measure critical or "rate-limiting" skills as important components of the driving task. If this can be demonstrated, measuring the effects of drugs on these skills may indicate more directly their potential to increase the risk of traffic crashes.

Other published studies describe the effects of drugs on measures of human behavior, but do not relate the results specifically to driving performance. However, since tests similar to those described above are used, these reports are also of interest. Still further removed are

investigations designed to elucidate the **nature** of a drug's effects in man. These studies are often theoretical, based on hypothetical constructs of psychological functions. Their results are of interest, if not readily applied, to highway safety. Such studies provide insight into the effects of the psychoactive drugs whose locus of action is the central nervous system. Finally, while quite distant from human driving performance, reports pertaining to the effects of drugs in animals are sometimes relevant. Studies of drug effects too dangerous for human subjects may be carried out in the animal laboratory. For example, many drug toxicity, drug interaction, and drug tolerance investigations must be performed in animals. Animal studies were selected for review in this study only if their relevance to this report could be justified.

In the following section, a representative group of studies is reviewed. They were selected on the basis of their relevance to driving performance as well as to the identification of drugs for further research in highway safety. The scope of the review is not exhaustive of material available in the psychopharmacologic or behavioral literature; it is designed to complement and update previous reviews of experimental studies. Although this review is not intended to include all studies, we hope to provide a clear picture of the present state of knowledge about the effects of drugs on driving performance.

4.2 Literature Review

Several reviews of experimental studies of the effects of drugs on driving performance or on skills believed related to driving are available (John 1977; Kielholz and Hobi 1977; Buttiglieri, Brunse, and Case 1972; Valentine, Williams, and Young 1977; Joscelyn and Maickel 1977a; Willette 1977; Ashworth 1975; Clayton 1976). Other reviews have dealt with one or several kinds of drugs (Hurst 1976; Linnoila 1976; U.S. Department of Health, Education, and Welfare 1973; U.S. Department of Health, Education, and Welfare 1974; U.S. Department of Health, Education, and Welfare 1975; Gordon 1976; Sharma 1976; Moskowitz 1976). In addition, compilations of literature in the form of annotated bibliographies contain

selected studies for experimental research in drugs and driving (Joscelyn and Maickel 1977b; Austin et al. 1977; Joscelyn and Donelson 1978). Where appropriate, materials from these sources supplement this review of recent experimental studies by providing material that summarizes current research in specific areas, e.g., the effects of marijuana. For in-depth discussion of some topics, the reader is referred to more detailed reviews, which are cited in the following subsections as well.

4.2.1 Overview. The difficulties inherent in summarizing the results of experimental studies have been described previously (Joscelyn and Maickel 1977a; Clayton 1976). The reported studies differ in their approach, aim, quality, experimental conditions, and designs. Drugs were administered in different dosages to different subjects, and their effects were measured at different times by different methods. Furthermore, where several tests were used, only one may have yielded significant results. An appreciation of these difficulties led to the development of Table A-1 in Appendix A, which summarizes the results of fifty-five experimental studies.

The information contained in this table includes the following:

- the dose of each drug and how it was administered,
- the number and type of subjects,
- the experimental design and conditions,
- each test performed, and
- the results obtained.

In general, the drugs are listed separately and in alphabetical order. Exceptions to this rule are the active constituent of marijuana, delta-9-tetrahydrocannabinol, and its synthetic isomer, delta-8-tetrahydrocannabinol, which are presented under "marijuana." Where possible, each drug is listed under its generic name, if a pharmaceutical. If the drug is a combination of active compounds, the trade name is used or it is listed once under one of its active constituents.

Unless otherwise indicated, all drugs were administered separately,

acutely, by mouth, and in solid form. If the mode or route of drug administration differed, this information is provided. Since some studies also investigated drug interactions, at times the drug listed was administered along with a placebo. The effects measured can be reasonably ascribed to the drug itself, but where this occurred, it is noted. Where several drugs were tested in the same procedures, the symbol "#" is placed next to the listed drug.

Subject characteristics are listed to the extent they are reported, within space constraints. Particular attention was given to age, sex, weight, health condition, and occupation of the persons selected. Unless otherwise indicated, all subjects were considered "healthy and normal." In crossover studies, the number of subjects is the number of subjects receiving the listed drug. In experiments designed with an independent control group, the number of subjects is the total from which groups were formed. The size and makeup of the experimental groups are indicated under "experimental design."

Under "experimental design," the basic design of the experiment is described briefly, along with pertinent information about experimental conditions, testing times, placebo inclusion, and group makeup. The experimental designs often reflect the inclusion of more than one drug plus placebo in a single study. Not included, for the most part, are the times after drug administration when the tests were given. In many cases, this information was not available. When the exact times of testing were available, the lack of similar studies for comparison prevented effective use of that data. An exception was made for studies designed to assess the time-dependency of the drug effects. Even here, space considerations allowed only the briefest mention of these results. However, the use of multiple, time-based measurements of drug effects is indicated under "experimental design."

Under "tests and outcome" are given the tests employed and the results obtained for the listed drug. Where a more descriptive test name is appropriate or available, it is included in brackets after the given test name. For example, after "Delayed Auditory Feedback," the function

tested, "mental performance," is placed. Often, a single test may provide data for several variables or "performance measures." Alternatively, the test conditions may be varied systematically to yield a set of closely related performance tests. Where possible, a single heading is listed. The number of individual tests or performance measures is given in parentheses.

An asterisk indicates where a statistically significant result was obtained. In most instances, if the asterisk is not followed by qualifying information, it may be assumed the drug effect resulted in impaired performance. However, if a significant improvement in task performance was found, this is noted in parentheses. Where several amounts of each drug were tested, and only one dose level resulted in significant effects, the dose responsible is noted. Where several test conditions or performance measures were studied, and only one or two were significantly affected, the variables so affected are specified. If performance was generally impaired, only an asterisk is given. However, this should not be taken to mean that every aspect of the test was affected by the drug. For more detailed information, the study cited under "reference" should be consulted.

Even the most cursory inspection of Table A-1, Appendix A, reveals prominent features of the literature on drug effects. In the fifty-five studies, fifty-two drugs were investigated. Of the drugs, diazepam (sixteen times), marijuana (eleven times) were investigated most often. As a group, the benzodiazepines were heavily represented with eight members, followed by the barbiturates (six drugs). While these numbers may not represent the actual distribution of drugs selected for study throughout the world, the heavy bias toward certain drugs or drug classes is obvious.

Even when a particular drug was studied several times, the dosage levels employed often differed. For amobarbital, seven different acute doses were studied along with two different chronic treatments. In contrast, for diazepam, a standard therapeutic dose (10 mg) was most often studied. In about half the studies, a single dosage level of drug

was used. Where several dosage levels were administered, dose-effect relations were noted. Often effects not seen at the lower doses were found at the higher ones.

The subjects selected for these studies were, in general, young (early twenties), male, healthy, normal, and from a student population. One cannot help but wonder what the overall evaluation of the drug effects would have been had different subpopulations also been tested. It is true that the random mixing of different subpopulations often serves only to increase the variability of results considered together. Yet, where such background variables as sex (e.g., Clayton, MacKay, and Betts 1973; Clayton, Betts, and Harvey 1975; Jaattela et al. 1971), age (Linnoila 1973a), health condition (Uhr, Polland, and Miller 1959), and personality (Clayton, Betts, and Harvey 1975; Morselli et al. 1976) have been studied, their influence on the effects of drugs has been found. This implies that many significant drug effects may be hidden by a continued disregard of these factors.

As pointed out in a recent review (Clayton 1976), three experimental designs were used most often:

- repeated measures, where each subject receives all treatments, usually in a randomized sequence;
- an independent control group design, where each subject receives only one treatment, following random assignment to drug or placebo groups, with testing performed after treatment administration; and
- independent control group design, where each subject received only one treatment, following random assignment to treatment or control groups, but where all subjects are tested before and after drug administration.

For studies investigating the effects of acute doses of drugs, the independent control group design (often with no pretesting) is used to minimize learning effects during the experimental procedure (e.g., Linnoila, Seppala, and Mattila 1974). However, if small groups of subjects are used, problems may result from the well-known and considerable

variation among individual subjects. Significant drug effects may not be observed due to large statistical variance. The baseline equality of performance between groups may not be maintained. To avoid these problems, the crossover (repeated measures) design is employed. Here, the same group of subjects is exposed to the same test situation as many times as there are different treatments. Thus, control values (no-drug or placebo treatments) are generalized, using subjects with (assumptively) identical characteristics. However, the repeated exposure of subjects to the test systems may in itself result in improved performance, or learning effects. Also, the subjects' mental or physical states may vary during these lengthy procedures, introducing another source of variation. Test designs and analytical methods are available to reduce both learning effects and intersubject variability, but these are rarely applied (Joscelyn and Maickel 1977a; Clayton 1976).

The tests applied in the studies listed in Table A-1, Appendix A, easily represent the total spectrum of those available to measure human behavior. Some tests listed in this table have little demonstrable relation to driving performance (e.g., tapping, electroencephalogram recordings). Also, few tests have a clear correlation with skills important in driving. It is true that each test may, in some way, tap significant components of driving behavior, but until these relations are established, there is no way to judge the relevance of physiological, psychological, or psychomotor tests of drug effects. For the sake of completeness, then, all tests used in these experimental studies are listed.

Not only are many methods available for testing drug effects, but many are used. Only a few groups have applied the same set of tests in separate studies. Consequently, there is no evidence of comparability even between those infrequent studies that have used the same dose of the same drug. When several tests have been used in a single experiment, significant drug effects are recorded in one, and not another. Within a given test, a single performance measure among several may be affected at a single time point among several tested. Where a drug has been tested many times (e.g., diazepam, amobarbital),

significant improvements in performance may be noted. These occasional observations introduce the element of inconsistency and serve to emphasize the critical lack of systematic effort in this area.

With regard to comparability in experimental research, two of the most important variables in drug effects research are rarely determined. These are the concentration of the drug in the blood (preferably) and the variation of the magnitude of the effects tested over time. Ideally, both these variables should be determined in the same experiment featuring repeated measurements over time. To some extent, the use of several increasing doses of a drug (a dose-effect study) compensates for "this serious defect" (Waller 1971, pp. 1478). Higher, albeit undetermined, concentrations in the blood are produced in the group of subjects as a whole. At some dosage levels, usually at the higher end of the dose series, significant effects begin to appear with greater consistency than if a single, lower dose was used. Unfortunately, several factors are introduced which appear to complicate this simple approach.

Higher doses of drugs not only produce effects in more people, but also often bring on the effects more quickly, result in more intense effects, and cause them to last longer. The sole use of high drug dosage levels may lead to an overestimation of the actual significance of drug effects in the general population. The time-dependency of drug effects in dose-response studies, as yet largely ignored, becomes a very important consideration. Hence, the exact time of testing takes on added significance as an experimental parameter.

The effects produced by larger amounts of drug not only become more intense, but they may also completely change in character. This is especially true of the antianxiety compound diazepam which, at high doses, is a sedative. Performance measures that reliably indicate the effects of low drug doses may not be appropriate when studying the influence of higher doses. This phenomenon may be reflected in test results as increased subject variability or lesser impairment.

The dose-effect approach to the study of drug effects has led to an appreciation of the differential sensitivity of individual subjects. In a

study of marijuana, its effects on human cognitive and motor functions were described (Borg, Gershon, and Alpert 1975). Analyses of variance indicated that there were individual differences of response on the tests, and that the individuals performed differently from each other during marijuana intoxication. The authors continued:

To describe marijuana as a drug that produces variable action may be true for the drug effect measured across tests between individuals within a group. However, the consistency of the intrasubject drug effect on a range of behavioral measures suggests that individuals may follow their own particular patterns of response. (p. 217.)

Upon further statistical analysis, it was shown that in the middle range of doses employed, the individuals maintained their own pattern of response on all tests. At the lowest dose and the highest (where individual sensitivity differences were washed out by the stronger drug effect) greater inconsistency was found.

The employment of several dosage levels may result in more consistent gathering of drug-effect data. But the use of different tests and test times makes the common parameter of drug concentration all the more desirable. As Sellers (1975b) has emphasized concerning the phenomenon of intersubject variation in performance:

These variations between subjects could be explained by differences in receptor responsiveness but this explanation is not tenable until inter-subject variations in fate of the [drug] in the body is ruled out. (p. 276.)

In the following sections the effects of specific drugs and drug classes are reviewed. When available, review articles are cited and only their primary conclusions summarized. Recent contributions to the scientific literature are included, but only for those drugs or groups of drugs for which significant information related to driving performance has accumulated since a previous review (Joscelyn and Maickel 1977a).

4.2.2 Marijuana. Research into the effects of marijuana has been

intensive, producing an immense (and still expanding) body of literature. No attempt is made here to repeat the published work of reviewers (Joscelyn and Maickel 1977a; U.S. Department of Health, Education, and Welfare 1973; U.S. Department of Health, Education, and Welfare 1974; U.S. Department of Health, Education, and Welfare 1975; Petersen 1977; Le Dain et al. 1972; National Commission on Marihuana and Drug Abuse 1973; Edwards 1974; National Commission on Marihuana and Drug Abuse 1972; Hollister 1974; Miller 1974; Caldwell and Sever 1974c; Jones 1977a; McBay 1977) or of bibliographers (Pagel and Sanders 1976). Fortunately, considerable interest has been focused on the highway safety aspect of marijuana use. Thus, recent reviews of the effects of marijuana on driving performance and on driving-related skills are available (Jones, 1977a; Willette 1977; Joscelyn and Maickel 1977a; U.S. Department of Health, Education, and Welfare 1975; Moskowitz 1976a; Moskowitz 1976b).

The impairment of human performance on a wide range of cognitive, perceptual, and psychomotor tests has been reported (U.S. Department of Health, Education, and Welfare 1975; Hollister 1974; Jones 1977a). These effects are dose-related (Schaefer, Gunn, and Dubowski 1977). Significant effects are more frequently reported in studies using higher experimental doses of marijuana. Dose-response studies, such as those outlined in Table A-1, Appendix A, have also demonstrated the importance of dosage level in the determination of marijuana effects. Actual driving performance, behavior in driving simulation, and driving-related skills are all impaired by marijuana (Joscelyn and Maickel 1977a; Moskowitz 1976a and 1976b). To quote Moskowitz:

In summary, actual car driving studies suggest some impairment of tracking ability under marijuana, and simulator studies find strong evidence for perceptual performance impairment. Risk-taking appears to decrease....Clearly, the laboratory examinations support the conclusions from the field car studies and the simulator studies that both tracking and perceptual functions are impaired by marijuana. The degree of impairment found for the perceptual functions

appears greater proportionately than that found for the tracking functions. (1976b, pp. 290-3.)

A conservative conclusion from simulator, laboratory and car driving studies suggests that marihuana can impair aspects of the tracking and car control components of driving. However, such decrement is likely to arise in conditions demanding considerable maneuvering skill or which involve demands on the perceptual functions. On the other hand, monitoring the environment for potential dangers and signals clearly is impaired at fairly low marihuana levels and in situations which do not have extraordinary demands for information processing. (1976a, p. 24.)

While socially ingested amounts of marijuana produce significant behavioral effects, intersubject variability has made general dose-effect relationships uncertain (Borg, Gershon, and Alpert 1975; Klonoff and Low 1974). This variability in response has been observed in actual driving tests as well (Klonoff 1974). "Thus, the problem of individual differences that has complicated developing and enforcing 'drunk driving' laws will probably recur when medical and legal discussions of the minimal allowable dose or blood level of cannabinoids begin" (Jones 1977a, p. 143).

The nature of perceptual impairment by marijuana was further studied by Moskowitz, Ziedman, and Sharma (1976). Two experiments were performed to compare the effects of marijuana and alcohol on objective measures of visual search behavior. While alcohol decreased these performance measures significantly, marijuana (200 mcg/kg b.w.) had no significant effects. These plus other results led the investigators to suggest that "whatever marihuana does that produces impairment of visual performance, it does not do so at the central nervous levels that control the ability of the eyes to track environmental stimuli" (Moskowitz, Ziedman, and Sharma 1976, p. 428).

Interest has also been shown in the "nonpharmacologic determinants of subject response" to marijuana (U.S. Department of Health, Education, and Welfare 1975, p. 86; Jones 1977a). Intersubject variability, troublesome for

experimenters, may be one concern that led to studies of background variables that influence marijuana's dose-effect relationship. In addition to "set and setting," conditioning undoubtedly contributes to the effects of marijuana, as shown by placebo studies (Borg, Gershon, and Alpert 1975) and the effects of suggestion (Hollister 1974). State-dependent learning, tolerance, past usage of the drug, and individual responsiveness have also been suggested to influence the study of marijuana effects (Borg, Gershon, and Alpert 1975; Cohen and Rickles 1974; Darley et al. 1976). Some of these factors may be related to marijuana's impairment of memory function, particularly in its storage aspect (U.S. Department of Health, Education, and Welfare 1975).

Recent studies have addressed the question of background variables. Peeke, Jones, and Stone (1976) studied the effects of practice on marijuana-induced changes in reaction time. Two groups of subjects were used. Group M-P, which received no undrugged practice, performed a complex reaction time (RT) task during marijuana intoxication for four consecutive days. On the fifth day, they performed while nonintoxicated. Group M-P performed the RT task on four consecutive days without the drug, then marijuana-intoxicated on day five. At the end of session 2, group M-P was performing equally to Group P-M. When conditions were reversed on day five, Group M-P showed no RT slowing while intoxicated. The experimenters suggested that reaction-time performance may involve two phases: an early, attention-demanding phase which is sensitive to drug effects and a later, "automatic" phase which results from practice and is more resistant to drug effects.

This idea receives support from a dose-effect study by Borg, Gershon, and Alpert (1975). Speed of response was the basic parameter measured across tests of increasing cognitive involvement. Significant dose-response effects of impaired performance were produced by marijuana in all tests. However, single automatic motor abilities demonstrated greater sensitivity than tests of greater complexity. Although an earlier investigator had concluded that the principal effect of marijuana on reaction time occurred through an impairment of an individual's capacity to maintain a

response set, vigilance or sustained attention did not seem impaired in this study.

Another study, testing the state dependency of marijuana effects, indicated that the background factor of practice or pretest training may have more impact on a subject's performance than the state (intoxicated or "no drug") in which the subject trained (Beautrais and Marks 1976). Marijuana users, however, may differ from nonusers in ways that complicate the study of this drug's effects. Casswell (1978) compared the driving behavior of users and nonusers of marijuana in close-course and actual driving situations. Users did not differ from nonusers in operation of vehicle controls, speed of driving, or measures of performance obtained in the closed driving course. Some results--overtaking behavior, use of indicators--suggested some differences may exist in the nonintoxicated driving pattern of users compared with nonusers. These findings were related to their interpretation of the driving task and their subjective perception of risks involved, rather than to performance skills. The implication is that worse traffic records among users of marijuana may stem from these differences rather than from the effects of marijuana.

Thus, subject factors such as motivation and ability to compensate in certain functional tests seem to complicate the experimental study of the effects of marijuana. These are important factors, especially in considering the influence of marijuana on behavior. Since the real-world driving task is essentially an "over-learned" behavior (Clayton 1976), and since compensation of marijuana-induced effects has been demonstrated in experimental subjects, the studies described above have considerable significance for those who would understand the effects of marijuana on driving performance.

4.2.3 Benzodiazepines. Since 1960, when they were first introduced in clinical practice, benzodiazepine compounds have become some of the world's most commonly prescribed drugs. They are utilized both as antianxiety (ataractic) and hypnotic agents. Since all the benzodiazepines given in sufficient quantity will produce sleep, the therapeutic distinction

is thought to arise from metabolic and pharmacokinetic differences among the drugs (Greenblatt and Shader 1975).

Diazepam and chlordiazepoxide are the most studied members of the benzodiazepine class. They are prescribed as antianxiety drugs, but their presence in greater than therapeutic levels in the blood of drug overdose (Sine et al. 1972) and driving accident victims (Garriott et al. 1977) suggests widespread misuse of these drugs.

As indicated in Table A-1, Appendix A, experimental studies in the literature are numerous for both diazepam and chlordiazepoxide. Unfortunately, firm conclusions about their effects on driving performance or driving-related skills are difficult to draw. In the case of diazepam, the very wealth of data has made room for inconsistency. The use of different test procedures, drug doses, and dose regimens makes comparisons among studies extremely speculative. Furthermore, therapeutic doses of diazepam and chlordiazepoxide are most often employed in experiments. These drug levels are less likely to result in significant effects on driving skills. In fact, the reverse is sometimes found (Linnoila, Saario, and Maki 1974; Clayton, McKay, and Betts 1973), perhaps due to the relaxing properties of these drugs.

In spite of these complications, a general picture of impairing effects has emerged for these centrally acting drugs. In his review, Clayton reached this conclusion:

Of the 25 different drugs cited in the text, only two, chlordiazepoxide and diazepam, have been widely studied. The results are sufficiently divergent, however, to allow only the most guarded of conclusions that both drugs, when given in single doses, appear to impair performance in the short-term. Little is known about the long-term effects of any of the drugs. (1976, p. 250.)

There are few doubts, however, regarding the ability of these drugs to impair performance related to driving. Dose-effect studies (Haffner et al. 1973; Idestrom and Cadenius 1963; Bye et al. 1974; Molander and Duvhok 1976; Salkind and Silverstone 1975) have clearly shown that impairing

effects at higher doses of benzodiazepines may be expected, and that these effects are dose-related. Low therapeutic doses, e.g., in the study of medazepam by Moore (1977), may produce some dangerous side effects in some patients, but may not have marked adverse effects on driving.

The benzodiazepine literature also indicates that there may be significant differences among class members with regard to the individual effects produced (Borland and Nicholson 1975b). For example, chlorazepate was reported to produce less drowsiness than diazepam (Dureman and Norrman 1975). Diazepam (Linnoila 1973a), nitrazepam (Malpas et al. 1970; Borland and Nicholson 1975a), and N-desmethyldiazepam (Tansella et al. 1975), but not flurazepam (Borland and Nicholson 1975a), produced residual or "hangover" effects. This, however, may be dose-related as well. For example, higher doses (Salkind and Silverstone 1975) and longer treatment periods (Saario and Linnoila 1976; Harvey 1975) result in residual effects with flurazepam. On the other hand, whereas single acute doses of diazepam have impaired performance, some results have indicated that long-term administration may not (Linnoila, Saario, and Maki 1974).

Linnoila, in his review of tranquilizers and driving, attributed only "mild impairment of psychomotor skills after single doses" of benzodiazepines (Linnoila 1976, p. 17). He considered most dangerous their tendency to accumulate with repeated doses. The build-up of active metabolites was associated with increased side effects. Though their effects are generally mild, the widespread (and varied) use of these drugs causes concern that this class of tranquilizers increases the likelihood of traffic accidents.

4.2.4 Barbiturates. Like ethanol and unlike diazepam (which can be differentiated from alcohol), the barbiturates are a class of general depressants. Depending on the particular compound, they may act quickly or produce long-term depression of biological functions. Depending on the dose, they are able to induce drowsiness as well as states of anesthesia. The effects of barbiturates on human-performance measures have been

studied for the most part with the intermediate-acting agents pentobarbital, amobarbital, and secobarbital.

Tasks which show impaired performance after alcohol also are sensitive to the effects of moderate doses of barbiturates. The laboratory tests reflect the impairing aspects shared by alcohol and barbiturate intoxication: impaired thinking, lack of emotional control, aggressive behavior, motor incoordination, and drowsiness (Sharma 1976). Similar to the hypnotic benzodiazepines, barbiturates such as pentobarbital and heptabarbital have long-lasting residual effects (Borland and Nicholson 1975a; Borland and Nicholson 1974). As indicated by the experimental studies listed in Table A-1, Appendix A, laboratory findings have consistently indicated that barbiturates have a great potential to increase the risk of a traffic crash.

4.2.5 Nonbarbiturate Hypnotics. As Harvey (1975) stated, "it should be pointed out that nonbarbiturate hypnotic agents share most of the disadvantages of the barbiturates and usually have, in addition, the drawback that much less is known about their pharmacology and toxicology" (p. 124). The same may be said for the experimental study of their effects on driving performance.

Widely used agents in this group (aside from the benzodiazepines) include meprobamate, ethinamate, ethchlorvynol, methaqualone, glutethimide, and methyprylon. They share in common the ability to produce nonspecific, reversible depression of the central nervous system (Harvey 1975). They may be expected to affect performance measures adversely in a dose-dependent manner. Their depressive effects are undoubtedly dangerous when combined with driving. The intensity of effect and the severity of impairment will depend on basic factors such as dose, how and when the drug was used, and the degree of central nervous tolerance to the depressive effects. Some of the published experimental studies are summarized in Table A-1, Appendix A, and in previous reviews (Willette 1977; Joscelyn and Maickel 1977a).

4.2.6 Other Psychotropic Drugs. The drugs and drug classes discussed above have received most of the attention devoted to the effects of drugs on driving-related skills. Other widely prescribed drug groups, especially the neuroleptics (major tranquilizers) and antidepressant agents, have been studied hardly at all, at least in the context of driving performance. Clayton, Harvey, and Betts (1977), however, compared the effects of two antidepressants, imipramine and viloxazine, on tests of driving performance in a closed course. Results showed imipramine, but not viloxazine, tended to increase the level of risk acceptable to the subject and also impaired other measures of performance.

Linnoila (1976) reviewed the laboratory studies of both the antidepressants and neuroleptics. Low doses of antidepressants generally do not result in the impairment of driving skills. Those with sedative properties, however, may interfere with information processing. Neuroleptics primarily affect this function, too, and to a much greater degree. Since many of the effects found are diminished upon regular administration of neuroleptics, chronic use of these drugs probably presents less of a hazard. Hofner (1978) reported a study that supports this conclusion. The effects of mianserin, a new antidepressant, were measured in tests of performance, including concentration, reaction time, motor coordination, visual perception, and subjective rating of symptoms. In addition to symptoms of fatigue and drowsiness, the tendency of most variables to show impairment decreased by the fifth day of study. Only impairment of concentration remained unaffected by prolonged administration of the drug.

Many drugs, both prescribed and available over the counter, have effects similar to but less intense than the general or specific depressants. In some instances, as in the case with over-the-counter drugs, these mild effects are considered safe for self-medication by the general public. With other drugs, the potentially impairing effects are "in addition" to the therapeutic effects of the medication. For example, antihistamines have sedative properties and also produce a variety of central nervous system effects (Douglas 1975, p. 607). As indicated by a

recent review of laboratory studies, antihistamines, antinauseants, and antivertigo agents have the potential to impair driving skills (Joscelyn and Maickel 1977a).

While alcohol is generally used for the purpose of intoxication, pharmaceutical and over-the-counter drugs are not intended for such use. Most laboratory experiments done to date have been concerned with dosage levels of drugs normally taken by patients for treatment of disease. Aside from the fact that (almost without exception) experimental studies utilize healthy, normal, young volunteers, another aspect of the effects of drugs is largely ignored: the effects of higher-than-therapeutic dosage levels. Substantial drug misuse has been recognized, and it is well known that pharmaceutical and other drugs are taken in greater than therapeutic amounts for nonmedical purposes. In addition, a whole group of drugs has emerged--the so-called drugs of abuse--which are used exclusively for the purpose of intoxication. Many of the altered mental and physical states so produced may and are considered, a priori, to be deleterious to driving performance, even by the users. The psychedelic substances and narcotic analgesics such as heroin are examples. Whether these effects actually impair driving-related skills in the laboratory is less critical information than how often users drive when under their influence. The scarcity of studies investigating the effects of these drugs, which may be partly due to ethical and legal concerns, is not surprising.

Methadone, a narcotic used in maintenance treatment of addicts, has been studied to a limited extent. Gordon (1976), reviewing the influence of narcotic analgesics on highway safety, has summarized the laboratory results thus far obtained. Single doses produce marked effects on performance. However, evidence from studies of reaction-time, psychomotor skill, and sustained attention suggests that "the performance of methadone patients who are well stabilized on the drug cannot be differentiated from the performance of non-drug-using individuals" (Gordon 1976, p. 6). The factor of stabilization is very important. Individuals treated with methadone are balanced between the physiological state of

withdrawal and the presence of opioid effects (Horns, Rado, and Goldstein 1975), both of which may impair driving ability.

Most of the drugs and drug classes discussed above are depressants. Depressed functions invariably impair performance in tasks requiring the alert, coordinated use of psychomotor skills and cognitive capacity. For some drugs, this fact is related to dose. But another group of drugs and drug classes produce the opposite effect: **stimulation**. Like other drugs with mood-altering ability, psychostimulants have the potential for misuse.

Among the most commonly used drugs in the world is the stimulant caffeine. Other drugs, such as cocaine, amphetamine and its congeners, and perhaps nicotine (Russell 1976), also have central nervous stimulation as their principal effect. It may be expected that drugs that increase alertness and other central functions improve the performance of driving-related skills. Hurst, reviewing amphetamines and driving behavior, wrote:

The major acute effects of amphetamines, in the normal clinical dose range, can be summarized very swiftly: they don't impair performance, they enhance it! The degree of enhancement is generally greater in fatigued subjects and in simple or repetitive as opposed to complex tasks such as reasoning or I.Q. tests. When subjects are not previously deprived of sleep, the effect is usually not a large one. Nevertheless, when any significant effect is found, most of the time it is on the positive side. . . . Driver-related behaviors, such as simple and disjunctive reaction time and various measures of vigilance and psychomotor performance, are among those showing positive effects. (Hurst 1976, p. 10.)

Of concern in highway safety is not central nervous stimulation per se, though slightly increased risk-taking behavior may result from the influence of these drugs (Hoffner et al. 1973). It is more the degree of stimulation and what happens when the effect wears off. Caffeine, the only stimulant drug socially accepted to any significant extent, has not been identified as a problem, though it is often and excessively used by

the general population (Goldberg and Havard 1968; Gilbert 1976). Amphetamine misuse, by oral or intravenous routes, has rarely been studied in the laboratory, for obvious reasons. As Hurst points out, "Nor would there appear to be any crying need for such research. There is ample documentation, from clinical reports and accident investigations, that amphetamines are dangerous when used excessively, although one does not know how often this occurs" (1976, p. 11). Neither have the acute or chronic effects of cocaine been investigated in regard to driving performance. The intense euphoria resulting from the ingestion of cocaine is relatively short-lived compared to that of amphetamine, but how often the drug is used just before or during driving is a matter for conjecture.

Reviews of the pharmacology and toxicology of the stimulant drugs are available (Gilbert 1976; Hart and Wallace 1975; Gay et al. 1975; Caldwell and Sever 1974a; Russell 1976). A monograph on cocaine was recently released by the National Institute on Drug Abuse (Richards and Blevens 1977). Grinspoon and Bakalar (1976) trace the social history of cocaine and the involvement of medicine, law, and intermittently, science.

4.2.7 General Pharmacological Effects. Along with the effects of selected drugs, certain pharmacological properties shared by many drugs have received increased attention. Chief among these are the following:

- effects after combined use ("drug interactions");
- residual drug effects;
- time-dependency of drug effects, including the biphasic action of drugs; and
- tolerance to drug effects.

"Drug interactions" refers to the effects of drugs so administered that their respective time courses of action overlap. "Residual drug effects" refers to the "morning after" or long-term effects of having taken a particular drug. The increased awareness of polydrug use and the common use of sleeping preparations make both categories of drug effect important to highway safety.

The ubiquitous consumption of alcohol and the pronounced tendency for the general population to superimpose drug-taking on alcohol-consumption patterns have focused attention on drug-alcohol interactions. Table A-2, Appendix A, presents a selection of drug interaction studies. As befitting known drug usage patterns, all but three of the forty-seven drug combinations include alcohol. Eight of the forty-seven combinations studied include diazepam and alcohol.

One of the curious features of the literature on drug interactions is the absence of standard definitions for the terms employed to characterize the resulting effects from the combination of drugs. "Additive," "potentiative," "synergistic," and "antagonistic" have all been used in different ways to describe the combined effects of drugs. Given that the effects of two drugs have been characterized for (1) the doses to be employed, (2) the times in which measurements will be taken, and (3) the methods used to assess their combined effects, one can expect that the "sum" of the effects of two drugs will be additive, less than additive, or greater than additive (Carpenter, Marshman, and Gibbins 1975). However, because of the complex nature of drug effects and the influence of dose, time of measurement, and behavioral task selections, laboratory results are not so simply characterized. Concerning the use of these descriptive terms for drug interactions, Carpenter, Marshman, and Gibbins (1975) have pointed out that "because none of the terms specifies the operations for deciding whether the observations fit the definitions, the terms are of limited usefulness" (p. 3). However, an alternative approach, the development and use of mathematical models, requires far more data than obtained in most studies.

In general, the results of drug combinations listed in Table A-2, Appendix A, do not indicate whether two drugs used at the same time, or nearly so, will result in "greater" effects than used separately. If two drugs administered simultaneously cause enhanced impairment compared to either drug-placebo condition used as control, the combination should be considered more hazardous to performance. With few exceptions, the data obtained do not permit further conclusions to be drawn as to the

nature of the drug interaction. Most of the words used to describe the results of the studies listed in Table A-2, Appendix A, were chosen by the authors of the report cited. Each reference of interest should be consulted for the specific type of changes observed.

As was noted in the discussion of the single drug studies listed in Table A-1, Appendix A, several features of the drug interaction literature become apparent when a selected group of reports is assembled in this fashion. Twenty-eight of the thirty-four drugs were studied only once, many at a single-dose combination of alcohol and drug. Even for those drugs studied more than once, different doses, test systems, and measurement times are employed. Thus, conclusions must reflect the difficulty of comparing separate studies.

Generally, drugs with similar actions (e.g., depressive) tend to enhance the impairment of performance observed with either one separately. An apparent exception to this statement may be the chlordiazepoxide-alcohol combination, where additive effects, when observed, are considerably less than for diazepam-alcohol combinations. Lessened effects are sometimes found (Teo 1975). When drugs with somewhat dissimilar actions (e.g., marijuana and secobarbital, marijuana and dextroamphetamine, or caffeine and alcohol) are combined, simple additive expression of both sets of effects is frequently observed (Hussar 1976; Evans, Martz, Rodda, Lemberger, and Forney 1976; Dalton et al. 1975). For example, if both sets of effects tend to impair performance, greater impairment is seen with the combination (Dalton et al. 1975). Of all the combinations studied, several have been singled out as particularly effective, and therefore dangerous. Diazepam-alcohol, bromvaletone-alcohol, codeine-alcohol, and nitrazepam-alcohol are among those combinations found particularly deleterious for driving skills (Moskowitz and Burns 1977).

Drug interactions are usually described using behavioral test systems, and the mechanism by which the drugs interact is rarely investigated. Enhanced drug absorption (particularly when alcohol is one drug used), modified distribution or metabolism, presence of modifying agents (e.g., in marijuana) (Dalton et al. 1976), and receptor-site competition have been

suggested as underlying causes for the effects observed. For many of these conjectures, the obtaining of drug concentration data is necessary before an adequate explanation can be provided.

Other reviews of drug interactions, mainly with alcohol, are available (Seixas 1975; Braithwaite 1976; Joscelyn and Maickel 1977a; Carpenter, Marshman, and Gibbins 1975; Linnoila and Mattila 1973a).

The occurrence of long-lasting effects beyond those experienced soon after drug administration is well-known, especially for alcohol (Seppala et al. 1976). "Hangover" effects have been observed also for hypnotic agents used to induce sleep (Borland and Nicholson 1975a; Salkind and Silverstone 1975; Saario, Linnoila, and Maki 1975). Related studies are those which test regular or chronic users of a drug but who are not under its influence during the time of the test. For example, consistent patterns of inferior performance were found for marijuana users on both manipulative and coordination skills (Salvendy and McCabe 1975).

The relative lack of such studies reflects the state of knowledge with respect to the time-dependency of drug effects. The qualitative and quantitative measures of drug effect may, and often do, depend on the time these measures are taken. Other variables include the type of measure used and the dose of the drug administered. Amphetamine, for example, induces an energetic and active euphoria; if too much drug is taken, the increased efficiency and generally enhanced performance decline, and test measures may indicate impairment. Postamphetamine effects include listlessness and depression (Hart and Wallace 1975). Depending on the time selected, several portraits of amphetamine effects could be obtained. For example, one study has indicated that a triphasic behavior pattern may result after a 10 mg dose of amphetamine (Mann et al. 1974).

Some drugs have nonuniform effects, depending on the time and dose selected for study. The long-term effects of a depressive drug may be the enhancement of performance ("rebound effect") (Borland and Nicholson 1975a). Marijuana, like amphetamine, has a "biphasic clinical action, with an initial period of stimulation (anxiety, heightened perceptions, euphoria)

followed by a later period of sedation (relaxation, sleepiness, dreamlike states)" (Hollister 1974, p. 248). Depending on the dose, amobarbital may have a stimulating effect, as has been shown by physiological and performance measures (Idestrom and Cadenius 1963). Carpenter, Gibbins, and Marshman (1975) found in one experiment that increasing doses of alcohol had a nonmonotonic effect on behavior, with best performance obtained between 0.29 and 0.46 g of alcohol per kg, followed by accelerating deterioration as dose was increased. That alcohol, a depressant, has stimulating properties is well-known and commonly experienced. Biphasic drug effects may be one factor in the experimental problem of intersubject variability and interlaboratory inconsistency.

Another pharmacological effect, tolerance, is little studied in drugs that exhibit this phenomenon. Tolerance, such as that seen in opiate addiction, may be described as the lessening of a drug's effect upon repeated administration. Alternatively, tolerance is the obtaining of a given intensity of effect with increasing doses of a drug. Another, related effect is "acute tolerance." Here, as the blood concentration rises and falls with acute drug administration, greater effects are observed on the rising portion of the time-based curve than on the falling, or later, portion.

How a drug is administered, as well as how often, may play a large role in the type and degree of effects obtained. Tolerance to opioid effects is the basis of methadone maintenance in the treatment of heroin addicts. The administration of the drug is designed to prevent withdrawal symptoms and, by producing cross-tolerance to heroin, discourage the use of heroin (Mayer 1968). Tolerance to desired as well as to undesired effects is found upon repeated exposure to some drugs. The clinical effects of diazepam diminish with chronic administration (Hillestad, Hansen, and Melsom 1974; Kanto et al. 1974). Improved performance on tests by patients through learning (Hillestad, Hansen, and Melsom 1974) and the possibility that diazepam induces its own metabolism (Kanto et al. 1974) have been offered as explanations for the reduction in effects of diazepam. Receptor desensitization in the central nervous system was

suggested for the failure of chronically administered flupenthixole to impair divided attention performance (Linnoila et al. 1975). Earlier, it had been shown that acute flupenthixole disrupted this driving-related skill (Linnoila 1973b). Chronic administration of diazepam, in contrast, proved more deleterious to driving-related skills when compared to single doses (Linnoila, Saario, and Maki 1974; Linnoila and Mattila 1973). These results may be related to the cumulation of diazepam and its N-demethylated metabolite (Hillestad, Hansen, and Melsom 1974). Thus, tolerance may develop to some but not all of the drug's effects.

As Cohen and Rickles point out, "as used by psychopharmacologists, the hypothetical construct 'tolerance' seems to be a catchall phrase to explain lessening effects of a drug with repeated usage" (1974, p. 328). However, whether this general effect is labeled "behavioral," "physiological," "cognitive," or "central nervous system" tolerance, the fact remains that the character and degree of drug effect may change upon chronic administration. Since many drugs are prescribed in this manner, more attention to differences in the effects of drugs engendered by dose regimens is warranted. Since cross-tolerance is also known to occur, e.g., between alcohol and a variety of central nervous system depressants including barbiturates (Caldwell and Sever 1974b) and perhaps marijuana as well (Jones and Stone 1970; Friedman and Gershon 1974), prior drug use by experimental subjects and drivers alike may influence the effect of certain drugs.

In summary, various pharmacologic effects are known but little studied in relation to driving performance. Yet such effects may significantly influence both the experimental evaluation of drug effects and the interpretation of epidemiological findings with regard to the type and amount of drug(s) present. The purpose of this review has been to describe the state of knowledge of these effects as related to driving performance. The literature available suggests that drug interactions and residual drug effects may be important factors in assessing the risk potential of certain drugs. The time- as well as dose-dependency of drug effects, as indicated by several isolated reports, deserves more attention

by those concerned with the experimental evaluation of drug effects. The phenomenon of drug tolerance, both long-term and acute, has been largely ignored in the experimental literature. "Drug concentration" as a unifying parameter in behavioral research has rarely been employed, thus making interstudy comparisons nearly impossible.

4.3 Summary of Research on the Effects of Drugs

The state of knowledge about the effects of drugs on driving performance is three-faceted, involving as it does three basic aspects of the scientific process:

1. Behavioral research methodology: the state of the art of behavioral testing, including definition and laboratory replication of the real-world driving task, method development and evaluation, determination of test reliability, and elucidation of background variables.
2. Experimental work: the appropriate utilization of testing systems, including application and execution of correct experimental designs, selection of a relevant subject population, and control of extraneous or confounding variables.
3. Published work: the accurate and detailed reporting of experimental results, including adequate exposition of analytical methods, and assessment of the significance and applicability of findings to the population-at-large.

A survey of recent reviews (Willette 1977; Joscelyn and Maickel 1977a; Kibrick and Smart 1970; Nichols 1971; Ashworth 1975; Silverstone 1974; Waller 1971; Clayton 1976; Moskowitz 1976a; Joscelyn and Maickel 1976; Zabik 1977; Orzack 1977; Forney and Forney 1975) reveals a consensus among investigators and reviewers regarding the evaluation of research on drug effects. There are deficiencies in behavioral research methodology, especially in definition and analysis of the real-world driving task itself, and in development of tasks demonstrably related to driving performance. The experimental work done to date is fraught with

methodological problems; major shortcomings are weak experimental designs and the selection of tests and subjects. The literature, in consequence, reflects these difficulties. Specific faults include incomplete reporting of methods for behavioral and data analysis; the stating of conclusions not supported by results; and the scattered nature of the literature body as a whole (Joscelyn and Maickel 1977a). The great number of drugs and drug classes, the wide variety of drug effects, and the diversity of tests used to measure their effects compound problems of evaluation. Information needs and problem areas in drug effects research are more fully examined in Section 7.0.

4.3.1 State of Knowledge of Research on Drug Effects. The number of studies performed to determine the effects of drugs on human performance is deceptively large. As frequently mentioned above, there are a considerable number of different drugs, drug effects, and separate methods by which to assess them. Also, drugs administered in different amounts have different effects: either the overall effect is augmented, or it may change in character. A very good example is diazepam, an antianxiety agent that in higher doses resembles a sedative. While the literature on drug effects is voluminous, it is not comprehensive. In his review of psychotropic drug effects, Clayton (1976) reached this conclusion concerning the research pertaining to barbiturate hypnotics, nonbarbiturate hypnotics, tranquilizers (minor and major), and antidepressants:

This review has demonstrated the lack of unanimity that exists in this area of psychopharmacology. The differences that exist in the methodology, tasks, drug doses, and subjects used make it extremely difficult to reach any firm conclusions as to the practical effects, upon the driving performance of patients, of any prescribed psychotropic drug. Of the 25 different drugs cited in the text, only two, chlorthalidone and diazepam, have been widely studied. The results are sufficiently divergent, however, to allow only the most guarded of conclusions that both drugs, when given in single

doses, appear to impair performance in the short-term. Little is known about the long-term effects of any of the drugs. (p. 250.)

Nevertheless, as one element in the process of risk identification, experimental research has decided value. While laboratory research represents "a fragmentary approach to the problem," it "has the advantage of ease and relative cheapness" (Ashworth 1975, p. 202). Preliminary assessments of a drug's effects can be made available without full-scale epidemiological investigations. Thus,

The experimental evidence represents a set of indicators suggesting the need for further examination of drug effects in the highway safety setting. The experimental results may be useful in establishing priorities for epidemiological inquiry and suggesting the dimensions of investigations. (Joscelyn and Maickel 1977a, p. 71.)

Previously noted as well, detecting some drugs in body fluids is not presently feasible, rendering determination of their impact on accident causation extremely difficult. Experimental results in these cases may be the only means of assessing their effects on driver performance (Clayton 1976; Moskowitz 1976a). Pharmacological data also provide a useful indication of certain drug-related phenomena. For example, it is widely demonstrated that excessive doses of drugs do cause impairment. Although one would not expect to encounter these amounts frequently, cases of drug misuse may be specifically overrepresented in the accident population. Also, some drug interactions as investigated in animal pharmacology may be too dangerous for experimental subjects. Laboratory results would remain the only source for information regarding these effects, especially after high doses.

As may be obvious, drug effects research is not a panacea for the lack of information in the area of drugs and driving. Even a quick scan of Tables A-1 and A-2 in Appendix A reveals the problems of interpretation inherent in laboratory studies. Leaving aside the relevance of certain performance measures to the actual driving task, it is apparent

that significant drug effects are recorded on some, but not all, of the tests used. Drugs are mainly tested on young, male volunteers, mostly students. While undoubtedly some students are prescribed these drugs, and even take them as prescribed, most people using prescription drugs are women and older. Many of these drugs are used in larger amounts and often in conjunction with other drugs, especially alcohol. However, high drug doses and certain drug combinations may present an unacceptable hazard to human subjects. Also, the expected degree of impairment would not contribute new information to the assessment of risk potential for these drugs and their combinations. More valuable would be knowledge of their actual prevalence in the at-risk driving population compared to accident-involved drivers. Thus, while research in drug effects is incomplete and not completely applicable for highway safety purposes, it is seen as one element in the overall process of assessing the risk potential of drugs for the real-world driving situation.

4.3.2 Methodological Approaches to Research on Drug Effects. Many investigators in this field are aware of the problems and limitations of research on the effects of drugs. Reports in the literature evidence several approaches to determination of the accident potential represented by drug effects. Linnoila and co-workers have conducted a series of laboratory studies on numerous drugs alone and in combination with alcohol. Using more than 1,600 subjects (by 1973), they have been able to compare drugs of different classes in the same test situation. In addition to care in subject selection, these investigators have confirmed some of their laboratory results by simulated driving tests. They suggest that carefully selected psychomotor tests can and should be used to provide data about the actions and interactions of drugs and alcohol on driving skills (Linnoila and Mattila 1973b).

Other investigators seek test situations and methods more closely related to actual driving performance or even in actual traffic. Perrine, in the context of alcohol-safety research, has sought to develop an alternative to:

. . . the practice [of inferring] alcohol impairment of real-world driving performance from the mosaic of fragmented bits of behavior examined separately in the laboratory and in part-task driving simulators (e.g, reaction-time, tracking, etc.). In addition to the problems involved in reasoning from isolated parts to a complex whole, several aspects of human behavior may set further limitations on the extent to which we can extrapolate from controlled experiments. (Perrine 1976, p. 23.)

To avoid such subject-oriented factors as the "grandstand effect" or Hawthorne effect, Perrine proposed to develop "valid, unobtrusive measures of alcohol impairment in real-world driving situations" (p. 24). Taking those behavioral variables showing consistent degradation in controlled alcohol experiments, inferences may be made to those aspects of actual driving performance differentially impaired by alcohol, especially "those alcohol induced changes in driving behavior which would serve to differentiate motorists with high BACs from motorists with zero or low BACs" (p. 24). Perrine reported one attempt to conduct a controlled study utilizing this approach.

In that study, while Perrine eschewed the "laboratory-only" approach, he relied heavily on its results to develop a basis for his subsequent investigation. Also, the convenience of measuring blood levels of alcohol by breath analysis contributed to the success of his approach. For marijuana, this approach is not yet feasible. First, the measurement of marijuana constituents is difficult and costly. Second, the exact effects of marijuana have not been determined. Recent investigations, such as the one by Moskowitz, Ziedman, and Sharma (1976) have shown that the effect of marijuana, while impairing, differs from that of alcohol. As Moskowitz has stated:

Currently, information regarding possible driving impairment by marijuana comes primarily from experimental studies of driving and driving-related tasks under administered marijuana. Unfortunately, these studies are limited in

predicting the accident probabilities associated with various marijuana dose levels, since they do not take into account such interacting factors as age, driving experience, and drug-use experience. These have been shown to be important covariables for alcohol, the only drug for which we have extensive information about effects on driving. However, experimental studies do have the advantage of potentially going beyond a correlation between task impairment and drug treatment to an understanding of the nature of the impairment. In the long run, knowledge of how various drugs produce impairing effects on driving may lead to more adequate remedial measures than the frequently offered panacea of a law which proscribes use of the drug. (Moskowitz 1976a, pp. 283-4.)

Knowledge of the nature of a drug's effect may lead to the identification of accident characteristics peculiar to a given drug or set of drugs. The importance of accident analysis to drug effects research also finds expression in the development of behavioral methodology which can measure driver-related functions. An example of this approach is the investigation of kinetic visual acuity (KVA) as a function directly related to the driving task. Suzumura (1968) has shown in a series of experiments that a combination of static and kinetic acuity scores may be a valuable discriminator of high and low accident-involved drivers. Recently, the KVA test instrument has been used as part of a test battery in studying the effects of various psychotropic drugs (Clayton 1975). The results of these studies may provide working hypotheses for field studies of the sort described by Perrine. Research on visual functions such as KVA is reviewed in more depth in Section 7.6.

4.3.3 Conclusions. The subsections above stress methodological and other issues present in behavioral research related to drugs and driving. Again, this is not to suggest that studies of drug effects are, at present, entirely without value. Rather, the discussion serves to emphasize their

limited value in assessing the potential of drugs to increase the likelihood of traffic crashes. The laboratory, indoors and out, does have a major role in determining the nature and extent of the drug and driving problem.

First, the experimental approach yields data useful in selecting a set of drugs or classes of drugs to focus field surveys of drug use among drivers. This approach indicates the kind and degree of effects that can be expected, at least for therapeutic doses in select populations of "normal" subjects.

Second, experimental studies seem required to correlate the levels of drugs in blood (or other body substance) and their effects on skills believed related to driving. Probably, relatively few cases for any one drug will be found by the case-control approach, within the practical limits of sample size and costs. Thus, a statistical determination of relative risk for different drugs seems remote. Data on the meaning of drug levels, however, will aid in the interpretation of epidemiological findings.

At the same time current approaches to the study of drug effects on driving performance must be improved. The development of sophisticated behavioral methodologies based on proven driving-related functions is among the most promising of approaches. The convenience and less-expensive nature of laboratory research can be combined with carefully designed and controlled experiments. The continued improvement of the methods currently available depends on the analysis of data from studies of actual driving, driving simulators and human performance testing. The functional analysis of the driving task itself will undoubtedly contribute to progress in the field of drug effects research. Current research in behavioral functions related to the driving task is reviewed in Section 7.0. Appendix B contains a review of research on drug concentration-effect relationships.

5.0 COUNTERMEASURES IN DRUGS AND HIGHWAY SAFETY: CONCEPTS AND CONSTRAINTS

Thus far in this report, topics pertaining both directly and indirectly to defining the problem of drugs and driving have been reviewed. In this section, various measures designed to reduce an identified drug-and-driving problem are reviewed. This review of the action component of drugs and highway safety is intended only to assess proposed countermeasures, not to suggest that unproven countermeasures be implemented. This preliminary discussion is intended to clarify the need for defining the problem in terms that permit effective drug measures to be rationally identified, developed, demonstrated, evaluated, and implemented.

Reviewed in this section are the underlying concepts of countermeasures and their constraints. Reports are cited that identify specific groups that, due to their patterns of drug use and driving, may face greater risk of accident-involvement. The objectives of countermeasures are described in terms of specific target groups where possible. A conceptual basis is presented for a rational, systematic approach for dealing with a drug and driving problem. Finally discussed are constraints on the development, implementation, and evaluation of drug countermeasures. Reference is made to the analogy of alcohol in highway safety.

5.1 Countermeasure Concepts

The need for systematic approaches to the development and evaluation of countermeasures has been recognized in alcohol-crash programs (Voas 1975) and, of course, the need is the same for programs addressed to the involvement of drugs other than alcohol. Systematic approaches have included both preprogram and postprogram elements:

1. **Preprogram Activity:** Identification of the target of control action.

2. **Program Design and Operation:** Development and implementation of actions directed at the targets.
3. **Postprogram Activity:** Evaluation of the effectiveness of the actions in reducing drug-related crash issues.

The current state of knowledge about drug-driving countermeasures with respect to these basic program elements is discussed in the following subsections.

5.1.1 Targets of Countermeasures. Few reports have attempted to define specific targets of drug-driving countermeasures. In reviewing literature on drugs and highway crashes, Waller (1971) concluded that two groups had an increased risk of crashes or citations for traffic law violations: (1) "persons with sociopathic patterns who repeatedly flaunt authority in a variety of ways including flagrant violation of traffic laws"; and (2) "problem drinkers who have high risk of accident-involvement in highway crashes largely because of their heavy use of alcohol" (Waller 1971, p. 1481). Waller also suggested that "persons who use prescription or nonprescription drugs to cope with everyday stresses of life and most teenagers and young adults who use marihuana only" may face increased risk of involvement in a drug-related crash.

In their review, Forney and Richards (1975) suggested a possible target group based on observed driver behavior and BAC:

Relatively few people whose only drug use is alcohol resulting in a blood concentration of (less than) 0.10% will drive so erratically that they will come to the attention of a patrolman.

When drivers are stopped for such an offense and their blood concentration of ethanol is (less than) 0.10%, other drugs should be suspected. They may be drug users not desiring or requiring much alcohol . . . They may include casual or responsible, though poorly informed, drinkers. In addition, this group would contain hypochondriacs on both prescription and over-the-counter drugs, and deliberate chemical misusers. The former group may not be aware of the addition of alcohol

effect to that of their drug. The latter may use alcohol to enhance the action of a poor quality chemical. (p. 7.)

Some studies of drug use among drivers support that hypothesis. Finkle (1969) compiled analytical data in a fraction of routine investigations of drinking drivers. Drivers were selected on the basis of lower than expected levels of alcohol, given their symptoms of intoxication (less than 0.15% w/v). A small number of cases with blood alcohol greater than 0.15% w/v were studied. Of a total of 700 analyses for drugs, 159 (22%) were positive. The results showed that drivers who had used drugs were also drinking drivers. In fact, "only six percent of those cases in which a clearly significant amount of drug was detected were negative for alcohol" (Finkle 1969, p. 182). The presence of drugs was related to the concentration of alcohol in the blood (BAC) as follows:

<u>BAC (w/v)</u>	<u>Number of Drug Occurrences</u>	
0 to 0.05	129	[60%]
0.05 to 0.10	21	[10%]
0.10 to 0.15	49	[23%]
more than 0.15	14	[7%]

Almost 75% of the drivers were male, 20-40 years of age, with levels of drugs that suggested drug abuse. The remaining 25% were female, mainly 40-50 years old.

Garriott and Latman (1976) studied a similarly defined group of drivers. Seventy-eight percent of analyses finding two or more drugs included alcohol. The range in age of drivers arrested for driving under the influence of drugs (DUID) was seventeen to fifty-six years, average 26.6 years. The average age of drivers arrested for driving while intoxicated (DWI) was thirty-seven years. The implication was that the incidence of drug use other than alcohol was greater in the younger age groups. The authors concluded that "the high incidence of drugs found in combination with alcohol tends to point toward abuse, as the additive effects of sedative drug medication with alcohol are well known" (p. 403). (This report is summarized in greater detail in Section 3.6).

Citing studies of alcohol and drug use and the effects among young drivers, Whitehead and Ferrence (1976) singled out younger drivers as a

specific target group for countermeasure activity. They emphasized, however, that safety problems arising from driving impaired by alcohol and by alcohol combined with other drugs are hardly unique to young drivers. Their focus on the young impaired driver was "largely due to the fact that their rates of damage-producing behavior have recently increased dramatically to a point comparable with large sectors of the adult population" (p. 70).

Groups of outpatients receiving drugs that may impair driving may also constitute special target groups. Maddux, Williamson, and Ziegler (1975) selected a group of patients maintained on methadone. Earlier studies had shown that heroin users had worse driving records than subjects selected for comparison. Two carefully designed studies had indicated before that heroin users who entered methadone maintenance programs had driving records that did not significantly differ from those of other drivers. In their study, Maddux, Williamson, and Ziegler (1975) analyzed self-reported moving violations and accident experience and compared these findings with driving records available for 104 of 174 subjects. Self-reports indicated that their annual rates of convictions for driving violations and accidents decreased when they began heroin use but increased moderately when they entered methadone maintenance. Driving records confirmed this moderate deterioration, and the subjects had driving records somewhat worse than drivers in general.

In Finland, Maki and Linnoila (1976) studied by questionnaire large groups of rheumatoid arthritis, tubercular, and psychiatric outpatients. They asked about their use of alcohol and drugs, driving habits, and involvement in traffic accidents. A control group was also given the questionnaire. The driving populations of all groups were matched as to their age and district.

A surprising finding was that 41% of controls used some kind of medication. As to the correlation between drug use and accident rates, the most important finding was that none of the nondrug-using patient groups had higher accident rates than that in the respective control group [nondrug users]. On the other hand, in the psychiatric group, subjects using one or

more drugs were involved in more accidents than the nondrugged patients. The psychotropic drugs may be a significant contributing factor to traffic accidents.

In the rheumatoid arthritic and tuberculous groups, the use of drugs did not increase accident rates

Among the heavy drinkers from both the control group and the psychiatric patients using 1-2 drugs, about half had been involved in accidents during the two years prior to the study. This high figure suggests that heavy use of alcohol, with or without the use of other drugs, increases the accident risk factor. (p. 44.)

Other studies have also suggested that persons who combine use of other drugs with alcohol may constitute a special high-risk group. Among first-time driving-while-impaired (DWI) offenders, a group of admitted drug users had a more serious pattern of alcohol abuse than the group not admitting drug use (Fine, Scoles, and Mulligan 1975). In a national study of nonmedical use among young men (O'Donnell et al. 1976) practically all the respondents had used alcohol, so that the use of alcohol was associated with use of all other drugs. However, the authors pointed out that, for several reasons, marijuana may be a key to the understanding of multiple drug use.

In most studies of drug-driving countermeasures there is a lack of hard data to show that any given group of drivers faces a higher risk of drug-related crash than other groups. **In any case, it cannot be said that a given individual from a suspected high-risk group should be singled out for countermeasure action.**

5.1.2 Drug Countermeasure Programs. In general, countermeasures may be directed at the use of drugs by drivers (or the general population) or at the operation of motor vehicles by drug users. The **specific** objectives of drug countermeasures are more varied. One approach may be to decrease the availability of drugs to drivers, for example, by influencing the prescribing habits of physicians. Another approach may be to prevent persons identified as drug users from driving perhaps either by

revoking their licenses, or incarcerating them, or both.

For the most part, countermeasures for drugs in the highway setting have not been discussed in the context of a rational, systematic approach as outlined in Section 5.1. Rather, suggestions have been offered on an ad hoc basis. Hence, their succinct iteration is difficult. To facilitate discussion, the following categories of countermeasure programs are used here to summarize the various countermeasure concepts:

- Legal
- Health
- Public Information and Education
- Technological
- Systems

Legal approaches are those that pertain to laws and their enforcement, leading to prosecution and sanctioning of violators. **Health** countermeasures involve the health care system, either in the delivery of drugs or information about them to patients, or in the treatment and rehabilitation of those who have used them. **Public information and education** programs generally involve presentation of media material to inform the general population or subpopulations in such a way that the incidence of high-risk behavior decreases. **Technological** approaches involve application of modern technology to reduce the influence of drugs on accident frequency—for example, roadside drug detection devices.

The **systems approach** provides a means of focusing on the whole problem as well as its component parts. The components of a problem are identified and interrelated so that the effect of a decision upon each element and upon the whole problem can be ascertained. While originally developed in an aerospace engineering environment, the approach may be applied to social problems as well, among them the drinking-driver problem (Joscelyn and Jones 1970).

The following sections review and summarize the various countermeasure approaches outlined above.

5.1.2.1 Legal Countermeasures. Legal countermeasures aim to deter potential drug driving through the threat of punishment. The traffic law

system (TLS) is the major mechanism in our society for applying legal countermeasures to deter unsafe driving behavior. According to Joscelyn and Jones (1972), the TLS performs four major functions:

- the generation of laws proscribing risky driving behavior,
- the enforcement of these laws,
- the determination of the guilt or innocence of individuals accused of violating these laws (i.e., adjudication),
- the imposition of sanctions against individuals found guilty of violating these laws.

The general social aspect of drug use is emphasized by laws that control the manufacture, sale, and dispensing of drugs. The control of drug use by law is best illustrated by the Comprehensive Drug Abuse Prevention and Control Act of 1970 (Swinyard 1975). This type of law at the local, state, and federal levels, and the establishment of legal drinking ages for alcohol, may indirectly influence the contribution of drugs to accident-risk by reducing or restricting their use in the general population.

More directly related to the drug and driving problem are laws that prohibit driving under the influence of drugs (DUID laws). Most states have DUID laws that either specify "any drug" or list specific drug substances, e.g., marijuana (Jones 1977b). Many of these laws are based on the provisions of the Uniform Vehicle Code (UVC). UVC Section 11-902.1 is based on the principle that no person should drive who is incapable of driving safely due to the use of drugs, regardless of the nature or amount of drug. Specifically prohibited from driving is any person who is:

1. a habitual user of any narcotic drug;
2. under the influence of any narcotic drug; and
3. under the influence of any drug to a degree which renders him incapable of driving safely.

Under an additional provision, the legal use of any drug which impairs driving ability is not excepted from the under-the-influence-of-drugs provisions. Twenty-nine states have laws conforming with provision 3 of the UVC; sixteen states specify types or categories of drugs (Nichols 1971;

National Committee on Uniform Traffic Laws and Ordinances 1965).

Table 5-1 presents a summary of legal countermeasures that have been proposed for dealing with the drug-driving problem. The countermeasures are grouped according to the four functions of the traffic law system outlined above. In addition, a class of countermeasures that uses a treatment approach to attempt to reduce crash risk is described. Some countermeasures specifically proposed for alcohol, but perhaps applicable to other drugs as well, are included.

Legislative countermeasures have emphasized facilitation of enforcement of DUID laws (e.g., establishment of objective standards for drug levels, eased requirements for collection of blood samples). Most of the authors cited favored countermeasures that would decrease availability of alcohol and other drugs. Greater enforcement of existing laws along with attention to impaired drivers having "low" BACs was not a commonly suggested strategy, perhaps due to the limited analytical capabilities of most forensic laboratories (California Highway Patrol 1974). A general deterrence approach to increase the perception of risk by drug-using drivers was a common objective of countermeasures designed to further the adjudication and sanctioning of drug-driving law violators.

One novel suggestion proposed making driver-associated persons also liable in cases of drug-impaired driving (accessory to the act). The establishment of a reward system that includes economic and legal motivators deserves consideration in the light of recent studies (Wilde 1975b).

5.1.2.2 Health Countermeasures. Countermeasures involving the health care community have also been suggested. Unlike alcohol, which is now rarely used in a therapeutic (medical) context, most other drugs are used in the treatment of disease symptoms. Psychoactive drugs, while sometimes used illicitly, are among the most frequently prescribed drugs. General measures to reduce abuse of medicines have been recommended (Council of Europe 1976c).

Prescribing patterns of physicians have been criticized with special regard to psychoactive drugs (Council of Europe 1976b; Parish 1971).

TABLE 5-1

CLASSIFICATION OF LEGAL COUNTERMEASURES FOR DRUGS OTHER THAN ALCOHOL ALONE

Function	(Proposed) Countermeasure	Objective	References
A. Legislative	Prohibition or restriction of distribution, sale, and dispensing of drugs.	Decreased availability of drugs to general public and/or drivers.	Swinyard 1975, Whitehead and Ferrence, 1976
	Raise previously lowered drinking ages.	Decreased incidence of alcohol use among young drivers and decreased incidence of multiple drug use involving alcohol.	Whitehead and Ferrence 1976
	Reduce legal BAC limit to 0.04% w/v.	Decreased influence of multiple drug use on accident risk.	Whitehead and Ferrence 1976
	Enact laws emphasizing co-responsibility of others for the act of drug-impaired driving, i.e., accessory to the act.	Increased social pressure to reduce drug-impaired driving.	Wilde 1975b
	Alter law to permit blood collection in all traffic accidents.	Facilitation of detection and enforcement of "driving under the influence of drugs" (DUID) laws.	Forney and Richards 1975
	Establish laws setting reasonable but arbitrary limits for blood levels of drugs but not legally premised on decrement of driving ability.	Facilitation of logical enforcement of laws related to use of drugs and driving.	Forney and Forney 1975 Forney and Richards 1975

TABLE 5-1 (Continued)

CLASSIFICATION OF LEGAL COUNTERMEASURE FOR DRUGS OTHER THAN ALCOHOL ALONE

Function	(Proposed) Countermeasure	Objective	References
	Alter law to permit random testing for drugs in the blood of motorists.	Reduced use of drugs by drivers, facilitation of enforcement of DUID laws.	Whitehead and Ferrence 1976, <u>Driver</u> 1976
	Laws restricting driving privileges of certain treatment groups, e.g., methadone maintenance patients.	Removal of high-risk target group from highway.	Maddux, Williamson, and Zeigler 1975
B. Enforcement	Increased levels of enforcement of existing laws, including random administration of drug tests.	Increased level of perceived risk by drug-using drivers.	Whitehead and Ferrence 1976, Roper 1976
	Training of law enforcement officers in detection of drugged drivers.	Increased efficiency in enforcement of DUID laws.	Jaeger, Fleming, and Appenzeller 1975
	Development of standards for measuring DUID with accurate testing methods.	Increased detection capability in enforcement of DUID laws.	Jaeger, Fleming, and Appenzeller 1975
	Crackdown on illicit drug traffic in schools.	Decreased illicit drug use by young drivers.	Roper 1976
	Concentrate enforcement against impaired drivers whose BAC is less than 0.10% w/v.	Increased detection of drivers impaired by drugs with or without concomitant use.	Forney and Richards 1976

TABLE 5-1 (Continued)

CLASSIFICATION OF LEGAL COUNTERMEASURES FOR DRUGS OTHER THAN ALCOHOL ALONE

Function	(Proposed) Countermeasure	Objective	References
C. Adjudication	Greater consistency of adjudication, i.e., increased frequency of prosecution under DUID laws.	Increased fairness and perception of risk among drug-using drivers.	Roper 1976
	Swifter adjudication of those apprehended under DUID laws.	Increased fairness and perception of risk among drug-using drivers.	Wilde 1975
D. Sanctions	Increase unfavorable consequences for (young) drivers who are apprehended for impaired driving, e.g., through extended probationary periods.	Increased perception of risk among drug-(young) drivers who use drugs.	Whitehead and Ferrence 1976, Roper 1976
	Swifter and surer punishment of drivers convicted under DUID laws, e.g., license revocation.	Increased perception of risk among drug-using drivers; reduced population of drug-using drivers.	Wilde 1975
E. Treatment	Establishment and operation of education and treatment modalities for drivers convicted under DUID laws.	Education and rehabilitation of drivers apprehended for drug-impaired driving.	Jaeger, Fleming, and Appenzeller 1975

TABLE 5-1 (Continued)

CLASSIFICATION OF LEGAL COUNTERMEASURES FOR DRUGS OTHER THAN ALCOHOL ALONE

Function	(Proposed) Countermeasure	Objective	References
F. Miscellaneous	Increased use of Citizens' Band communication for the identification of high-risk driver behavior.	Extension of enforcement capability of DWI and DUID laws, increased perception of risk by drug-using drivers due to social pressure.	
	Establishment of economic or social rewards for adherence to safe driving, e.g., lowered insurance rates, licensing fee reduction, removal of "points" from driving record.	Increased motivation for drivers to maintain low-risk driving profile.	Wilde 1975

Changes in physicians' prescribing habits have been suggested as an effective countermeasure for decreasing availability of prescription drugs (Milner 1972; Whitehead and Ferrence 1976). Hollister (1974) has listed precautions that physicians should take upon deciding to prescribe a psychoactive drug:

- warn patient of possible drug effects on driving;
- use dosage schedule to minimize possible driver impairment; and
- advise patients that alcoholic beverages interact with all psychotherapeutic drugs even though experimental proofs are as yet incomplete.

Ashworth (1975) and Silverstone (1974) also conclude that, given the present state of knowledge in drugs and driving, physicians must warn patients of possible driving impairment and about dangers of drug interactions with alcohol. These countermeasures would decrease the chances of **unsuspected** impairment among patients using psychoactive drugs.

The participation of health care agencies in the treatment of problem drinker-drivers is well known. Similar education and treatment modalities have been suggested for drug-using drivers (Jaeger, Fleming, and Appenzeller 1975; Fine, Scoles, and Mulligan 1975). These might function on a voluntary or court-referred basis. However, increasing attention has been paid to countermeasures involving precrash participation of the health care system, particularly to the concept of "physician reporting of driver impairment" (Hames 1975). In this approach, doctors would report, voluntarily or under law, patients unfit to drive due to medical condition, medication, or patterns of drug use (Linnoila 1976). The medico-legal issues involved have been briefly discussed by Hames (1975).

5.1.2.3 Public Information and Education Countermeasures. Public information and education countermeasures have been widely proposed for dealing with the drug-driving problem. Most suggestions are related to the use of mass media to decrease the use of drugs and to decrease the use of drugs while driving (Jaeger, Fleming, and Appenzeller 1975; Roper

1976). A recent example is Sweden's "alcohol and drug-free traffic" propaganda year mentioned by Bonnichsen (1975). For alcohol, Wilde (1975a) has suggested mass communication with an immediacy to the drinking situation itself, for example, beer-can labels warning of alcohol-driving dangers. A prominent warning could also be affixed to all drug containers.

Wilde (1975a) has also recommended more constructive reporting of road accidents to inform the general population of the problem's magnitude and has stressed the need for field research in maximizing the effectiveness of mass communications. Wilde cites the absence of program evaluation as a hindrance to development of a "truly scientific knowledge of how to influence behavior through mass communications. . .":

For this knowledge to be further developed, a number of conditions must be fulfilled. First, no major campaign should go unaccompanied by serious and thorough research into its effects. Second, the evaluative research should be conducted in agreement with the requirements of good experimental design including adequate control data and nonreactive measurement. Lack of adherence to rigorous research methods has weakened the conclusiveness of the results of many alcohol campaigns carried out so far. To work in the field rather than in the laboratory is no excuse for sloppiness. (Wilde 1975a, p. 820.)

Other countermeasures related directly or indirectly to the problem of drugs and driving have been initiated in response to increased "drug awareness." General drug education programs designed with the objective of reducing drug use and its attendant problems have been reviewed and evaluated by Globetti (1975). Appraisal of their impact is limited by methodological issues and the lack of a central information exchange. If the efforts have had the aim of stopping all illegal drug use, the author concludes the programs have been ineffective. The greatest hindrance was seen to be the inaccurate and distorted nature of drug education materials and their lack of credibility among young people. The ineffectiveness of information unattended by other behavior modifiers was

also cited as a reason for program failures. The social context of drug use and the need to understand the underlying reasons for drug use were emphasized in the consideration of alternative approaches.

In reviewing countermeasures to diminish the traffic risks caused by tranquilizers, Linnoila (1976) concluded that:

The best countermeasure at present would be easily available information about drugs at schools, pharmacies, gas stations, open care units and hospitals. This could be supported by campaigns in mass information media. The quality of the information should be such that it reduces unnecessary use of drugs, but does not cause fears among patients needing drugs for their treatment. Medical personnel should be able to inform patients at the individual level, which requires that more attention be paid in teaching clinical pharmacology. (p. 18.)

Public information and education countermeasures have been described as essential concomitants of law enforcement campaigns (Whitehead and Ferrence 1976; Wilde 1975a). Also, "the general public and the law makers should be exposed to whatever is scientifically known about accident causation in order to reduce the likelihood of the introduction of laws and other countermeasures that may not be effective" (Wilde 1975a). "A majority either didn't know to the extent they offered no opinion, or believe the law only applies to alcohol or illicit drugs. People who drive after using alcohol or drugs are **more likely to not know the law**" (Jaeger, Fleming, and Appenzeller 1975, p. 87, emphasis added). Finkle (1975) and Linnoila (1976) have also emphasized the importance of the well-informed individual in dealing with the drug-driving problem.

5.1.2.4 Technological Countermeasures. The use of instruments for breath-alcohol analysis is well known. Other technological approaches would prevent the use of motor vehicles by impaired drivers, specifically, persons who are alcohol-impaired (Voas 1970). Instruments for analyzing breath-alcohol are used in conjunction with legal and health approaches. Similar techniques are in demand for the roadside detection of marijuana

(Guthrie 1976). Attempts have been made to develop methods to detect marijuana constituents in the breath (e.g., Bryant et al. 1975). However, with the exception of drug analytical methodology used for body fluid analysis for drugs, technological countermeasures have not been developed or applied to the problems of drugs and driving.

5.1.2.5 Countermeasures Using the Systems Approach. The systems approach is characterized by its concentration on the whole problem along with its component parts. It has been described as:

. . . an approach that insists on looking at a problem in its entirety, taking into account all the facets, all the intertwined parameters. It is a process for understanding how they interact with one another and how these factors can be brought into proper relationship for the optimum solution of the problem. (Ramo 1971, p. 11.)

There is no evidence that a systems approach to the problem of drugs and driving has ever been attempted. NHTSA's nationwide Alcohol Safety Action Project (ASAP) was the only large-scale attempt application of the systems approach in the field of alcohol-safety (McKnight, Adams, and Personeus 1971). In the ASAP program, target groups were defined according to alcohol usage patterns and times of the day when there was a greater incidence of alcohol-impaired drivers. Rehabilitation and deterrence were the objectives of the safety program aimed at problem and heavy social drinking-drivers, respectively. Evaluation of the program's effectiveness was emphasized in ASAP.

Because of its complexity, the problem of drugs and driving also requires a comprehensive approach of the type embodied in the systems approach. Piecemeal approaches run the risk of suboptimization and could overlook important interactions between the many societal systems that attempt to manage highway crash risk. Lessons learned in ASAP should be valuable to designers of systems approaches to the problem of drugs and driving.

5.1.3 Evaluation of Countermeasures. Although some countermeasures

have been implemented on a limited basis, the literature provides no evidence of any rigorous evaluation of their effectiveness in reducing drug-related crash losses. Thus, there is no firm basis for recommending any of the above countermeasure concepts for immediate implementation. **In fact, given the present lack of knowledge about the nature of the drug-driving problem and the effectiveness of proposed countermeasures in dealing with that problem, there is ample reason for not recommending specific countermeasures.** If a problem exists, it is clear that future drug-driving programs must build in carefully designed evaluation components to provide risk managers with a basis for selecting and refining countermeasure designs.

5.2 Countermeasure Constraints

A number of factors exist that constitute constraints on countermeasures that have been proposed to deal with the drug and driving problem. The most basic constraint is the lack of knowledge about the role that drugs play in traffic crash causation. This problem has been repeatedly noted in prior sections of this report.

A constraint on some countermeasures is the present state of the art of analytical methods for drug detection and quantitation. The necessary equipment, methods, and personnel do not exist to support large scale enforcement of existing drug and driving laws. This constraint is complicated by the fact that the significance of drug concentrations for many drugs has not been established. Thus, even in the case where a drug is detected and quantified, it may not be possible to interpret the results to establish that the driver was impaired. Of course, if the drug concentration indicated gross abuse or overdose, some statements about impairment could be made. However, the more common instances create far more difficult challenges, given the present state of knowledge.

Other legal issues become important if the criminal law process is to be relied on as a countermeasure approach. In most cases blood (possibly along with other body fluids) will be required to conduct chemical testing for drug presence. Obtaining such samples will require permission, search incident to an arrest, or some other process such as implied consent.

Most of the experience with enforcement of driving under the influence has been with one drug—alcohol. The odor of alcohol on the breath of a subject, the presence of liquor bottles, or other collateral evidence when coupled with evidence of unusual driving behavior is generally viewed sufficient to constitute probable cause for arrest and a chemical test. Other drugs pose more difficult problems. No odor may be present. The drug container may be a legally obtained and possessed prescription bottle. Enforcement of driving under the influence of drugs laws simply poses greater evidential problems. Bonnichsen (1975) has summarized problems encountered in Sweden in the enforcement and adjudication of drug and driving laws. He notes many of the same problems discussed above.

The countermeasures proposed to deal with the drug and driving problem in many instances flow from the experience with alcohol. Legal countermeasures are frequently suggested that parallel existing alcohol countermeasure programs. The validity of these approaches has not been established. The reliance of the suggested approaches on parallels between alcohol and other drugs causes some concern. As noted previously, alcohol is a unique drug both in a chemical sense and in its use in our society. The chemical properties of other drugs of interest and the wide variations in their usage strongly suggest that simple reliance on the experience with alcohol is unwise.

5.3 Summary

The lack of knowledge of the role that drugs play in traffic crash causation constitutes the most basic constraint on countermeasure development. Thus, the conduct of research that defines the drug and driving problem should supply the basic information needed in the area of countermeasures.

Countermeasure programs suggested in the past generally parallel those suggested for alcohol, with elements that include legal, health, public information and education, technological interventions, and general systematic approaches.

Each of these is dependent upon information about the nature of a

drug and driving problem to identify targets for actions. The legal approach has already been implemented in skeletal form. Many states have laws that make it illegal to drive while impaired by drugs. The present state of the art of drug analytical methodology makes the detection and quantification of drugs difficult. The necessary equipment, methods, and personnel are not available to support large-scale enforcement efforts. The problem is compounded because the state of the knowledge of drug effects is not sufficiently advanced to allow accurate interpretation of drug concentrations in body fluids for many drugs likely to impair driving ability.

General research needed to accurately determine the existence of a drug and driving problem and define its characteristics will meet many of the information needs of countermeasure development.

The use of drugs poses problems identified in other areas of society. It would be desirable to carefully monitor and evaluate other programs designed as countermeasures to reduce, for example, drug abuse, as well as those to promote the proper use of drugs within the system to deliver health care. Drug abuse control programs conducted by federal, state, and local agencies should be monitored for their potential application to the drug and driving area.

Alcohol has been demonstrated to increase the risk of traffic crashes and has been the subject of many countermeasure programs. Alcohol countermeasure programs should be carefully examined to determine the applicability of the effective techniques to other drugs. As this is done, the unique status of alcohol as a drug and its use in society must be kept in mind.

This section has reviewed concepts of countermeasures in the area of drugs and highway safety. We reemphasize here that there is as yet no proof that a problem exists. Research to identify countermeasures must follow that need to define the problem. The present state of knowledge is itself the greatest constraint in research on countermeasures in drugs and driving.

PART TWO

PROBLEM AREAS AND INFORMATION NEEDS
IN DRUGS AND HIGHWAY SAFETY

PREFACE

Part Two of this report completes the assessment of the state of knowledge in drugs and driving. It brings together issues identified in the review of literature and defines major problem areas. The main focus is on issues in the direct study of the relationship between drugs and highway safety (both epidemiological and experimental approaches). Information needed to advance the state of knowledge is specified. This part of the report also presents general insights which, gained in the course of the study, pertain to future research in this area.

Three sections make up Part Two. The first and second deal respectively with epidemiology and experimentation in drugs and driving. A summary section concludes this part of the report with general statements on the state of knowledge and on the nature of research on drugs and highway safety.

6.0 EPIDEMIOLOGICAL RESEARCH: PROBLEMS IN MEASURING THE USE OF DRUGS IN POPULATIONS OF DRIVERS

The aim of epidemiological research is to describe the use of drugs in driving populations and, to the extent possible, to indicate the role of drugs in traffic crashes. As the review of literature shows, not much information is available on this subject. The problems in measuring the use of drugs among various populations of drivers relate to:

- the design of research,
- the execution of field surveys, and
- the comparability of studies in this area.

6.1 The Epidemiological Approach and Its Application in Drugs and Driving

The methods of epidemiology, the science of the incidence, distribution, and control of disease in a population, have found increasing application in the study of such social phenomena as drug-related problems (Robins 1975; Rootman and Billard 1975). As O'Donnell et al. stated, "While it is questionable whether the analogy of a disease is appropriate for drug use, some of the concepts of epidemiology are useful in an effort to describe patterns of usage" (O'Donnell et al. 1976, p. 48).

Prerequisite to the control of a disease is "the study of the determinants or etiological factors responsible for the observed distribution" (Wigle 1975, p. 3). According to Wigle, the traditional notion of causality in disease ("one disease, one cause") has been a hindrance in the study of nonacute disease and noninfectious conditions in general. He described an ecological approach to disease where the assumption is made that any illness is a result of interactions between host and environmental factors and the role of probability in determining disease distribution is emphasized.

These general points relate directly to study of the drug and driving

problem. For example, it has been stressed that drug presence does not necessarily mean drug effect. "The finding that a drug is present in a crash victim or driver does not, by itself, establish a causal relationship between the drug's presence, driver impairment, and crash causation" (Joscelyn and Maickel 1977a, p. 84). The analysis of many factors is necessary to determine what factors contribute significantly to drug-related crashes. As Stewart (1970) has pointed out, epidemiology is particularly appropriate for the study of conditions with multiple manifestations and complex interrelations, where correlation represents interaction, rather than cause and effect.

An ecological model has been applied to the problem of drugs (other than alcohol) and driving by Colburn and Garland (1974) who describe a model with two stages or phases:

(1) The ecology of substance use

Person (Stage 1)

Substance Environment

which precedes or coincides with:

(2) The ecology of driving

Person (Stage 2)

Vehicle Environment

Person (Stage 1) may, obviously with substance and environment influence, become a "different" person at Stage 2.

We must also recognize that "person" [in the two stages above] prior to or independent of substance use (Stage 1) may be a major determinant of the interaction at Stage 2. For example, the disease processes that require a person to use prescription drugs may be important factors in crash causation. Similarly, attitudes and feelings—anxieties, depression, hostilities, paranoia, desire to take risks--that precede or lead to non-medical use of drugs including alcohol may contribute to or

compound the problems arising from the effect of drugs on the operation of motor vehicles. Furthermore, it might be expected that some persons whose distractions, anxieties or other problems are reduced by moderate doses of prescribed drugs may have fewer problems in driving with their drugs than without.

In using the ecological model in this situation it is, of course, necessary to concentrate on the substances and on aspects of persons that are particularly drug-related. It should not be forgotten, however, that the vehicle and driving environment--road, weather, time of day, etc.--should be expected to be as important, if not more important, in the etiology and prevention of drug-related as of non-drug-related crashes. (pp. 9-10.)

In the context of disease control, Wigle (1975) has emphasized that complete knowledge of a "causal web" is not required to develop control measures:

The identification and control of only the significant strands may alter the whole structure and allow substantial reduction of disease frequency. Thus, a key issue in disease prevention is the discovery of sufficient factors to control disease, realizing that knowledge of all related factors is probably impossible and, furthermore, not necessary. (p. 22.)

In the epidemiological approach, "case-control" studies are employed to assess the relative significance of various factors that may contribute to the incidence of a disorder. Richman (1975) has described this method in terms of general drug-related problems:

Case-control studies identify risk factors, those factors which are more frequently correlated with the disorder. Risk factors may be estimated from representative samples of those persons with and without disorder. In considering a risk factor, one must also have regard to **attributable risk**, the

proportion of cases which might be attributed to that risk factor. Thus, a characteristic which has a very high relative risk, but is infrequent in the population, is implicated in a relatively small proportion of cases. (p. 40.)

To define the role of drugs in traffic crashes, studies may focus on the significance of drugs as risk factors. In the context of highway safety, risk is the probability of a traffic crash and associated losses. To assess the contribution of risk factors to crash risk, comparable samples from populations of accident- and non-accident-involved drivers must be selected and the presence and amount of drugs determined by the analysis of body fluids. For example, the Borkenstein study of alcohol and highway safety (Borkenstein et al. 1964) used the case-control approach in studying the problem of alcohol in highway safety. Here, the amount of alcohol present in drivers was an important factor in estimating the relative risk attributable to alcohol.

Large-scale field studies similar to that carried out for alcohol by Borkenstein's group (Borkenstein et al. 1964) simply do not exist for any other drugs. As reviewed by Nichols (1971, pp. 43-44), information on the use of drugs by the general population may be used to estimate the prevalence of drugs in the driving population. But because the distribution of drugs in the general population may not be the same as the distribution in the driving population and because the patterns of drug use in the general population are not accurately known anyway, direct knowledge of drug use by drivers is critical for assessing the accident risk posed by drugs. Further,

. . .The presence of drugs in a certain proportion of crashes provides no clue as to the frequency with which these drugs have contributed to the occurrence of such crashes. This can be determined only by . . . a comparison of the frequency of various drug concentrations in persons who have been involved in crashes and in persons who have been using the roads under similar circumstances of time and place but who have not

crashed. (Waller 1971, p. 1479.)

Efforts made to determine the prevalence of drugs in the driving population have established the presence of drugs in the driving and crash populations. However, few data have yet accumulated which would define the influence of drugs on highway safety. Kibrick and Smart (1970), in reviewing the epidemiological literature, concluded that:

An assortment of figures on "drug" incidence in accident and non-accident drivers is available, but few investigators have inquired about the same drugs. Still fewer have made laboratory screenings for them. Also, no two investigators have used similar criteria for selecting their cases and thus different populations are described. Many 'procedures' for data collection do not seem to be reliable nor can they be reproduced by others for comparative purposes. (Kibrick and Smart 1970, p. 82.)

Five years later, Joscelyn and Maickel reached similar conclusions in their appraisal of epidemiological studies:

The existing literature is limited in scope and quality and does not provide an adequate explanation of the relationship (presuming one exists) between drug usage and traffic crashes. The studies do establish the presence of drugs in the driving and crash populations.

Two problems exist, however, with the interpretation of these findings. First, the role the drug played in altering driver behavior or in traffic crash causation is generally undefined. The studies report drug presence but not drug effects. A very limited number of cases of extremely high dosage levels have been reported, where gross impairment can be reasonably inferred from the known pharmacological action of the drug. Such instances are very limited.

Second, the studies simply cannot be generalized to either the general driving or accident populations. The populations

studied are not samples in a random or representative sense.

Thus the results must be viewed as indicators rather than proof of a drug/driving problem. (1977a, p. 93.)

If, as Colburn and Garland recommend, "a thorough investigation of drug use by crash victims would help reduce much of the uncertainty and speculation about the effects of drug use on driving . . ." (1974, p. 19), then carefully designed studies, giving particular attention to the sampling of a comparable control population are required. This recommendation has been consistently advanced by researchers for the last ten years.

6.2 Problem Areas in Epidemiological Research

As Mercer and Smart have stated, "Methodological problems in epidemiological research and indeed in all social science research generally derive from two basic areas: reliability and validity" (1974, p. 305). Basically, two problem areas are identified by reviewers in discussing the unreliability of past field studies. One, a methodological issue, is study design, including the method and scope of inquiry and the sampling procedures. The second pertains to the methods used for drug analysis and the range of drugs detected.

6.2.1 Factors in Study Design. In the first of these two problem areas of epidemiological research, the problem is to design studies that accurately assess the role of drugs in traffic crashes. Among the many facets of this problem are the nonhomogeneous and uncharacterized patterns of drug usage, missing data rates from nonaccident drivers, and the absence of multifactorial accident analysis in drug-related crashes.

6.2.1.1 Drug Usage Patterns. That a variety of drug-usage patterns exists in the general population has been indicated earlier in this report (Section 3.0). Factors in the nonhomogeneity in drug use are the type of drugs consumed, the frequency with which drugs are used, and the quantity ingested. For example, it cannot be assumed that urban and

rural populations use the same drugs to the same extent (Michigan Department of Public Health 1975; Jaeger, Fleming, and Appenzeller 1975). Even in sampling districts with similar characteristics the patterns of drug use may differ. Intercity comparisons of drug-involved deaths have revealed significant differences in the types of drugs responsible (Dinovo et al. 1976). Unfortunately, some questions remain about the sources of these variations, as both different methods of drug analysis and regional differences could be responsible.

Neither can drug usage patterns be considered static. Although Finkle (1969) noted that annual statistics were similar for the three-year Santa Clara County study of drugs in drinking drivers, Garriott and Latman (1976) observed a significant yearly shift in drug patterns among drivers arrested for "driving under the influence" in Dallas County. Thus, heterogeneity in drug use may result from the influence of population characteristics and the passage of time.

Various factors have been identified that differentiate patterns of drug use by a population. These include:

- living area (urban and rural),
- political characteristics ("liberal" or "conservative"),
- age (young or old),
- ethnicity or background, and
- sex.

Numerous other confounding variables might be listed. Time of day, type of roadway, and drug availability may influence survey findings. Sampling designs employed to assess the use of drugs by drivers should take into account the effects of nonrandom drug distribution in the driving population.

6.2.1.2 Subject Compliance and Legal Problems. In regard to the actual collection of data, the design of epidemiological research faces two major hurdles: missing data rates and legal constraints. In the past,

Studies which attempted to use a sampling approach were

often thwarted by non-cooperation of the driving population or other participants whose cooperation was necessary to ensure an adequate data base. Missing data problems are so severe in several studies as to render the results inconclusive. (Joscelyn and Maickel 1976, p. 13.)

As Milner observed,

The Grand Rapids study by Borckenstein et al. [1964] not only established 'the role of the drinking driver in traffic accidents', but pointed the way for research into the overall drugs and driving question. Pilot trial studies are essential and the co-operation of police and public must be won. Interviewers need special training in eliciting information on subjects associated with social stigma; **the public needs assurance that the information obtained will not be used by the police**; normal traffic flow must not be so disturbed as to create extra hazards (Milner 1972, p. 75, emphasis added.)

In a major roadside survey of drug use among drivers (Glauz and Blackburn 1975), the investigators' sensitivity to missing data rates was quite evident. Nevertheless, of almost 1,500 motorists who were stopped, only 78% cooperated with the interview. Almost all who agreed to the interview provided breath and lip swab samples. Likewise, nearly all consented to give a urine sample, but only 75% (69% of the total sample) were able to produce a sufficient quantity on demand. In anticipation of difficulty in obtaining blood samples, one of the secondary objectives of the study was to determine the effect of offering payment on securing blood samples. About 85% of the people interviewed (66% of the total sample) agreed to provide a blood sample. This rate was slightly influenced, but with only marginal significance, by the offer of payment. The amount, in general, did not influence the consent rate. Interestingly, there were significant regional differences in the percentage of those interviewed who were willing to provide blood samples. The acceptance

rate was far higher in Lincoln, Nebraska (94%) than Dade County (Miami), Florida (74%). The results of this study, in addition to those of Borkestein (Borkestein et al. 1964), should provide a basis for further development and testing of methods designed to enhance voluntary cooperation.

Joscelyn and Maickel (1977a) analyzed the legal issues arising from data collection activity in epidemiological research and countermeasure efforts:

Investigators may be concerned with the nature and extent of drug presence in the driving population and the accident population. In the same sense, managers of countermeasure programs may be concerned with determining drug use among participants in the program. In either instance, the data collector needs to obtain information from an individual. The information may be provided by simply answering questions, or more intrusive methods, such as extraction of a blood sample, may be required. In each instance, the data collector is dealing with a subject who must give informed consent. The subject must be advised of the use of the information requested as well as the potential for disclosure.

In a practical sense, this poses significant problems for any inquiry. The information sought, if revealed, may well subject the individual to criminal prosecution and/or civil liability. Even if legal action is unlikely to result, the potential social stigma associated with disclosure may cause an individual to refuse to participate. In many cases, the use of prescription drugs is a very private matter which the user may not wish disclosed.

It is unlikely that a representative sample of the general driving population or accident population can be persuaded to cooperate with researchers unless adequate legal protection ensuring the confidentiality of the information provided

exists. Until a privilege exists, no reputable researcher will seek to collect data without fully advising a subject of the risks of disclosure. Such a warning is most likely to result in refusals to cooperate, so that the study results are biased.

In the same sense, it is unlikely that adequate cooperation can be developed in countermeasure programs until the confidentiality of communications can be assured . . .

A researcher or manager who knows that information may possibly be disclosed and does not advise a subject of the potential for disclosure may be held legally liable for the consequences of disclosure. In addition to civil liability, in some cases criminal liability may exist under provisions of the Right of Privacy Act of 1974. Censure or other disciplinary action is likely for those who are members of a profession.

The lack of privilege for researchers and program managers is a significant constraint that precludes adequate investigation of the drug and driving problem. Serious consideration must be given to legislative protection such as that afforded drug researchers and drug treatment programs funded through DHEW and DOJ. (Joscelyn and Maickel 1977a; pp. 50-1.)

6.2.1.3 Inclusion of the Multiple Factors Approach in Study Design.

Other features of study design in the epidemiology of drugs in drivers require attention. One area of increasing concern is the need to include both accident analysis and the sociological study of drivers who use drugs. In studying kinetic visual acuity as a driving-related function, Clayton found that psychotropic drugs have the potential for changing the time taken to detect a moving target, thus possibly increasing the probability of road user error. However, such findings, despite their direct applicability to driving behavior, remain working hypotheses:

To test such a hypothesis, it is necessary to work . . . long

two main lines of research.

Firstly, we need much more epidemiological data about the incidence of psychotropic drugs amongst road users. I use the words "road user" advisedly as the error potential of such drugs may be equally as great amongst pedestrians as amongst drivers. Certainly this appears to be true for alcohol. Apart from general incidence data, however, we need much more detailed accident data than are presently available. In other words, can we demonstrate, if only on a case history basis to begin with, that certain psychotropes have a role in error causation? (Clayton 1975, p. 3.)

One such case history has appeared for marijuana, where driver behavior which led to a fatal car accident was associated with high levels of drug constituents in the blood and urine (Teale and Marks 1976). However, few studies have "clinically examined traffic crashes to ascertain the behaviors that led to the crash and document the role drugs played" (Joscelyn and Maickel 1976, p. 12). Even in the case of alcohol, little is known about the factors that may, in a causal set, interact with the influence of alcohol to increase accident risk. Waller has decried the lack of comparability resulting from the paucity of accident data:

In short, I am suggesting that the time has passed when we could be satisfied with doing epidemiologic studies of the contribution of alcohol alone. Rather, especially for international comparison, we need to know the nature and extent of other factors that simultaneously contribute to the problem. There have been extremely few such studies. Results of laboratory and simulation studies are reasonably transferable from one country to another. Work involving epidemiology in the field, however, is often not comparable unless all the major contributing factors are well defined. (Waller 1975, p. 6.)

Among the factors that may contribute to the influence of drugs on

traffic crashes are the characteristics of drivers, the presence of alcohol, and such environmental factors as traffic density and weather conditions. Selzer has pointed out that "the percentage of drunk drivers who are alcoholics and/or problem drinkers remains a latter day conundrum" (Selzer 1975, p. 13). Nevertheless, Waller has argued persuasively for the differentiation of drug users as a basis for explaining traffic crash and citation rates (Waller 1971). In studying the characteristics of accident- and non-accident-involved drivers who smoked marijuana, Sterling-Smith and Graham (1976) found significant differences. Alcohol, along with drugs, is often detected in drivers, raising unanswered questions concerning drug interactions as a factor in accident causation.

6.2.2 Factors in Drug Analysis. In no other aspect of epidemiological research is information more required than for the analysis of drugs. Invariably, drug analytical methodology is singled out as an aspect of epidemiological study that limits the utility of the data, whatever its source (Joscelyn and Maickel 1977a; Kibrick and Smart 1970; Nichols 1971; California Highway Patrol 1974; Ashworth 1975; Colburn and Garland 1974; Waller 1971). As briefly indicated earlier in this report (Section 3.5 and Table 3-2), the existing screening methods used to detect drugs in body fluids are generally regarded to be incomplete, insensitive, nonquantitative, or all three.

6.2.2.1 Drug Screening Methodology. Efforts to obtain a representative sample of driver body fluids from both accident and nonaccident populations will be wasted if the techniques employed to detect drugs are inadequate. What this means is that the range of drugs detected by the chosen analytical methods must include all "drugs of interest," and that the level of sensitivity of these methods must equal the lowest drug concentrations of significance. "Significant" drug concentrations would include (at the minimum) low therapeutic levels of drug, if a pharmaceutical. In addition, drugs may be biotransformed in

man to yield metabolites that are pharmacologically active. Provisions to detect these metabolites should be made in designing analytical systems to screen for drugs.

The poor sensitivity of many screening systems results in the failure to detect many drugs, including many of today's powerful psychoactive agents. This is especially problematical since many of these drugs, including diazepam and marijuana, are among the most frequently prescribed drugs. For example, in studies which have analyzed for diazepam, including drug overdose (Darley et al. 1976; Shapiro and Jick 1975) and intoxicated driver studies (Garriott and Latman 1976), this antianxiety agent has been the most frequently detected drug other than alcohol. This has not been the case in studies that either did not include an analysis for diazepam (Finkle 1969; Finkle, Biasotti, and Bradford 1968; State of California 1967), or that used methods considered too insensitive (Glauz and Blackburn 1975).

An examination of the methods used in some of the studies raises further questions about the validity of the data reported. In some cases, the testing methods used would not detect the most likely form of the drug; the fact that some drugs act through a metabolite has been previously noted. Several studies that purport to test for drugs made no provision for testing for metabolites. Thus, negative findings cannot be presumed to be conclusive.

Other studies have used tests that are quite unsophisticated and that may result in false positives. These limitations make it necessary to examine each study and the findings. (Joscelyn and Maickel 1977a, pp. 82-3.)

However, incomplete reporting of methods, data, and analytical techniques compound these methodological issues, and often completely obscure them.

Drug metabolites with significant pharmacological activity may contribute substantially to the effects of the parent compound if present in large amounts. Such metabolites may accumulate during the chronic

administration of a therapeutic agent such as diazepam (Korttila, Mattila, and Linnoila 1975). Drayer (1976) has reviewed the subject of pharmacologically active drug metabolites. The therapeutic and toxic activities along with plasma and urine data in man were presented. In the therapeutic context, Drayer concluded that "if a drug has an active metabolite, determination of the parent drug alone may cause misleading interpretations of blood level measurements. The plasma level of the active metabolite should also be determined and its time-action characteristics taken into account in any clinical decisions based on drug level monitoring" (Drayer 1976, p. 246). Of course, this conclusion applies directly to epidemiologic studies of the incidence of drugs among drivers.

The influence of study design on drug analytical methodology must also be considered. Sample collection and handling procedures may introduce artifacts, depending on the separation and detection methods used. Definitional problems, such as what "fatality" means (Waller 1975), must also be solved for the comparison of different studies. For example, when interpretation of drug concentration in body fluids is concerned, the time of the sampling after an accident may be a critical factor.

In summary, the standardization of reliable methods is essential if progress is to be made toward understanding the role of drugs in highway crashes. Effective epidemiologic research requires development and utilization of an adequate screening system. Such a system cannot be based on a single analytical technique to determine an adequately wide range of drugs. Several of the recent technical advances in drug analysis should be considered for inclusion, especially immunoassay and gas chromatography-mass spectrometry-computer methods. Certainly for some drugs, marijuana to name one, the choice may be limited to such techniques. (This topic is more fully developed in Appendix C, which deals specifically with drug analytical methodology.)

6.2.2.2 Quality Control and Laboratory Proficiency. The problems of quality control (both intralaboratory and interlaboratory) as well as

laboratory proficiency also must be considered. Interlaboratory comparisons have been made using standard samples of drugs, either alone or in combination (Sellers 1975b; Dinovo and Gottschalk 1976). The results of these and other studies should discourage the use of several laboratories for a single type of analysis. Methods of proficiency testing in forensic drug chemistry have been reported (Frank 1975) and may be considered for the selection of laboratories.

Preferred methods must first be identified for the screening and quantitative analysis of selected drugs. Rigid quality control procedures should be specified and coordinated from a nonlaboratory vantage point. Above all, single-drug methods should be carried out in a single laboratory. Should several laboratories be required for general drug screening, as in the case of specialized techniques, standards for sample handling and interlaboratory transfer will need development. Intermethod comparability and data interpretation problems must be minimized at the analytical stage. As will be discussed later, the interpretation of drug concentration data is difficult enough without the possible influence of analytical variables.

Proficiency in drug analysis is not the only factor to be considered in the selection of laboratories. The type of laboratory may also be important. The classical toxicology laboratory may be poorly suited to doing the kind of analytical work required in a field survey of drugs in drivers. Forensic procedures accepted in the courtroom are not necessarily the most sensitive or appropriate for this type of work. Newer technology is often not employed by forensic toxicology laboratories because it has not been accepted by the criminal justice system. For the purposes of epidemiology in drugs and highway safety, a new type of laboratory is virtually a necessity. It must combine the best in:

- analytical chemistry,
- technology and instrumentation, and
- pharmacology.

Any attempt to utilize a laboratory lacking expertise in all three of these areas would risk the value of the research study itself. (See Appendix C for a more detailed discussion of quality control, proficiency testing, and methods of drug analysis.)

6.2.3 Comparability in Epidemiologic Research as a Function of Study Design. International concern over the influence of drugs including alcohol on accident rates has been evidenced by international meetings (Israelstam and Lambert 1975; International Committee on Alcohol, Drugs, and Traffic Safety 1977) and numerous field surveys (Joscelyn and Maickel 1977a; Section 3.0, this report). The general interest in defining the drug and driving problem lends import to Waller's comments concerning alcohol and the lack of comparability between studies (Section 6.2.1.3).

In discussing crucial concepts in the epidemiology of drug-related problems, Richman (1975) emphasized the need for comparability in epidemiologic research:

Comparability is critical in epidemiologic research. Too frequently generalization is not possible because of the lack of definition of the cases studied.

It is essential to have **systematic** methods for describing the characteristics, course and outcome of various kinds of drug-related problems

Standardized methods which promote comparability are essential for generalization and for assessing whether possible differences should be explored further. Comparability can be enhanced through use of terms and definitions which already exist (such as the Federal Census questionnaires), **participation in collaborative projects**, or the development of systematic approaches and agreed-upon definitions

(p. 40, emphasis added.)

The cost in effort and money to determine the relative incidence of drugs in accident-involved drivers demands that studies extract as much

relevant data as possible during the course of investigation. Maximally efficient use of the collected data would depend on the comparability of studies conducted in several regions, even several countries. "No single research study conducted in any country can provide the extensive knowledge needed about drugs and driving" (Milner 1972, p. 74). Addressing these concerns, Goldberg and Havard (1968) proposed a "co-operative integrated research programme":

. . . it is most important that standardised analytical techniques should be used in surveys of hospital traffic accident victims, fatalities, accident and non-accident driver studies, etc., and that criteria for recording any other factors in such studies should be standardised so as to allow [for] cross-national comparisons. (p. 60.)

The aims of cooperative studies were also described, and are given here:

- to enhance the output of the efforts made and of the money spent, by co-ordination and integration of research facilities,
- to extend the scope of the problems by attacking a project from different angles,
- to enhance the validity of the results by increasing the size of the material studied and of the number of countries participating,
- to reduce the time necessary to conclude a project by co-operation between several groups of researchers; and
- to reduce the delay in the introduction of new measures, whether of a legislative, educational or informative nature, by exchange of ideas, of practical experience and of information on scientific results and technical data. (p. 48.)

In its latest review of alcohol, drugs, and traffic safety, the O.E.C.D. has continued its call and support for international cooperation and coordination of research (O.E.C.D. 1978).

The existence of certain legal and ethical constraints (Joscelyn and Maickel 1977a) and the issue of privacy in research in this country (Joscelyn 1976) make the idea of international cooperation in drugs and highway safety research quite attractive, especially for roadside surveys. But aside from issues pertaining to the engendering of transnational research programs, the establishment of reliable methods of research must proceed in order to have a basis for standardization. The development, application, and evaluation of superior study designs, sampling methods, and analytical techniques should be a part of present-day epidemiologic efforts in drugs and driving research. In this regard, the integration of accident analysis findings with drug incidence data should be of prime concern.

Other reports in the literature discuss related problems in epidemiology. Problems found in research on drug abuse have been discussed in Richards and Blevens (1977). Griedel (1977) has summarized epidemiologico-statistical problems in identifying the effects of drugs on traffic safety.

6.3 Summary

Major problem areas in epidemiologic research on the drug and driving problem are the insufficient data on drug usage patterns and the lack of drug use data on non-accident-involved drivers. Factors in study design require further research and development. Without substantial improvement in the design of epidemiological studies, especially field surveys involving drug analysis, the involvement of drugs in traffic crashes cannot be determined.

One approach to epidemiologic study that requires development is the analysis of causal factors other than simple drug presence. The characteristics of drivers and the possible contribution of drug effects to driver error are examples of factors that should be investigated.

Among the basic design factors of greatest concern are those dealing with missing-data rates in the population of nonaccident drivers, and the

influence on design of nonhomogeneous drug usage patterns. The development, evaluation, and utilization of adequate drug screening methodology is critical. The methods chosen must reflect practical considerations such as drug concentrations expected in body fluids. The prior selection of drugs of interest will allow the design of screening systems to be based on published data in the literature.

The design of studies capable of collecting varied and reliable data appears to be the most general and most pressing need. The generalizability of research findings depends on the use of systematic and standardized methods. Effective, comparable epidemiologic research awaits these developments.

7.0 EXPERIMENTAL RESEARCH: PROBLEMS IN MEASURING THE EFFECTS OF DRUGS ON DRIVING PERFORMANCE

The purpose of this section, similar to that of the preceding discussion on epidemiology, is to outline problem areas in the experimental study of driving performance per se as well as the effects of drugs on behavior believed related to driving. In particular, it reviews efforts to develop valid measures of driving behavior, especially of the behavioral variables underlying the driving performance itself. Briefly, the objective of this section is to describe the state of the art in methodology to assess the potential of drugs to increase the likelihood of traffic crashes.

7.1 The Experimental Approach and Its Application in Drugs and Driving

In contrast to the epidemiological approach, where field work is performed to ascertain the incidence and distribution of certain conditions, experimentation takes place under more rigidly controlled conditions. An experiment is usually performed in more restricted settings than the real-world situation. Almost without exception, a closed experimental system is simple compared to the real world. In this way, variables may be objectively and precisely controlled, at least theoretically.

By systematically varying factors of hypothetical significance, their interactions in terms of the system can be characterized. The statistical significance of drug effects can be used only as a preliminary assessment of their real-life importance. Until experimental findings are validated, the actual meaning of the results is uncertain.

The effects of drugs on driver performance cannot reasonably be studied in actual traffic situations. In addition to safety concerns, there are legal and ethical constraints (Joscelyn and Maickel 1977a). Further, selection and measurement of driver behaviors during such field studies present problems unsolved as yet. Typically rare outcome variables, like traffic crashes and fatalities, would not be appropriate for (precrash)

experimental observation. Therefore, drug effects on driving performance are most often determined in a laboratory setting, including closed driving courses.

The experimental determination of "accident risk" focuses on the influence of drugs on human behavior. Tests are used which have some relation, often undefined, to the driving task. All the attendant difficulties of studying "real-life situations" in an artificial, laboratory arrangement are assumed in this approach. Chapanis (1967) has summarized the relevance of laboratory studies to practical situations:

By their very nature laboratory experiments are at best only rough and approximate models of any real-life situation. First, of all the possible independent variables that influence behavior in any practical situation, a laboratory experiment selects only a few for test. As a result, hidden or unsuspected interactions in real-life may easily nullify, or even reverse, conclusions arrived at in the laboratory. Second, variables always change when they are brought into the laboratory. Third, the effect of controlling extraneous or irrelevant variables in the laboratory is to increase the precision of an experiment but at the risk of discovering effects so small that they are of no practical importance. Fourth, the dependent variables (or criteria) used in laboratory experiments are variables of convenience. Rarely are they selected for their relevance to some practical situation. Last, the methods used to present variables in the laboratory are sometimes artificial and unrealistic. The safest and most honest conclusion to draw from all these considerations is that one should generalize with extreme caution from the results of laboratory experiments to the solution of practical problems. (Chapanis 1967, p. 557.)

As a consequence, where a real-life solution to a problem is required, the experimental assessment of relevant factors remains indicative, not definitive. With respect to the problem of drugs and driving, the determination of drug effects on behavior related to driving leads to the

assessment of potential risk of accident-involvement for a given drug or set of drugs. The determination of actual accident risk requires application of epidemiologic approaches.

Section 4.3 notes that use of experimental findings in the literature is limited for estimating the potential highway safety risk of drugs. The state of knowledge partly reflects the nonsystematic approach used in evaluating drug effects. The noncomparability of separate laboratory studies and the uneven distribution of research efforts over the possible range of drugs of interest were two specific drawbacks observed. Underlying these difficulties, however, are problem areas which touch on fundamental methodological issues in the assessment of drug effects.

On one hand, there are theoretical objections to the experimental study of real-life events or processes, described above. On the other hand, there are purely practical constraints which hinder faithful reproduction of real-world situations in the laboratory. Cost factors and the state of the art in behavioral methodology are examples of problems faced by researchers in this area of drugs and driving. Together, these restrictions limit the validity of laboratory findings assumed to correspond to real-life driving, and the reliability of measuring driving-related skills assumed important to safe driving performance.

Three general problem areas have been identified in the experimental approach to determine drug influence on driver behavior:

1. Analysis of Driving Behavior;
2. Laboratory Reproduction of the Driving Task; and
3. Validation of Laboratory Findings.

In the following subsections, the areas of greatest concern are briefly discussed. Examples from the experimental literature are provided.

7.2 Analysis of Driving Behavior

Aside from issues of experimental design that characterize the literature, there exists the problematical relation of test methods to actual driving behavior. The individual skills or behavioral variables that comprise the driving task have not been completely described, nor has their interrelationship been determined. Their relative importance to

safety is also unknown. For example, a driver using a drug shown to impair a specific skill or behavior may **compensate** for the decrement during actual driving. So, even if every other methodological flaw were to be removed from the laboratory study of drug effects, the validity of test results would still be in question. Therefore, the general consensus among both researchers and reviewers has been that "the first major problem associated with the assessment of effects of drugs on driving behavior is that the driving task is not well defined" (Joscelyn and Maickel 1977a, p. 44.)

Nevertheless, research efforts designed to analyze the driving task have lagged considerably behind the empirical study of drug effects on skills (presumably) related to driving. In fact, there are theoretical and practical limitations involved in the study of actual driving behavior.

First, the driving task is complex. Personal, vehicular, and environmental factors must play a role in its analysis. Taken only from the human standpoint, many physical skills as well as sensory and cognitive functions are involved. Further, they are integrated (in an unknown fashion) into total behavior and thus are interactive.

Second, the experimental study of the driving task has its own drawbacks. Use of actual driving tests in natural highway settings is to be preferred, of course. In this, the ideal case, the analysis of many behaviors are hampered by the difficulty of precise measurement. Which measures describe behavioral variables significantly related to safe driving during actual driving is another question neither fully understood nor adequately resolved.

Where the effects of drugs on actual driving performance are concerned, it might be argued that the use of control groups receiving no drug treatment might alleviate some of these practical difficulties. However, the ever present problem of portable instrumentation is compounded by cost and safety considerations as well as by possible ethical and legal issues (Joscelyn and Maickel 1977a). The use of dual-control cars and the overall artificial setting are of questionable validity for determining drug effects on "actual" driving behavior.

7.3 Laboratory Reproduction of the Actual Driving Task

Efforts have been made to bypass the difficulties inherent in analysis of real-world driving behavior and its influence by drugs. Two experimental approaches attempt to preserve or reproduce the actual driving task--the closed driving course and driving simulator studies. These illustrate the second general problem area: laboratory reproduction of the actual driving task.

Some studies based on closed close driving have examined the effects of drugs (e.g., Clayton, Betts, and Harvey 1975). But little research has focused on developing a series of tests designed to sample the wide range of driver behaviors that may be influenced by the equally wide range of psychoactive drug effects. In this regard, studies of driving maneuvers (e.g., that by Koppa and Hayes [1976]) may provide a basis for the design and development of closed driving course tests using gross but valid measures driving performance.

Viewed by Moskowitz (1975), the driving simulator has certain advantages over restricted driving situations.

The disadvantage of the latter technique is that by restricting the environment to provide safety, many sources of stimulation characteristic of actual traffic situations are lost. Since one major reason for traffic accidents is failure to perceive important elements of the environment, an impoverished environment removes opportunities to study the effects of drugs upon perception. The simulator is the technique of choice also because it is more capable of ensuring replication of exactly the same stimulus presentation to all subjects. Finally, instrumentation is easier for simulators than for cars. This is true not only for stimulus presentation and response measurement but for measuring the time between stimulus and response. (p. 295.)

The research requirements for a simulator to determine adequately the influences drugs have on driving performance were also described by Moskowitz.

Primarily it requires that demands placed upon the subject

include those behavioral elements which are required for driving and which have the potential to be affected by the drug under investigation.

Since researchers desire to investigate a wide variety of drugs and one cannot predict which behavioral elements each drug might affect, a driving simulator is required that contains a representative sample of all the behavioral demands of driving. Thus, to construct such a simulator, it is necessary to analyze driving systematically so as to describe and enumerate all major components of the driving task in their proper proportions. A representative sample of the behavioral items could then be incorporated into a simulator. Finally, to validate the simulator as a test instrument, the performance of subjects in the simulator must be correlated with their performance in typical traffic situations on the road. Unfortunately, no such simulator exists nor is likely to exist for some considerable time. (pp. 295-6.)

Thus, the basis of the experimental dilemma lies in the nature of the driving task itself and its measurement. While skills of coordination and other functions rest with the person who drives, the effective expression of **driving behavior(s)** by the experimental subject depends on adequate reproduction of the actual driving environment. Yet, a laboratory rendition of the driving task, even as now understood, poses insurmountable difficulties, given current technology. One important but missing element is the actual risk involved in driving, although perceived risk might be introduced into experimental designs. Cost factors as well as insufficient researcher interest may contribute to the overall situation.

One is tempted to describe the predicament in terms of Joseph Heller's absurd paradox, Catch-22. For reasons both practical and sociolegal, we cannot study drug effects directly in the real-life driving situation. We cannot assess the influence of drugs on actual driving behavior in the laboratory because we do not know the relation of our limited test methods to the driving task. For reasons practical and theoretical, we cannot effectively study the actual driving task and assess

the relative significance of behaviors associated with it (perhaps the behavioral research equivalent of the Heisenberg Uncertainty Principle). Thus, all our experimental results, freed of every other methodological flaw, are still of questionable validity when applied to the drugs and driving problem.

Fortunately, this sort of double-bind does not hold (completely) in practice. While it is necessary to determine the relationship between laboratory behavior and actual driving performance (since deleterious drug effects may or may not be important for driving, or may not be observed at all), it is not essential that the respective behaviors, actual and experimental, be accurately defined and correlated. Experimental results may be validated by comparison with real-world findings. For example, the detrimental effects of a drug determined in the laboratory may be reflected in its disproportionate incidence in the accident population. This approach leads to the third general problem area under consideration.

7.4 Validation of Experimental Methodology

As discussed above, the experimental approach in drugs and driving has theoretical and practical limits. Published studies show methodological flaws that further limit their value. How valid are findings of significant drug effects in behavioral tests? What weight should be assigned to experimental results in assessing the safety risk incurred by drivers who use drugs?

An experiment's validity depends on its design, control of extraneous variables, and other methodological factors. But to infer validly from experimental data is the crux of the scientific method. Inferences are matters of judgment, and investigators may draw invalid inferences from otherwise sound data. Unfortunately, knowledge is rarely complete, and many inferences must stand for want of a judgmental basis to decide questions of validity. Nearly always, additional research must link experimental results with real-world situations. The behavioral testing of drugs to assess their effects on driving performance is the case in point. To infer driving impairment from the results of behavioral tests is the general problem.

Legal and safety concerns prevent the testing of drugs on subjects in actual traffic situations. Other behavioral tests, both complex and simple, are next best, ranging from closed course driving to psychomotor skills. These behavioral tests may show that a drug has significant effects on some aspect of human performance, but also needed is the real meaning behind statistical significance. To what extent does the magnitude of effect indicate driver impairment? And how does the type of each drug effect relate to actual driving or its component skills? That current research fails to provide the needed answers illustrates the importance of validating existing methodology for research on drugs and highway safety. Without validation much experimental work is interesting but without context.

Several approaches to validating behavioral methodology and experimental results are possible. Epidemiologic studies that determine which drugs or types of drugs are overrepresented in accident samples are usually mentioned in this regard. The chemical analysis of driver body fluids for drugs is necessary; most experts consider data from self-reports of drug use while driving unreliable. Another approach correlates results of complex behavioral tests (e.g., driving simulators) with driving records. Tests that correctly distinguish good from poor drivers could be considered valid measures of driving performance. In the past only poor correlations have been found, but other factors may intervene (see below). A third approach is the test battery method: important components of driving performance may be defined as simple, specific behavioral variables; these are measured for drug impairment. Defining these "important components," both in the driving task and in behavioral tests, has proven difficult (Willette 1977, p. 16).

Because the driving task is complex, complex behavioral tests that resemble driving may present subtle problems of validity. For example, variables found in actual traffic situations are absent in closed-course driving. Their absence, combined with difficulty in selecting and measuring driving behaviors, limit this method of studying drug effects. Driving simulators have other problems:

It can be concluded that all current simulators sample only a

restricted range of the possible behavioral demands met upon the road. This limits the conclusion to be drawn from the presence or absence of any drug-performance interaction found in a given simulator. Thus, if we desire to examine the reliability and validity of drug simulator studies, it is necessary, firstly, to understand the specific behavioral demands of the simulator used and, secondly, to compare drug-performance changes in the simulator with the nature of accidents when under the influence of the drug. Unfortunately, there has been no systematic analysis of what various simulators require from the behavior of subjects. They have been constructed to sample behavior either in accordance with the builder's theoretical assumptions (which are rarely explicated), or they have been built to incorporate whatever is available in the technological state of the art in constructing simulators. As a result of the lack of clarity regarding the behavior demands on the subjects in different simulators, the source of variability in results cannot be determined. (Moskowitz 1975, p. 296.)

Developing a valid test battery approach may require systematic research. The study of impaired skills or driver error in accidents with drug presence may yield a set of behavioral variables related to accidents involving drugs. Drugs may then be evaluated for their ability to impair performance on these variables. This approach requires coordination of accident analysis, behavioral research, and drug analysis. This complex approach to a complex methodological problem may be necessary for effective research in this area of drugs and driving.

Information needs in research on drug effects derive from these problem areas in behavioral methodology. To develop a systematic research approach, reliable measures of the effects of drugs on driver behavior must be identified and validated. Behavioral methods that are valid predictors of accident risk must then be used to test a wide variety of drugs and to generate needed data on the relationship between the levels of drugs in biofluids and their effects. Attention to principles of

experimental design and to factors that may influence the effects of drugs are required. These aspects of experimental research--effective research design and identification of significant background variables--are particularly important for the study of psychoactive drugs.

In summary, methodology to assess the potential highway safety risk of drugs should at least be conceptually related to some aspect of the driving task. More importantly, methods should measure significant behavioral variables whose relation to actual driving performance has been established. Response measures must reliably determine drug effects, but even more at issue is the extent to which significant drug effects are confirmed by increased traffic risk. Separate validation studies are required, largely epidemiological in nature. Finally, to interpret the levels of drugs found in drivers, the concentration-effect relationships for the drugs are required.

Some research questions may be stated to emphasize the dual concerns of reliability and validity:

- Which behavioral tests measure important driving-related variables?
- Which of these tests have been validated by correlation with actual driving experience?
- In the analysis of drug effects, which behavioral tests reliably measure the influence of drugs?
- Do drug-induced deteriorations of driving-related skills increase accident risk?
- What is the relationship of dose (concentration) and the effect of drugs on behavioral variables critical to driving?
- Are results obtained by use of behavioral methods valid indicators of "risk potential" for drugs?

Awareness of the problems discussed above has led some researchers to design systems whose sole purpose is to test behavior functionally related to driving performance. The following section reviews, attempts to identify and measure behavioral variables and to use them in evaluating effects of drugs.

7.5 Behavior Variables Related to Driving

The experimental approach in drugs and driving has led to attempts to reproduce the driving task as well as to use relatively simple psychophysical tests for evaluating drug effects. In either case, the effects of drugs were often evaluated in terms of measures derived from the test itself with little regard to the behavioral variables involved. A different strategy is evident in a third approach to this problem, in which behavioral variables important to driving performance are identified and measured in terms of response variables. Behavioral variables are usually complex skills or human functions that must be measured indirectly. Response variables are simpler, measured directly to infer changes in behavioral variables. For example, eye movements may be observed as pursuit velocity, fixation duration, and distribution of fixations. Changes in these variables may be taken to infer effects on the more complex function of information processing.

The conceptual analysis of driving performance has led to the tentative identification of visual, perceptual, cognitive, and psychomotor functions as part of the driving task. The development of methodology to describe changes in the measures of these behavioral variables may proceed in one of several directions. For a "simple," lower-order function, specific methodology for its determination may be developed. The definition of measures directly related to the variable is required. In other words the variable must be operationally defined from a behavioral standpoint.

The behavioral expression of higher cognitive functions may be elicited by various means, although higher central functions may require more complex methodologies. Existing test methods may be analyzed for their reliability in assessing these variables. The analysis of performance demands leads to an identification of measures useful in evaluating drug effects.

Finally, the use of a test battery may be considered. As an alternative to defining one or more driver-related behavior functions, driving performance ability may be viewed as a composite of personal "attributes." Even as the driving task remains ill-defined functionally, the

operational definition of these attributes has not progressed so far as to allow development and design of specific tests to measure their degree of operation in each individual. However, just as individuality reflects personal characteristics (which may be assessed by personality tests), so might individual differences in driving ability be associated with variation in constant aspects of human performance (i.e., behavioral variables). The experimental approach is by its very nature indirect, and may be likened to development of any aptitude test. The preliminary administration of many different tests to a large group of persons (whose relevant characteristics have been independently assessed by accepted methods) may result in a set of test parameters which correlate with real-world performance. The test-battery approach may lead to the identification of reliable and valid markers that may be classified and used to assess individual differences in driving "aptitude." These markers remain indirect indicators, because they are derived from behavioral tests, not behavioral functions. Their exact relation to functional aspects of driver ability remains unknown, however useful they may prove to be.

The literature of behavior research methodology is quite limited with respect to basic research in drugs and driving. Very few examples could be identified that illustrate the functional assessment of the effects of drugs on driver behavior or driving performance. Nevertheless, reports representing each type of investigation described above were identified. In separate subsections, the following examples are reviewed:

- visual functions, representing lower-order central functions important to the driving task;
- driving simulation, representing complex methodology used to assess specific driver functions, and
- behavior methodology used in the "test-battery approach" to assess driving performance ability.

7.5.1 Visual Functions. Tests of visual activity, common in examinations for licensing drivers, have long been studied for their relation to driving performance (e.g., Hofstetter 1976). The development and application of a kinetic vision tester by Suzumura (1968), and its

subsequent use to determine the effects of drugs on "kinetic visual acuity" (KVA) illustrate well the functional approach described above. The following paragraphs briefly describe the research pertaining to this driver-related function.

Differing from "static visual acuity" (SVA), which is simply the basic ability to see, KVA is the ability to perceive an object approaching the eyes, perpendicularly to the face. The function of accommodation and possible involvement of retinal and higher central nervous processes make KVA a separate eye function (Suzumura 1968). Its importance as a driver-related function has been investigated.

Variables influencing this function were first studied. KVA was found to decrease with increasing speed of stimulus presentation, with increasing age of subject, and with certain eye conditions (Clayton, MacKay, and Betts 1972; Suzumura 1968). Fatigue associated with aircraft piloting, physical exertion, and sleep deprivation influenced KVA but not SVA (Suzumura 1962; 1963). Professional drivers were found to have higher values for both SVA and KVA than a group of nonprofessional drivers. Persons with the same SVA values often differ significantly with respect to KVA (Suzumura 1968).

To demonstrate the importance of KVA as a driver-related function, Suzumura conducted a survey to study the relation of KVA to accident frequency. A group of 153 highway patrolmen were used. Using a criterion based on SVA and KVA values and their difference, two subgroups were formed, and their accident records were compared. Accident frequency was much less in the group having the better visual aptitude rating. Further, a considerable reduction in accident frequency was associated with improvement of eye conditions and correction of functional abnormalities which affected KVA but not SVA (Suzumura 1968).

Recently, the effects of drugs, alone or with alcohol, have been studied using the kinetic vision tester (Malpas et al. 1970; Clayton 1975). Clayton reports:

The results of these studies on kinetic visual acuity have tended to show more significant results than did those for static vision, although a different and wider range of drugs

have been studied. However, the results remain far from clear-cut. This state of affairs is perhaps to be expected if only because wide intersubject differences tend to be a feature of psychopharmacological research.

It appears from the results of these studies that certain psychotropic drugs at least have the potential for changing the time taken to detect a moving target. Obviously, therefore, such changes have direct implications for the driving task. (Clayton 1975, p. 3.)

In previous work, Clayton performed an accident-based analysis of road-user errors (Clayton 1972). A significant proportion of errors related to vision, including "failure to look" and "misperception," were found. Other conditions known to decrease visual acuity were also identified in the accident sample. However, basic differences were found in the causal factors associated with the various types of errors. To test the hypothesis that kinetic visual acuity and its influence by drugs contributes to increased accident risk, Clayton has recommended study of drug incidence in drivers, increased attention to accident data, and more research into the effects of drugs and their interaction with such factors as age, sex, alcohol, and personality (Clayton 1975). Thus, the influence of drugs that alter KVA on accident frequency remains to be established.

Another related visual function has also been described. Burg (1966; 1967; 1968) has defined "the ability" to discriminate an object when there is a relative movement between the observer and the object" as "dynamic visual acuity." As briefly reviewed by Clayton, MacKay, and Betts (1972), DVA is inversely proportional to speed of target movement and subject age, and along with SVA, is higher in males than in females. Unlike KVA, dynamic and static visual acuity tests show good correlation. Most importantly, DVA was:

. . . by far the most closely related variable to driving record, followed by S.V.A., visual field, and night vision. When related to the **numbers** of accidents and convictions, good D.V.A. was found to be positively related to poor record. An explanation in terms of age effects was given by

Burg that young drivers have the best vision and the poorest driving record whereas older drivers have the poorest vision as well as a relatively poor record. When related to accident and conviction rate categories, good D.V.A. is, with a few exceptions, positively related to good record. (Clayton, McKay, and Betts 1972, p. 201, emphasis added.)

Finally, Shinar (1978) reported an evaluation of a fully automated battery of visual tests related to driving. Licensed drivers ranging in age from seventeen to eighty-nine participated in the study. The test measured static central visual acuity (SVA) under conditions of optimal illumination, low levels of illumination, and glare; dynamic visual acuity (DVA), visual field, movement detection threshold in the central and peripheral fields, and visual search-and-scan ability. As a battery, the tests were "relatively highly associated" with accident involvement. Most important among them were DVA, SVA under low levels of illumination, and ability to perceive small rates of lateral movement. But the results showed that correlations between each test and measures of accident involvement were relatively low. Differences related to the age of subjects and to conditions of driving (day vs. night driving) appeared to affect the correlations most.

While the effects of some drugs on eye movements (DriscHEL 1968) and parameters of visual search (Moskowitz, Ziedman, and Sharma 1976) have been studied, no studies on the influence of drugs on DVA have been reported. Silverman and Harvie (1975) have listed adverse effects of commonly used drugs on the human eye.

7.5.2 Driving Simulators and Driver-Related Functions. The general behavioral task presented by most driving simulators is complex, like the actual driving task. Yet, in contrast to studies of visual functions, driving simulators "are generally viewed as having severe limitations as a valid measurement instrument" (Joscelyn and Maickel 1977a, p. 45). The sources of variability in experimental drug studies are discussed below, along with problems related to the identification of driver-related functions tested by the simulators.

Driving simulators are diverse in types and vary in their behavioral demand characteristics (e.g., simple tracking vs. dual-task). In addition, there is often uncertainty as to the exact behavior tested. Further, in dual-task performance, the influence of different subject strategies in handling behavioral demands may render the results inconsistent. As Moskowitz (1975) has shown, consistency among simulator studies improves when drug effects are not based on measurements of response variables per se, but are categorized according to the concurrent performance of several defined subtasks.

There is considerable reliability in the sense of agreement among simulator studies when the emphasis of the analysis is upon the **psychological function** affected by the drug, rather than upon the response variable in which the particular psychological function is exhibited. Thus, to examine the issue of validity or relevance of the results in the simulator, one must first isolate the **behavioral functions** that are being affected by the drugs. (Moskowitz 1975, p. 300, emphasis added.)

In the experimental design of simulator studies, investigators have often chosen to include subsidiary tasks. The simplicity of the tracking task itself in combination with subject motivation renders the device rather insensitive to effects of drugs or other conditions. Inclusion of a secondary task increases the behavioral demands placed on a subject. As a result, the sensitivity of response variables to the effects of conditions such as drugs, stress, and fatigue is enhanced. However, complex interactions between tasks may complicate the interpretation of simulator data.

Welford [1968] summarized some of these studies using subsidiary tasks, both with driving and with other tasks, and concluded that an increase in the load of either the primary or the secondary task beyond a critical point can impair performance on one or both tasks. In studies where driving has been the primary task, the subsidiary task has tended to be sensitive to changes in the load imposed by the demands

of driving, but the effect of the subsidiary task on driving performance itself is not clear. The addition of an extra task in monotonous conditions could serve to keep attention at a higher level and result in better driving performance. If, however, the combined effect of the additional vigilance task and increasing fatigue was to push the load on the subject past the critical point, the decline in performance in one or both tasks should be greater and occur sooner than for either task carried out alone. (Boadle 1976, p. 218.)

In comparing simulator studies of drug effects, the level of behavior demand becomes a critical variable. This variable is probably related to the function of information processing. Its measure, however, remains uncertain. Subject-related factors such as prior experience, motivation, and fatigue-resistance may interact significantly with the behavior under study. The subsidiary task itself may assume primary status, as was the case in a visual search behavior study (Moskowitz, Ziedman, and Sharma 1976).

Edwards, Hahn, and Fleshman (1977) reported their attempt to evaluate laboratory methods for the study of driver behaviors. The tests measuring coordination, reaction time, and timing could predict scores of selected components of simulator performance, albeit with low significance. The component scores termed "brake" and "speed" were more important in determining overall performance on the simulators. On-the-road performance was best predicted by "changing lanes without a signal" and "excessive speed."

These examples demonstrate the need to characterize adequately the types of behavior and behavioral functions under study with a chosen method. The interaction of several variables may invalidate the significance of drug effects on performance measures, or may totally obscure them. There is, therefore, a great need for standardized methods whose measures of behavioral functions have been tested for reliability.

Few studies describe the type of accidents drivers incur while under the influence of drugs. Thus, data required for validation of simulator results, even for alcohol, are scarce. Nevertheless, "while there is little

validating from either on-site accident studies or experimental field studies, what there is conforms with conclusions regarding the nature of alcohol impairment drawn from studies done in simulators" (Moskowitz 1975, p. 301). Results of marijuana studies, the second most studied drug in driving simulators, also lack validation. However, the approach itself, in determining drug effects on some variables related to driving performance, appears sound.

7.5.3 Other Behavioral Methodology: The Test-Battery Approach.

Although the driving task is complex, analysis may yield a set of behaviors related to driving performance. The interaction of a drug and a living system is itself complex; a drug may have several effects. Therefore, adequate assessment of the effects of drugs on complex tasks such as driving cannot be achieved by the use of one or two simple behavioral tests. As Saario and Linnoila stated, "no definitive conclusions about the psychomotor effects of drugs should be based on single psychomotor variables" (Saario and Linnoila 1976, p. 390). The test-battery approach attempts to circumvent the inherent limitations of simple behavioral methodology by testing a set of behavioral variables related to critical driving skills. The relation of simple tests of human performance to accident frequency has been investigated (Hakkinen 1958; Goldstein 1961). Hakkinen (1958) conducted an extensive statistical and psychological study of accident-proneness in drivers. The subjects of the study were vocational drivers, many of whom possessed several years' driving experience and lengthy employment records. These characteristics also limited intersubject variability to some extent. A complete test battery was used to assess driver characteristics, including intelligence, mechanical aptitude, psychomotor abilities (simple motor speed, coordination, choice reaction, and driving apparatus tests), psychomotor personality, and personal questionnaire and interview variables.

Validity was made the first consideration in the investigation of individual tests. Results showed that certain tests were significantly correlated with accident rate, including complex coordination and choice reaction tests. Other tests, including mechanical aptitude, reaction time,

and simple motor speed, did not yield significant or valid results. Cross-validation studies were then carried out. The validity correlations for an abbreviated test battery were significant in every case and of the same magnitude as in the basic study.

Linnoila and co-workers based their selection of methods to assess drug effects on the results of Hakkinen's validation study. Utilizing choice reaction, coordination, and attention tests, these investigators have studied the effects of a wide range of drugs administered acutely and chronically, with and without alcohol. Preliminary efforts were made to confirm these results and to assess their relevance to actual driving, using a sophisticated driving simulator (Linnoila and Mattila 1973a). However, validation of their research findings on the effects of drugs awaits epidemiological studies.

Hakkinen (1976) later reported a follow-up study on the relation of performance on psychomotor tests to traffic accidents. Validity of selected variables was again demonstrated in comparing the driving history of "safe" and "accident" drivers. Analyzing the data by multiple regression, the multiple correlation varied from 0.70 to 0.80, meaning that 50-60% of the total variance of accidents was explained by the test variables used. This study showed that no significant changes in personality factors affecting actual driving performance have occurred during 20 years. Thus, the test battery developed by Hakkinen appears to provide a basis for continued development of standardized methods by which to study the effects of drugs on driving performance.

7.6 Behavioral Test Complexity and Validity of Experimental Findings

It has been shown that driving simulators that involve subsidiary task performance measures are more sensitive to the influence of drugs and other subject-related conditions. In addition, it has been shown that certain behavioral tests with increasing complexity are more sensitive indicators of accident risk factors. In Hakkinen's study:

The complex coordination and choice reaction tests resulted with rare exceptions in higher validity correlations than did the simple motor speed, coordination and choice reaction tests

even though all of the factors mentioned seem to be valid to some degree . . . the situation for the time being seems to be such that the validity of complex tests is greater than that which could be achieved by any combination of simpler tests. (Hakkinen 1958, p. 180.)

The relationship between **validity** and the **complexity** of the psychomotor test is itself complex, however. Hakkinen pointed out that detailed analysis of complex tasks may yield certain factors which are independent of specific "ability variables," and some of these factors are personal characteristics.

Such traits have been obtained both by analyzing different sorts of errors during the different stages of the test and by splitting up the total motor performance into parts . . . The component performances may be uncorrelated, some of them being valid while the others are not. The variables descriptive of the total performance, too, may be of no consequence from the point of view of accident proneness . . . Yet these variables were not opposed to each other as regards their nature, but were partly saturated **on the same factor**" (Hakkinen 1958, p. 180, emphasis added.)

This important finding was also made in relation to driving simulation, as described above. As demonstrated by Moskowitz (1975), the identification of information processing as a behavioral function significantly impaired by alcohol established the reliability of apparently inconsistent simulator findings. Further study confirmed that hypothesis (Moskowitz, Ziedman, and Sharma 1976) and has opened up the possibility of fruitful field study along these lines.

Moskowitz (1977), however, has cautioned against adopting tests for the effects of drugs solely on the basis of correlations between test results and predictions of driving performance.

Correlations with long-term safety records and examinations of the immediate proximal causes of accidents suggest that the most important behavioral factors involved in accidents are perception, attention, and information processing.

The above areas to investigate are a good place to begin due to their obvious importance for skills performance. However, this is not completely adequate, since a particular drug could produce a deficit in behavior normally assumed to have little correlation with skills performance because of its small variation range in normal adults. For instance, the range of visual acuity in the driving public is little correlated with driving accidents, but a drug which reduced acuity to 20/600 might well produce greater probabilities of accidents. Therefore, beyond the behaviors most highly correlated with skills performance an adequate survey of the possible effects of drugs on safety must examine functions which appear to show only small correlations with skills performance but which a logical analysis of the skills suggest are necessary component capabilities (p. 88-9.)

As Moskowitz goes on to suggest, to assess the possibly adverse effects of drugs on driving performance may require a systematic approach, one that can detect functional impairment of component skills called upon in driving.

On the basis of the research reviewed above, it appears that certain basic behavioral functions can be isolated which, in some behavioral test systems, are only one of several kinds of behavior being tested at the same time. Usually, the response variables or test parameters measured as "behavior output" do not clearly distinguish among the various functions (e.g., attention, coordination, speed of response in choice reaction time). In addition, some or all of the behavior in a complex task may be affected by a given drug. Differential sensitivity to different drug effects can also be expected. Thus, each drug may have a different behavioral "profile." It should not be surprising, therefore, that a group of studies indiscriminately employing such tests should produce results which are inconsistent, contradictory, and, above all, incomparable. Such is the situation with much research on drug effects.

7.7 Related Information Needs in Behavior Research Methodology

Several important research questions pertain indirectly to behavior research methodology. The question of driver-related functions, their identification and evaluation, concerns the medical profession. Doctors must warn drivers who (1) have medical conditions which may increase accident risk, or (2) have to take certain drugs in treatment of medical conditions, either or both of which may increase accident risk.

Given that adequate behavior methodologies are developed, inter-subject variability often presents problems where the evaluation of psychoactive drug effects is desirable. The determination of drug concentration-effect relationships in terms of driver-related functions is of direct concern in the field of drugs and highway safety.

The following subsections briefly discuss these issues.

7.7.1 Driver Impairment and Therapeutic Drug Effects. Identifying the behavioral functions related to driving is a concern in the area of clinical pharmacology as well as in highway safety. Drugs are most often used to alleviate medical conditions. Physiological and psychological conditions may in themselves result in impaired driving ability. The risk potential of drugs prescribed for medical purposes may be greater or less than that indicated by experimental studies using healthy subjects. Silverstone (1974) has addressed this issue:

We require additional information sufficient to answer the following two questions:

1. Do psychotropic drugs given to patients in clinical dosage significantly impair driving behaviour in these patients?
2. Are accidents more common among patients taking these drugs than among similar patients not taking them?

It is not enough to show that these drugs can impair certain psychomotor skills in normal volunteers, although such information might provide a priori evidence of a potential risk. We need to know whether a patient for whom his doctor considers a psychotropic drug advisable on clinical grounds actually drives better or worse with the drug (pp.

While many clinical studies describing the therapeutic effects of drugs have been reported, little research has been conducted to relate clinical effect to driving-related skills. One exception is the study of drug effects in anxious patients by Uhr, Pollard, and Miller (1959). (Healthy volunteers were also included in this study.) Meprobamate and Tranquil[®], an over-the-counter bromide preparation, were administered chronically to patients selected by interview with a psychiatrist. An objective behavioral test battery, administered after the treatment periods, included a complex driving task containing a subsidiary reaction time task. Only in anxious patients taking meprobamate were reaction times slowed and accuracy at fast speed lessened. In a time estimation test with distracting influences, the performance of patients taking meprobamate was enhanced. An effect of meprobamate, increasing the ability to concentrate, was suggested to explain the conflicting results. As with alcohol, however, decrements in the response to the subsidiary reaction task suggest an effect of meprobamate on information processing.

In another study, this one employing measures of actual driving performance, Biehl (1974) found that diazepam and clobazam influenced only braking behavior out of twenty-nine variables in subjects selected for "high neuroticism." Unfortunately, "to avoid interference of results by personality characteristics," and "to have a representative sample with respect to consumers of tranquilizers" (Biehl 1974, p. 3), no "normal" control group was used. Thus, whether the effects of these drugs on drivers with these personal characteristics are specific or not remains unknown.

Moore (1977) also reported a study of an antianxiety drug on the driving ability of anxious patients. Braking and driving simulator tests were not adversely affected by medazepam, administered to fourteen anxious hospital patients in a double blind crossover design. In real driving conditions those taking the drug made more "technical" than "dangerous" errors. Unfortunately, the dosage used in these trials was below therapeutic levels. Even at these doses, however, such side effects as "drowsiness, ataxia, and released aggressive behavior" were observed.

These findings and the small number of subjects make further study of medazepam necessary.

Finally, Collins (1977) studied some effects of sleep deprivation on tracking performance and their reversal by d-amphetamine. He found significant decrements in dynamic (whole-body angular acceleration) performance, and less consistent impairment in static (no motion) performance. D-amphetamine, administered after fifty-five hours of sleep loss, reduced error for both static and dynamic tracking. Although performance of both tasks remained poorer for sleep-deprived subjects, their scores for static tracking did not differ from control (rested) subjects two hours after ingestion. Collins concluded that the benefits of the alerting drug, while undeniable, were only partial. He suggested that clearer tests were required before forming conclusions about the use of such drugs for enhancing performance in sleep-deprived states.

In conclusion, research on drug-disease-driving interactions remains scarce despite the potential for driving impairment by both medical conditions (Waller 1973) and the drugs used to treat them. As behavioral functions important to driving performance become identified and validated with accident data, available tests should be used to assess the **influence of medical conditions for which psychoactive drugs are prescribed**. The performance of persons with these conditions, with and without medication and compared to the "normal" population, should be measured to determine the risk potential of drugs in patients. As valid behavioral methodologies become available, the testing of new drugs for their potential accident risk prior to their marketing might be required.

7.7.2 Intersubject Variability as a Methodological Issue.

Characteristics of experimental subjects, including age, sex, and personality, are known to influence the intensity and even the nature of drug effects. Differences among subjects in an experiment give rise to variability in test results. In fact, **intersubject variability** is often a problem in studies of drug effects. In testing barbiturates and tranquilizers, for example, intersubject differences in response may stem from cross-tolerance in subjects who are heavy users of alcohol or in

mental patients exposed to a wide range of drugs. Statistically, large variances in test measures increase uncertainty and render results insignificant, even though significant effects are observed in many subjects treated.

As an element of study design, subject selection may be employed to minimize intersubject variability. This approach has two drawbacks. First, to apply research findings from a small, select, homogeneous special population to a large, diverse general population is difficult, to say the least. Second, variability among subjects points to underlying factors that may be just as important to assess as the drug effects themselves. To reduce variance by eliminating what may be significant human factors in drug impairment is probably not the best approach to studying drug effects on driving performance. Nevertheless, these conflicting aims--to obtain significant results and to obtain results meaningful in a larger context--make intersubject variability along with subject selection key methodological issues.

Past research on the effects of drugs shows little concern for the influence of subject factors. As noted before, most studies use subjects drawn from samples of convenience; young, mostly male, student volunteers predominate. Subject characteristics known to influence drug effects are usually treated as controlled variables, or are avoided altogether. In these experiments, their significance and their contribution to variations among subjects remain unknown. Yet, the few experiments designed to study multiple variables have shown (1) that subject factors can and do alter the behavior effects of drugs, and (2) that significant drug effects can be detected that otherwise would remain buried in the variance of test results.

In resolving these issues, the following questions are important:

1. In determining the potential of drugs to impair driving performance, which subject factors (driver characteristics) interact significantly with the behavioral effects of drugs?

To reduce variance in test results, subject factors that interact with drug effects must be identified and

controlled. On the other hand, some subject factors (e.g., age, sex, drug usage) are characteristic of large groups in the driving population. In which case, these subject factors are better studied than controlled. A "multiple variables" approach is indicated.

2. In assessing the safety risk of drugs to the general driving population, how important are factors that influence the behavioral effects of drugs?

One of the aims of research on drug effects is to measure the potential of drugs to impair driving performance. Whether the testing of drug effects involves complex psychomotor tasks or specific components of driving behavior, the issues of intersubject variability and subject selection remain. The extent to which subject factors interfere with and contribute to the knowledge of drug effects should be determined.

3. Are there substantial subpopulations within the general driving populations whose characteristics increase the risk potential of drugs?

Age, driving experience, life style, drinking habits, and other variables characterize the nonhomogeneous driving population. Awareness as well as lack of awareness of the possible drug effects may figure in a person's response to drugs. Most experimental samples do not represent the general driving population. For example, older persons take more prescription drugs and probably have less knowledge about their side effects than do the younger, perhaps more drug-wise subjects on whom these drugs are tested. The whole complexion of research on drug effects might be changed by selecting other, more diverse groups of subjects. An accurate estimate of drug risk to highway safety may depend on this information.

In sum, insufficient regard to subject factors and their importance as

co-determinants (along with the drug) of behavioral effects is a common deficiency in the design of current research. Intersubject variability is both a consequence and an indicator of subject differences. In lieu of selecting subjects from restricted populations and thereby limiting the value of research findings, alternate study designs should test the effects of drugs and their influence by selected subject characteristics. The "multiple variables" approach may be necessary if the laboratory study of drug effects is to be relevant to the general population, and if intersubject variability, a limiting factor in past studies, is to be avoided.

7.7.3 Drug Level Determinations and Behavioral Methodology.

Intersubject variability in experimental studies may also stem from simple differences in drug absorption, metabolism, and disposition; from differences in individual responsiveness due to physiological states such as fatigue or tolerance; and from differences in psychological states, including motivation and personality traits. It is well known that drug dosage is only an approximate measure of active drug concentration. Large variability in resulting blood concentrations has been reported following a given dose in small numbers of subjects. These considerations underscore the necessity of determining drug concentrations as a co-variable with behavior measures.

Problems are raised by the inclusion of drug analysis requirements in experimental designs. Specific, reliable techniques along with trained personnel are not widely available for some widely-studied psychoactive drugs, such as marijuana and diazepam. Simultaneous sampling of blood and behavioral testing may influence the study of drug effects in certain procedures (Linnoila, Seppala, and Mattila 1974). Characterizing the personal pharmacokinetics of each subject prior to behavioral testing may negate such effects, but increases experimental costs. Required for such studies are continuous performance tasks or simple functional tests that can be repeated often, since blood concentration sampling should be performed frequently. This is particularly true for acute dosage studies.

The lack of information on drug levels in experimental studies of their effects contributes to the difficulty of comparing research results. In

addition, the linking of drug levels to the impairment of driving-related skills is a continuing need in highway safety.

7.8 Summary

The lack of progress in three problem areas—analysis of driving tasks, reproduction of actual driving performance in the laboratory, and validation of experimental findings—hampers attempts to assess the potential of drugs to increase the likelihood of traffic crashes. To enhance the value of experimental results, component behaviors associated with driving and their interrelationships should be determined. The absence of this information has had two major consequences:

1. The significance of laboratory results has remained uncertain.
2. The literature of drug effects on "driving-related" skills has become a patchwork of suggestive but insubstantial findings.

Literature on the effects of drugs also reflects the absence of a systematic, coordinated effort to characterize the nature and extent of the potential driver impairment resulting from drug use. The systematic evaluation of drug-risk potential depends on the resolution of fundamental methodological issues.

Issues of reliability and validity are major problems in behavior research methodology. The current literature does not satisfy information needs regarding how commonly used behavioral tasks relate to actual driving performance. Only a few behavioral functions have been identified. However, the effects of drugs on some aspects of the driving task have been studied, and significant deterioration of behavioral functions has been observed.

It is essential, as illustrated by the research described,

1. to analyze behavioral tests for performance factors that are valid indicators of driving performance;
2. to analyze performance tests for factors that are differentially affected by drugs, thus characterizing drug effects potentially dangerous to driving ability;

3. to study the effects of drugs on validated, well-defined performance measures and to determine the influence of interacting variables, such as dose, time of measurement, subject characteristics, etc.

In this regard, although the experimental literature appears beyond the reach of systematic analysis, the study of selected reports for certain drugs may clarify the nature of their effects on performance. Validation of the available experimental results awaits epidemiologic research on drugs and highway safety and more in-depth analyses of accidents involving drugs.

Further research in behavioral methodology is required before the effects of drugs on driving performance can be determined experimentally. Knowledge concerning the influence of other factors that may alter the effects of drugs is necessary before accurate predictions of accident risk are possible.

8.0 RESEARCH IN DRUGS AND HIGHWAY SAFETY: SUMMARY, EVALUATION, AND INSIGHTS

From the perspective of the requirements for research, we have outlined problem areas and described the kinds of information needed to define the role of drugs in traffic crashes. What we have learned from the review of literature and the evaluation of research linking drugs and highway safety is summarized in this section. In addition, we share the insights gained in the course of this study. In doing so, we reemphasize the close (albeit conceptual) relationship between the two main branches of drug and driving research--epidemiology and experimentation. By repeating this theme, we stress the overall need to coordinate and systematize research, to better collect, analyze, and disseminate data that indicate the significance of drugs as risk factors in highway safety.

8.1 Research on Drugs and Driving: Summary of Issues

In the context of highway safety, the potential of drugs to increase the likelihood of traffic crashes and associated losses depends on factors related to their use and effects:

- the patterns of use in the general population, including information on where, why, how, how often, and in what amounts;
- the patterns of use among drivers, the population at risk (which, if known, supersedes data less directly related);
- the ability of drugs to produce greater effects when combined (drug interactions); and
- the population of users, which may have characteristics that interact to increase the crash risk of drugs (e.g., inexperienced drivers, older drivers, users of alcohol, etc.).

The factorial approach seems required to select the drugs of interest in research on highway safety. No single, objective criterion presents

itself in research published until now. This approach has been suggested before, of course, in drugs and driving (Forney 1977; Smart 1977), for experimental research (Moskowitz 1976b), and for epidemiologic studies (Waller 1975).

By any standard, the general population consumes great quantities of drugs frequently. The drugs range from doctor-prescribed to street-bought, from innocuous systemic to powerful psychoactive. The patterns of use appear to be complex. Age, sex, region, degree of urbanization, personality, and numerous other variables influence the nature and extent of drug use. Only alcohol seems to enjoy universal acceptance and homogeneous consumption with respect to discrete areas. Yet even with alcohol, and certainly with other drugs, **who** uses drugs and **how** they are used may be important factors with respect to highway safety.

While the available data suggest complex and nonhomogeneous patterns of drug use, detailed information is generally absent. In particular, multiple drug use remains uncharacterized. Some drugs are available through two or more channels. Barbiturates, for example, are both widely prescribed and illicitly marketed (Wesson and Smith 1977). Different patterns of use for a single drug or class of drugs have significant implications for assessing the potential highway safety risk. The importance of data on the meaning of drug levels becomes apparent. The overall need for valid measures of drug effects is obvious, as well.

The most useful information, describing drug use by the driving population, is not available, of course. Some data from questionnaire and driving record studies have been reported. In these studies, the outcome variable of greatest value--accident-involvement--may result from subject-related factors other than drug use per se. Unfortunately, these "other factors" remain largely unidentified.

The direct epidemiologic approach to determine the prevalence of drugs in driving populations has seldom been applied. The limited scope of inquiry and deficiencies in the analysis for drugs have made existing studies only preliminary indicators of the risk of drugs. The problem of drivers impaired by drugs other than alcohol remains one of the unknown

dimensions. Past studies indicate a minimum level of drug incidence; actual levels may be much higher.

Among the sets of data from which information may be gathered for assessing the potential crash risk of drugs, the incidence of drugs in drivers should be weighed most carefully. Methodological problems in the few exploratory studies done to date prevented an adequate determination of drugs in the driving populations they examined. Present data almost certainly underestimate their true prevalence, and, more critically, the methods of drug analysis did not even detect all the drugs of interest.

Far more numerous are reports of the effects of drugs on human behavior. Yet, despite a wealth of experimental studies, methodological problems also limit this approach to the drug and driving problem. As for epidemiologic data, one critical drawback is the unknown comparability among reported studies (Waller 1975). Unfortunately, many aspects of drug use may not be considered proper for experimentation, such as the chronic administration of drugs to normal subjects, administration of drugs in excess of therapeutic doses, and the combined administration of two or more drugs.

The literature on the effects of drugs provides an extensive, diverse, but nonintegrated body of data. True, the concern about the influence of drugs on highway safety is recent and only one of several areas in which the effects of drugs are studied. But even reports concerned with the effects of drugs as potential factors in traffic crashes do not present a coherent picture (Clayton 1976). Nevertheless, combined with information on drug use in the general population, these findings are probably the best source of data for estimating the potential involvement of drugs in traffic crashes.

8.2 The State of Knowledge

Present knowledge in drugs and highway safety may be summarized as follows:

- the potential of drugs to increase the likelihood of traffic crashes has not be estimated;
- the extent to which drugs (alone or with alcohol) increase

crash risk has not been determined; and

- the causal role of drugs (other than alcohol) has not been established.

Research to determine the effect of drugs on driving has been neither thorough nor systematic. The prevailing uncertainty proceeds from limitations both in the designs of past studies and in the present methodology.

Probably no single set of data will adequately describe the relationship between drugs and highway safety. The dilemma of research in drugs and driving is reflected in the research issues listed above. Neither approach to drug and driving research--epidemiology or experimentation--appears likely to solve the problem.

Epidemiological studies seek to associate the use of drugs and traffic accidents. Detecting drugs in the blood of drivers is a direct approach. We have noted before that the presence of a drug does not necessarily indicate drug effect; the amount of drug present may relate to driver impairment, although this is unlikely for all, or even most, drugs. Even when the amount of drug(s) is measured in the blood of an accident-involved driver, other factors must be considered along with blood concentration data. Such complex interactions as "type of drugs, frequency of use and quantity per occasion, circumstances of use, sociocultural and psychological contexts, inherent driving ability, and demands of the driving task" (Waller 1977, p. 38) must be considered for determination of accident causation. The nonhomogeneous nature of accidents in terms of both driver characteristics and error causation has been indicated, for example, by Clayton (1972). Adequate assessment of the role of drugs seems to require at least some accurate accident data along with the study of driver characteristics. To deal with these issues, field studies of greater scope and complexity are needed.

Experimental studies, however reliable the methodology, measure the effects of drugs within a causal set containing many factors not found in the actual driving situation. As discussed earlier, interactions of drugs' effects with these factors make uncertain the extrapolation of laboratory findings to real-world accident risk. Even rigid control of all extraneous

variables in the laboratory may not be enough:

Unfortunately, this very power of a laboratory experiment constitutes its major weakness. Behaviour in the real-world is subject to all sorts of uncontrolled variability. Take automobile driving, for example. All sorts of people drive: the young, middle-aged and old. Men and women drive. So do the quick, the halt and the lame. They drive under all sorts of conditions of illumination and traffic. They drive when they are well rested and when they are fatigued or have just taken an anti-histamine pill. The cars they drive range from shiny new vehicles to decrepit pieces of machinery scarcely recognizable as automobiles. And so on through all the conditions that are involved in the practical business of highway transportation. When we try to extrapolate from laboratory experiments on reaction time, or tracking, or steering, to automobile driving what we hope is that the results of the laboratory experiment are large enough to show up when we put them into this huge melange of real-world conditions. And, of course, we should not be disappointed to find that our laboratory findings are often so small they get swallowed up and lost in the avalanche of uncontrolled variables that operate in life.

In focusing on statistical significance a laboratory experiment completely ignores the problem of practical significance. It is a curious paradox: the more successfully a laboratory scientist increases the precision of his experiment, the more likely it is that he will prove statistical significance for effects that are practically trivial. This is, none the less, one of the major difficulties we face when we try to generalize from laboratory experiments to the solution of practical problems. The results of a laboratory experiment may tell us that we are dealing with a statistically significant effect, but they never tell us whether the effect is practically important or unimportant. (Chapanis 1967, pp. 571-2.)

8.3 The Relationship Between Epidemiologic and Experimental Approaches

This report has stressed the two approaches to determine the role of drugs in traffic crashes. Within the sphere of each approach are research requirements and information needs peculiar to the respective approaches. In both epidemiologic and experimental research are important "approach-specific" variables that may modify the apparent effects of drugs. In the epidemiology of drugs and driving, road conditions, visibility, and traffic density are among the factors that may augment or diminish the role of drugs in accidents. In experiments, subject characteristics, time of testing, and the amount of drug administered are some variables that may alter the effects of the drug under investigation. The identification of background variables that influence the study of drug effects in the actual driving situation and in the laboratory aids in the interpretation of data and permits the characterization of their interaction. In this way, accident analysis and behavior analysis uniquely contribute to the determination of drug influence on driver performance.

Nevertheless, a full understanding of the role of drugs in traffic crashes must ultimately depend on both research approaches. As briefly described in Section 2.2, the experimental and epidemiological approaches are at once distinct and interdependent. Most likely, only in the laboratory can a sufficient number of observations be made to characterize the concentration-effect relationship for a given drug. On the other hand, the exact experimental replication of real-world driving performance is not presently feasible. The influence of drugs on driving performance may bear little resemblance to the behavioral effects of drugs measured by laboratory tests. In terms of risk, a drug which in the laboratory shows a significant potential to impair driving may not pose a significant traffic safety problem in the actual driving situation. For example, the weak, though significant, effects of one drug may be compensated for by drivers aware of decreased driving ability. A drug with powerful psychoactive effects may be used so infrequently by the driving population that little concern is warranted. This latter point also

applies to other extremely rare events with very high negative impact on highway safety, for example, highway accidents caused by an aircraft attempting to use the highway as a landing strip. The converse situation may also arise, depending on how the drug is used by the driving population. A drug may produce few impairing effects in laboratory subjects when administered in experimental doses. However, the drug may be used in excess of prescribed amounts quite frequently among drivers, may produce substantial impairment, and thus may pose a significant accident risk. These examples illustrate the inconclusive nature of epidemiological and experimental research considered separately.

The need to integrate laboratory results and data from field surveys is best illustrated by analogy to the alcohol and driving problem. Like alcohol, drugs will be found in varying amounts in the driving population. To ascertain the degree of drug influence resulting from drug presence, the blood concentration of the drug must be related to a probable effect, in this instance to accident-involvement. Unlike the case of alcohol, the relatively low incidence of any given drug, combined with limited funding for research, may make quite difficult the statistical proof of increased accident risk on the basis of blood concentration data.

Because neither approach to drug and driving research stands alone, the interspersion of elements common to the laboratory and the real world deserves special emphasis. Perhaps the most important of these are unifying variables that describe general relationships between drugs and driving performance. These include personal characteristics, drug concentrations in body fluids, and behavioral functions important in the driving task. The existence of common variables or functions gives rise to the possibility of interrelating results from laboratory studies and field surveys in a practical, operational manner. For example, as various drug effects are defined in terms of driver-related behavior functions, such as information processing, the identification and characterization of accidents involving drugs may become feasible. Thus, the disparate research approaches inherent in epidemiology and experimentation are seen to be complementary in the field of drugs and highway safety.

The following section describes the functional coordination of

epidemiologic and experimental study in drugs and highway safety. General requirements for the successful combination of research objectives are specified.

8.4 Coordination of Research in Drugs and Highway Safety

Because only limited resources are available for defining the drugs and driving problem, needed large-scale epidemiological studies may be justified only when data indicating the possible magnitude of the problem are generated. To this end, the efficient use of available resources is essential. Increased utilization of pharmacological findings from relevant clinical, behavioral, and toxicological studies is desirable, as is information on patterns of drug use. To focus preliminary research, the identification of the drugs of interest should precede data collection and analysis. The National Center for Statistics and Analyses, newly established by the U.S. Department of Transportation, will, among other functions, facilitate collection, analysis, and dissemination of accident data. The National Accident Sampling System (NASS) is intended to provide a reliable and representative method of collecting accident data nationwide (Smith 1977). Thus, what is required now are methods and procedures to integrate the data on accidents and the data on the effects of drugs for the purposes of drugs and highway safety.

In this regard, the interdependency of epidemiological and experimental research efforts deserves reiteration and further emphasis. In the field, the amount of drug ingested and the time of ingestion are uncontrolled variables. To interpret correctly the degree of drug influence in any accident, the significance of drug levels in biofluids must be known. Experimental studies, applying tests of skills believed related to driving, may establish ranges of drug levels associated with impairment. In turn, experimental efforts are hampered by the lack of knowledge concerning the relation of behavioral functions to the behavior of drivers that causes accidents. In the real-world context, the relative contribution of each performance skill to safe driving varies from moment to moment, depending on environmental factors. Error analysis for accidents in which the presence of drugs was detected may provide information regarding the

type of driver impairment. Behavior functions thus implicated in drug-influenced accidents could become the basis of laboratory investigations.

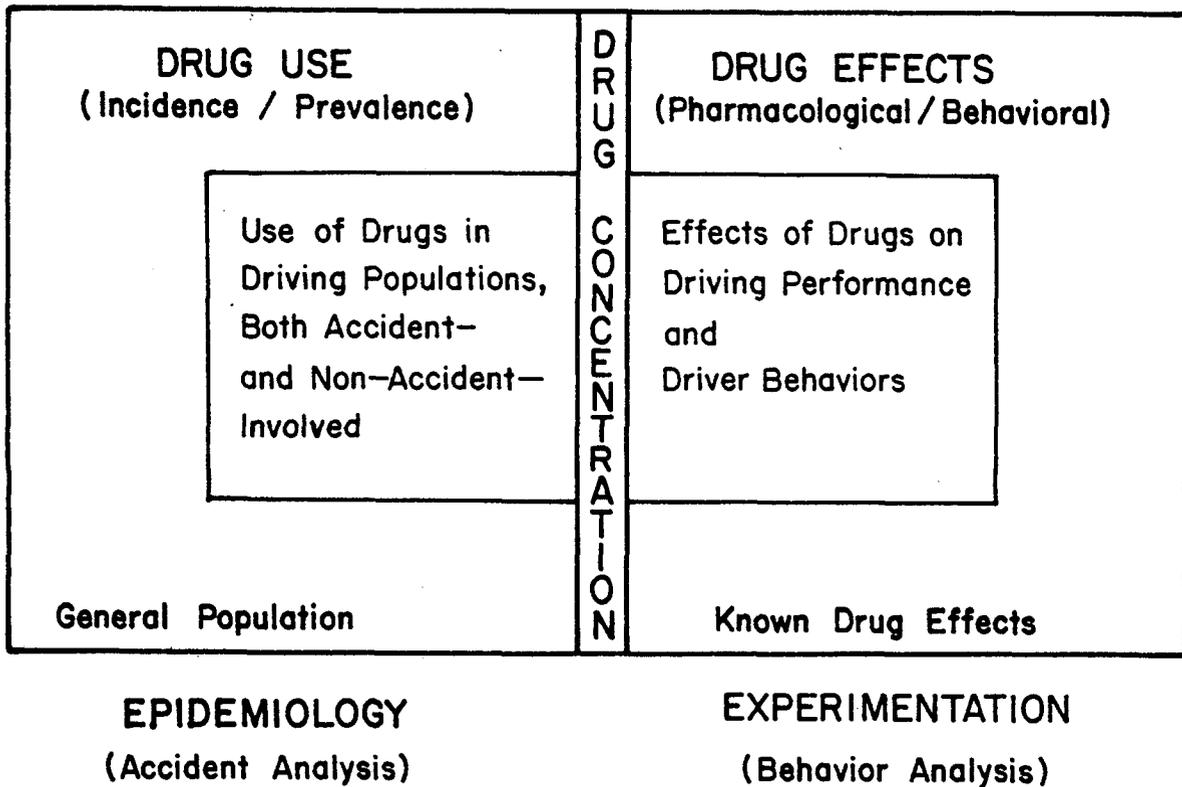
Figure 8-1 illustrates the complementary relationship between epidemiological and experimental research. Within the universe represented by the general population, drug use is characterized by prevalence and by incidence. These terms, used in the correct epidemiological sense, indicate respectively the "number of users at a given time" and the "rate of development of new cases" (Blackwell 1975, p. 114). Of direct concern is the proportion of the general population engaged in concurrent drug use and driving. The duration of drug use is defined by the operation of effects attributable to the ingestion of drugs.

By use of sampling techniques, researchers can estimate the prevalence of drugs in the driving population. By indirect means, such as questionnaire studies, actual drug use and driving frequency figures for the driving population may be approximated. By direct assessment, including body fluid analysis for drugs, sample populations may be compared and the relation of drug use to accident-involvement may be determined.

Drug effects result from drug use. These effects may be characterized in one of several ways, according to the methods applied for their study. Within the universe of known drug effects, we are particularly concerned with drug effects in man described by changes in measures of driving performance and driver behaviors. The experimental approach determines the nature and degree of drug effects resulting from use of drugs.

Epidemiology and experimentation are brought into conjunction by the desire to correlate real-world effects with drug usage by the general population or a defined subpopulation. For example, actual overrepresentation of drugs in accident-involved drivers may be associated with known drug effects on driving performance. Here, traffic crash causation is at issue. The objective study of the effects of drugs and the type of drug use must be brought together. Drug concentration is one common variable, as determined in the body fluids of drivers and

FIGURE 8-1. RELATIONSHIP BETWEEN EXPERIMENTAL AND EPIDEMIOLOGIC RESEARCH ON DRUGS AND HIGHWAY SAFETY

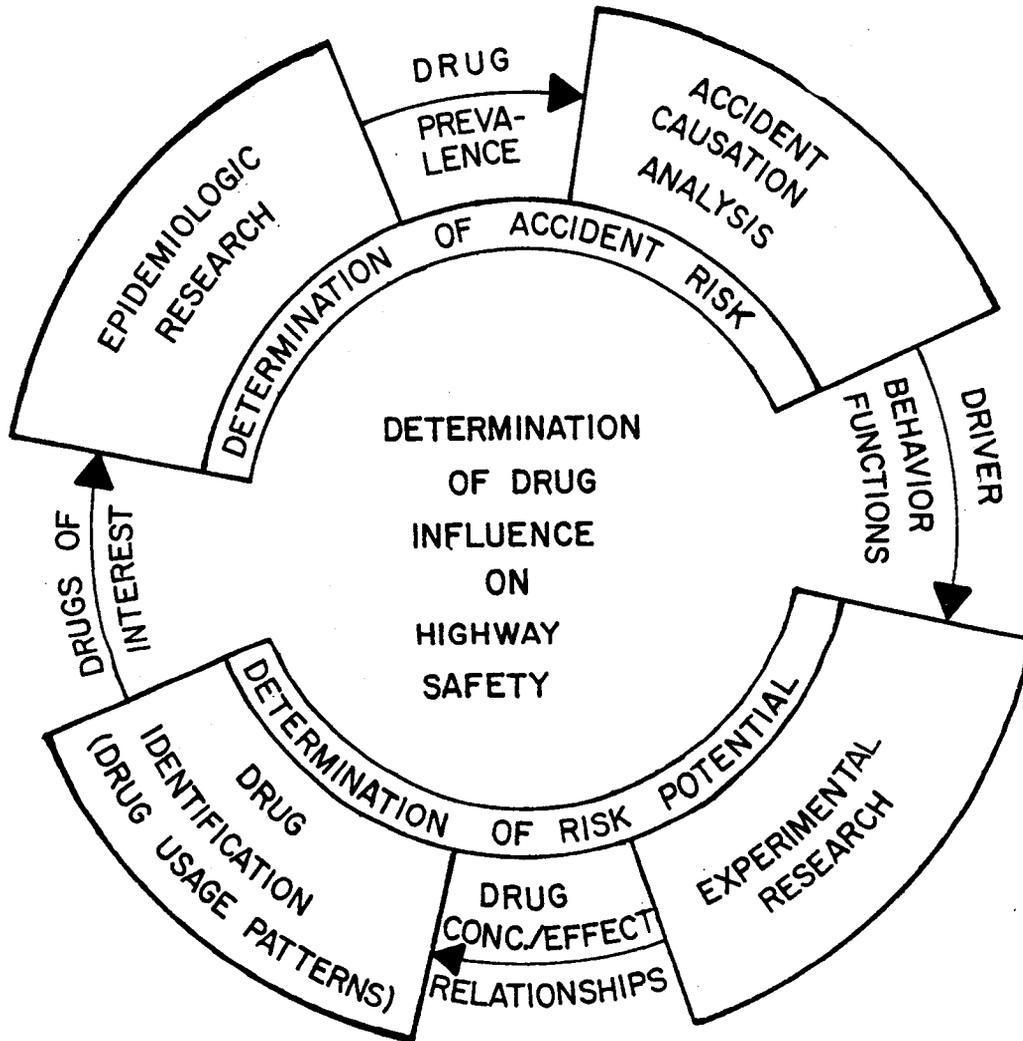


experimental subjects. Other variables or factors are shared by both universes, including driver-subject characteristics and driving behavior functions. These also may be utilized to the extent they are known and characterized by the subdisciplines of accident and behavior analysis.

Figure 8-2 illustrates dynamic interactions between related research areas in the field of drugs and highway safety. Overall, the diagram represents the effort to determine the influence of drugs on highway safety. The upper half of the diagram is concerned with determining actual accident risk attributable to drug use. The lower half pertains to determining potential accident risk ascribable to drivers who use drugs. The arrows indicate the potential flow of information.

The process is circular and repetitive. Initially drugs may be identified as having a significant potential to increase highway safety risk. Input comes from past experimental research, known drug usage patterns, and the pharmacological-psychological-behavioral profile of known drug effects. The prevalence of the identified drugs may be determined by field surveys involving both questionnaire and drug analysis techniques. Perhaps the greatest advances will follow the development of roadside testers or portable devices for drug detection. The role of drugs in traffic crash causation may be determined through analysis of accidents in which drug presence was detected. Estimates of actual accident risk may depend on the depth of analysis as well as the scope of variables included for study. Thus, driver error analyses and other collateral data may be required at this stage of investigation. Driver behavior functions, those important to safe driving performance and susceptible to impairment by drugs, may be identified for experimental study of drug effects on driving performance. Concentration-effect relationships may then be generated for those drugs investigated in the driving population. The significance of drug incidence in the body fluids of accident-involved drivers may be assessed on the basis of these data. Further field work may be considered, depending upon the patterns of drug usage and their fluctuation, and the depth of research required to establish accident risk. Epidemiologic studies focused on specific drugs may be required, if one or more have a higher incidence rate than expected based on known drug

FIGURE 8-2. INFORMATION TRANSFER AND UTILIZATION IN DRUGS AND HIGHWAY SAFETY



usage patterns.

At present, the absence of large-scale field studies of drug prevalence in the driving population, the population at risk, has prevented a natural continuation of prior research efforts. While much work has been done to indicate the potential of drugs to impair driving skills, field surveys are now required to advance the state of knowledge in drugs and driving. Actual accident risk of drugs such as marijuana cannot be assessed without field surveys that measure drug prevalence in accident- and non-accident-involved drivers.

8.5 Summary

Epidemiological and experimental approaches in drug and driving research serve different but complementary purposes and the problems in this research area cannot be solely defined by either approach. If the accident risk posed by drug use and the risk potential of drugs in the driving population are to be accurately assessed, then investigators using each approach require information from the other.

Information from diverse sources can contribute to a better understanding of the role of drugs in accident causation. Means for integrating available data indirectly related to drugs and driving safety (such as drug concentration-effect information) are desirable. For such functions to become operational within the research context, the coordination of ongoing efforts will be required, probably at the national level. Without a doubt, systematic efforts to solve drug-related problems in highway safety are essential for the efficient use of limited resources.

PART THREE

CONCLUSIONS AND RECOMMENDATIONS

Preface

Parts One and Two of this report form the basis for Part Three. The extensive review of literature in drugs and highway safety provided background for a discussion of problem areas and information needs in this field. Section 8.0 stressed the relationship between the two main approaches in research: epidemiology and experimentation. Part Three presents the findings of this study in summary form, including conclusions and recommendations, and suggests a way to implement them through a systematic program of research.

9.0 CONCLUSIONS AND RECOMMENDATIONS

This section presents in summary form the main findings of the study. The length and detail of preceding sections alone mandate this approach. Subsections below present these topics:

- General Findings
- Research Strategies
- Information Needs
- Research Priorities
- General Recommendations

In addition, another subsection describes some insights developed during the course of the study. These are suggestions for current action by operational agencies concerned with drugs and driving.

9.1 General Findings

The review of the literature on the topic of drugs and driving has not uncovered any significant advancement since our 1975 review (Joscelyn and Maickel 1977a) of the state of knowledge about the role that drugs play in traffic crash causation. Existing information is not sufficient to determine:

- the extent to which the use of drugs (alone or with alcohol) increases the risk of a traffic crash;
- the manner in which drugs may alter human behavior to increase the risk of a traffic crash;
- the significance of the results of experimental studies that demonstrate effects of drugs on human behavior, because the relationships of the effects and the driving task are not established; and
- the significance of drug concentrations in body fluids, because the relationships between drug levels and driving impairment are not known.

The existing research literature is interesting but fragmented. Limited information exists on many topics of interest; however, the literature, taken as a whole, does not establish that drugs are a priority highway safety problem. Nonetheless, the literature presents sufficient evidence to cause concern and to warrant further careful inquiries focused on defining the problem.

9.2 Research Strategies

The state of the current literature suggests that a need exists to adopt the following general strategies for research on drugs and driving:

1. The basic concern should be to establish the role that drugs (either alone or in combination with other drugs, including alcohol) play in traffic crash causation. The objective should be to establish the relative risk potential of specific drugs.
2. The role of drugs as a highway-safety problem should be established before countermeasure development is started. Demonstration of countermeasures should not be attempted until both a development phase is completed and countermeasure efficacy is objectively established.
3. The fragmented past research and the minimal return from small-scale studies must be recognized. Large-scale research efforts that are deliberately planned and coordinated will be required to make any progress in defining the scope of the drug and driving problem. While the level of funding for separate projects will increase, the practical yield in terms of usable data will more than compensate for increases in cost.
4. The nature of drug use by drivers must be recognized. The potential for increased crash risk does not flow only from the abuse of drugs or only from illicit drugs. General use of legal drugs, alone or in combination with alcohol, is as much of a concern.
5. Since research funds are necessarily limited, it will be

necessary to select a priority set of drugs as an initial focus for inquiry. Realistically, all drugs with the potential to impair driving behavior cannot be studied in the near future.

6. Research on drugs and driving involves many disciplines. At present, there is no central coordinating force. If any coherence is to be established, a deliberate attempt to set up better communication and coordination must be made. This can best be done through efforts to enhance information exchange and use within the research community.

9.3 Information Needs

The basic need to establish the role that drugs play in traffic crashes has been identified as the underlying research issue in the area of drugs and highway safety. This general issue establishes general information needs that have been discussed in the body of the report within the following topic areas:

- Drugs of Interest
- Epidemiologic Research
- Experimental Research
- Detection and Quantification of Drug Presence
- Countermeasures

The prior sections of the report have developed information needs and research requirements in detail. The objective of this section is to briefly summarize significant information needs in each topic area to establish a basis for the research priorities described in the following section.

9.3.1 Drugs of Interest

The basic information need is to identify a limited set of drugs that should be the focus of drug and driving research conducted in the near future. Information needs in this area include:

- drug-usage patterns (where, when, how often, and by whom drugs are used),

- drug availability (how much is available for use),
- pharmacology (the nature and intensity of the pharmacological actions and the associated behavioral effects),
- crash involvement (collation of existing information on the drug involvement in traffic crashes).

9.3.2 Epidemiological Research. The basic information need is to identify the prevalence of drugs in drivers who are involved in crashes and in drivers in the general driving population. This information will support an assessment of the risk of a traffic crash due to drug use by drivers. The relationship between drug presence and crash causation must also be determined. Information needs in epidemiological research include:

- the determination of the identity and amount of drugs, including alcohol, in drivers from general and accident-involved driving population;
- the determination of the nature and extent of multiple drug presence;
- the definition of prevalent types of drug-involved accidents;
- the comparison of driver characteristics between drug-using, accident-involved populations and suitable control samples;
- the determination of the relationship between drug presence and accident causation; and
- the investigation of possible interaction between other accident causation factors and drug influence on driving performance.

9.3.3 Experimental Research. In the context of this report the phrase "experimental research" has been used to refer to the class of studies concerned with the determination of the effects of drugs on driver performance. Such studies are usually conducted under controlled conditions in laboratory settings. Information needs in experimental

research include:

- the adequate analysis of the actual driving task and the identification of behavioral functions significantly related to safe-driving performance;
- the assessment of drug effects in terms of important behavior functions or, alternatively, in terms of valid measures of driving-related skills;
- the determination of subject and other background variables that may significantly influence the assessment of drug effects on driving skills;
- the assessment of psychotherapeutic drug effects in patient groups;
- the quantification of drug effects in terms of drug concentration in body fluids;
- for drugs of interest, the specification of threshold body fluid concentrations that are associated with impairment of driving performance and related skills; and
- the determination of the time-dependency of drug impairment, comparing acute and long-term drug administration.

9.3.4 Detection and Quantification of Drugs. The conduct of both epidemiological and experimental research studies to establish the role of drugs in traffic crashes is dependent upon technology that can detect and quantify the presence of drugs in drivers. If drugs other than alcohol are established as a highway safety problem, it is likely that countermeasures will also have to rely on such technology. Thus, it is necessary to develop adequate drug screening techniques and valid, reliable, realistic methods of determining drug concentrations in body fluids. Information needs in the drug analysis area include:

- the development and evaluation of methods for drug analysis to support epidemiologic and experimental research;
- the assessment of various techniques for cost

- effectiveness in general drug screening;
- the standardization of methods used in drug analysis, including sample collecting and handling procedures;
- the development and evaluation of methods for the sensitive and simultaneous determination of drugs and pharmacologically active metabolites;
- the identification and evaluation of laboratories that perform drug analysis in body fluids; and
- the development and evaluation of quality control and proficiency testing procedures.

9.3.5 Countermeasures. It has been stressed that extensive research on the development of countermeasures should follow the definition of the drug and driving problem. Pending resolution of that issue, it will be desirable to collect information on existing programs designed to reduce drug-impaired driving, to reduce drug abuse or misuse, and to ensure proper use of drugs. Each program should be evaluated to determine its efficacy and appropriateness for use as a drug and driving countermeasure. Information needs in the countermeasure area include:

- the identification of existing countermeasure approaches designed to reduce the risk of drug-impaired driving;
- the identification of approaches designed to reduce the abuse or misuse of licit and illicit drugs;
- the identification of approaches designed to increase the appropriate use of drugs (e.g., appropriate prescribing, dispensing, and instruction for use of prescription drugs); and
- the evaluation of the efficacy of identified approaches.

The priorities for research formulated below rest on this listing of general information needs.

9.4 Research Priorities

Each of the information needs identified in the previous section suggests research that should be undertaken to define the role that drugs

play in traffic crash causation, and to develop effective countermeasures if a problem exists. This section identifies the research that has the highest priority. Thus, all information needs previously identified are not addressed.

We conclude that the following research should have the highest priority for the near future:

- The specification of a set of "drugs of interest" that have the greatest potential to increase crash risk.
- The conduct of large-scale epidemiological field studies to determine the prevalence of the drugs of interest in the accident population and the nonaccident population of drivers.
- The development of analytical methods that can adequately detect and quantify drugs of interest in body fluids easily obtained in a field study setting (e.g., saliva).
- The conduct of large-scale, coordinated experimental studies to determine the driving-related, behavioral effects of drugs that are overrepresented in crashes.

We believe that drugs of interest can be identified relatively quickly by using existing information and by relying upon the best judgments of the drug and driving research community. Any list may be altered by subsequent data, but an initial list can be developed to allow epidemiological research to proceed.

The highest priority thus becomes the conduct of large-scale field studies to determine the prevalence of drugs in populations of accident- and non-accident-involved drivers. Until this is done, the drug and driving problem will remain an undefined issue.

Our recommendation is consistent with views expressed by researchers for the last ten years. The present state of knowledge is in disarray primarily because adequate epidemiological studies have not been conducted. Advancement of knowledge about the drug and driving problem requires research to address this priority.

NHTSA has funded efforts to study methodological problems in drug and driving research, as well as to study the incidence of drugs in

drivers. One project will produce an initial set of drugs of interest. The list will be subject to modification as the state of knowledge advances. Another project will study the incidence of drugs among fatally injured drivers. These projects represent first steps to fulfill requirements for research and information. Alone, they will not satisfy all the required efforts to define the drug and driving problem.

9.5 General Recommendations

Two additional priority areas, in addition to those set forth in the paragraph above, should be addressed to facilitate drug and driving research. These concern the coordination of research efforts and improvement in the use of existing information.

NHTSA should establish a mechanism to improve communication and coordination among researchers examining research topics related to drugs and highway safety. Two suggestions are made:

1. Research Advisory Group: NHTSA should establish a working group of researchers to advise on the future direction of NHTSA programs in the area of drugs and highway safety. Periodically, technical meetings should be held by this group with other interested researchers to discuss specific methodological issues. Such meetings could be held in conjunction with regular scientific meetings of the involved disciplines.
2. Research Information Bank: NHTSA should establish a central repository of information on drug and driving research. The fragmented nature of the field and the lengthy delays before formal publication occur have been noted previously. A central information repository that could be queried by interested researchers would enhance communication. To be effective, the system should allow a dialog. Researchers should be able to put in information on their activities and their reviews of the activities of others. A computer conference approach would be most appropriate and would enhance research coordination as well

as information utilization. Dissemination of research information should be a priority objective.

9.6 Insights

The conclusions and recommendations discussed above concern information needs and research requirements. The present state of knowledge does not allow the development of broad recommendations for countermeasure activity. In fact, because the nature and extent of the drug and driving problem is unknown, countermeasure development itself is not a priority. The literature, however, does offer some insights that have import for operational agencies that must deal with highway safety problems on a day-to-day basis.

We offer here some suggestions for operational agencies on the basis of current knowledge. These suggestions should not be viewed as firm conclusions and recommendations. They are, rather, the views of the authors, developed from study of the drug and driving issue. We believe these suggestions for current action are sound, but they are not established with the same level of objective data as the prior conclusions and recommendations. Thus, a reader should be careful to make an independent assessment of their utility and validity.

First, the literature and other sources make it quite clear that drugs can impair driving ability. Drugs are used and abused--with driver impairment as one result. Existing laws in most states prohibit driving while impaired by drugs. Enforcement personnel should be sensitive to the potential for drug impairment (either from drugs alone or in combination with alcohol). Obviously impaired drivers should not be ignored simply because the full extent of a national drug-and-driving problem has not been defined. Impaired drivers should be detected, apprehended, and dealt with according to local law.

Second, the existing literature clearly indicates the potential of many licit drugs (prescription and over-the-counter) and industrial chemicals to impair driving. The combined effects of alcohol and such drugs can also create impairment. This information should be made available to individuals who are using drugs or who are exposed to such substances.

Particular responsibility for accurate communication of this information lies with the personnel of the health-care delivery system who prescribe, dispense, and administer licit drugs.

Because many individuals self-diagnose and self-medicate with prescription and nonprescription drugs, broader educational programs on drugs are needed. Including information on alcohol and drugs in driver education programs would be highly desirable. This could be done in the context of formal driver education programs, as conducted in the schools in most states, or in a less formal manner by including information in driver license manuals.

Again, it is not necessary to wait for a complete definition of a national drug-and-driving problem to disseminate information on the known effects of common medications and their potential for impairing the performance of certain tasks—like driving.

9.7 Summary

The general conclusions and recommendations of the study have been summarized here and priority research requirements have been identified. Research that has the highest priority is field studies to identify the prevalence of drugs in the accident-involved and the general driving population. This kind of research is needed to advance the state of knowledge of the role that drugs play in traffic crash causation.

This section has provided an overview of information, research, and support actions needed to define the drug-and-driving problem. These needs should be addressed through a comprehensive research program. The following section provides a description of a program structure to illustrate how a systematic research approach could be implemented.

10.0 DRUGS AND HIGHWAY SAFETY: A PROGRAM OF RESEARCH

This report has thus far outlined requirements for research on the relationship between drugs and highway safety. A review of the state of knowledge served to identify major issues and needed information. Priorities for future research were then listed. One of the objectives of this study was to rank future efforts to define the problem of drugs and driving. Section 9.0 dealt generally with this requirement. In this section, recommendations for research are arranged in a systematic scheme, as projects in a program of research.

We have emphasized before in this report the need for systematic research on drugs and highway safety. The complementarity of the major approaches to research—epidemiology and experimentation--indicates the need for coordinated efforts. Also needed in this multidisciplinary field is the improved utilization of available information among related areas of research. In satisfying these needs, a program of research should amalgamate the scattered efforts that have characterized research on drugs and driving. Although the development of an extensive program depends on the nature and extent of the problem, systematic research is still essential for immediate work to define the problem.

First, an outline of the program for research on drugs and highway safety is presented in terms of separate **program areas**. Then, projects within each area and their objectives are briefly described. Relative priorities are assigned to each, based on current needs for research. Finally, future efforts are arranged in a systematic scheme. The sequence of projects is determined in part by their requirements for methodology or information.

10.1 Program Areas in Research on Drug and Highway Safety

Comprehensive research on drugs and highway safety must involve most, if not all, of the specific research areas reviewed in this report.

The program to be described, however, reflects to a large extent the current requirements for epidemiologic research. This is consistent with our conclusion that definitive field research constitutes the greatest research need and is of the highest priority among possible concurrent efforts. Nevertheless, because other program areas contribute substantially to the projected research efforts involving field surveys, field research does not by any means constitute the whole of the program.

The general outline of a systematic program of research is presented in Figure 10-1. The four separate program areas correspond to areas of research to define the drug and driving problem. The following paragraphs describe these areas and their role in the overall program.

Program Area 1000, State of Knowledge Assessment, includes projects that satisfy requirements for the review and evaluation of ongoing drug and driving research and related topic areas. Project activities will:

- maintain an up-to-date base of information on which to make decisions affecting the research program and its direction;
- establish central data depositories for use in related projects; and
- identify for resolution methodological and other issues that may hamper research in other program areas.

The function of this program area is to determine what has been done and what ought to be done.

Program Area 2000, Epidemiologic Research, includes surveys of drug use in driving populations. Research in this area satisfies the general requirement for determining the actual crash risk attributable to drugs.

Project activities include:

- determination of the identity and amount of drugs, including alcohol, in drivers both accident-involved and from the general driving population;
- identification of drugs associated with increased accident risk; and
- analysis of drug-involved accidents, including investigation of responsible driver characteristics and accident typology.

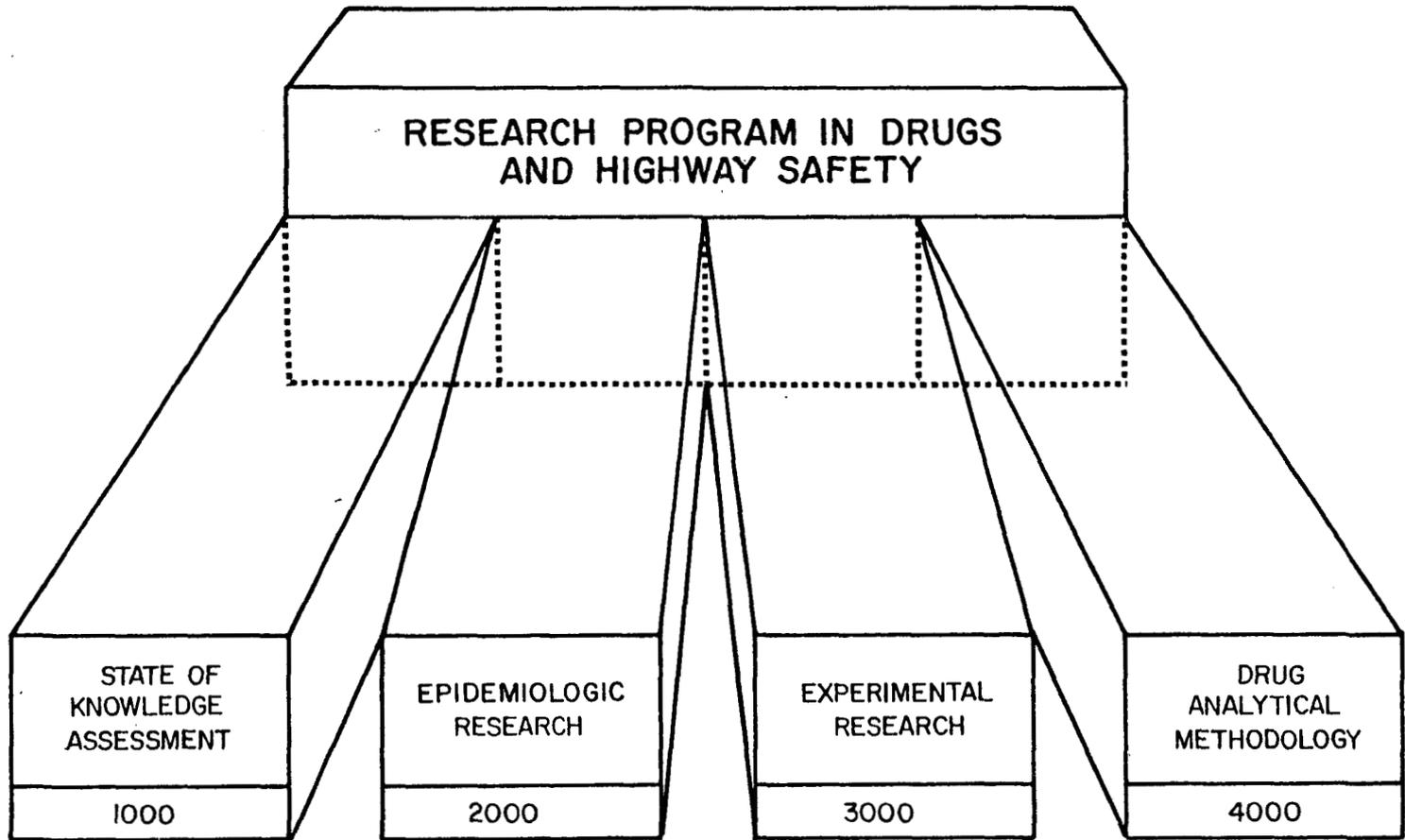


FIGURE 10-1. SYSTEMATIC RESEARCH ON DRUGS AND HIGHWAY SAFETY

This program area is expected to provide reliable data necessary for the identification, development, evaluation, and implementation of sound control measures. The specificity and effectiveness of countermeasures is directly related to the validity and scope of epidemiologic projects.

Program Area 3000 is designated as Experimental Research. Laboratory projects in this area are expected to satisfy specific requirements and information needs proceeding from field research. In particular, once it is established that certain drugs do increase risk of traffic crash, research projects may focus on these "drugs of interest." Project activities include those which:

- describe the levels and metabolic patterns of drugs in human body fluids;
- characterize the behavioral correlates of drug levels in body fluids; and
- establish the temporal aspects of impairment.

The function of this program area is to facilitate the interpretation of data generated by field surveys. Experimental research may also be required to develop a data base to support implementation of certain countermeasures.

Program Area 4000, Drug Analytical Methodology supports projects requiring the analysis of biofluids for drugs. Priority research needs include field survey requirements for the detection and quantitation of drugs and metabolites in biofluids. Project activities include:

- development of general drug screening systems in support of comprehensive field research; and
- evaluation and standardization of methods to support the implementation of certain drug countermeasures.

The support function of this program area is critical to the success of epidemiologic research.

These four program areas address both general and specific requirements for research. The areas involved would satisfy basic information needs as well as resolve any identified methodological issues. Projects within each area form discrete elements of the program. These are described below.

10.2 Projects in a Program of Research on Drugs and Highway Safety

Figure 10-2 presents an expanded outline of the program of research. Listed under each program area are three or more research projects. Although projects are serially numbered according to program area, the project numbers do not necessarily specify the order in which research efforts should be engaged within the program category. The order in which the projects may be activated is described later in this section. Letters (A, B, or C) follow the project headings; these indicate the relative ranking of research efforts within the overall program. The following paragraphs present the program outline in greater detail.

10.2.1 State of Knowledge Assessment (Program Area 1000). Three projects are included in this program area. The projects have distinct objectives related to specific program functions. Although the research projects are separate, they should operate in conjunction with each other.

1001 Literature Search and Review (A). Periodic and comprehensive literature surveys are desirable to update past reviews. This project includes all activities associated with reviewing the state of knowledge in drugs and highway safety. The identification, collection, review, and critical evaluation of literature pertaining to relevant research areas are required. The objectives of this project are to assess the progress of research, to build and maintain an extensive literature base, and to provide needed reference material to researchers in the field.

1002 Methodology Studies (A). Research efforts are often hampered by methodological issues. The purpose of this project is to identify and resolve such issues for drug and driving research. The output of this project should (1) facilitate research in other program areas, (2) direct attention to important problem issues, and (3) specify needed research.

1003 Data Bank (B). A centralized data base is a requirement for research in a multidisciplinary field. The purpose of this project is to create and maintain collections of data for use by researchers in the area of drugs and driving. The objectives of this project include development of appropriate information communication systems, evaluation and

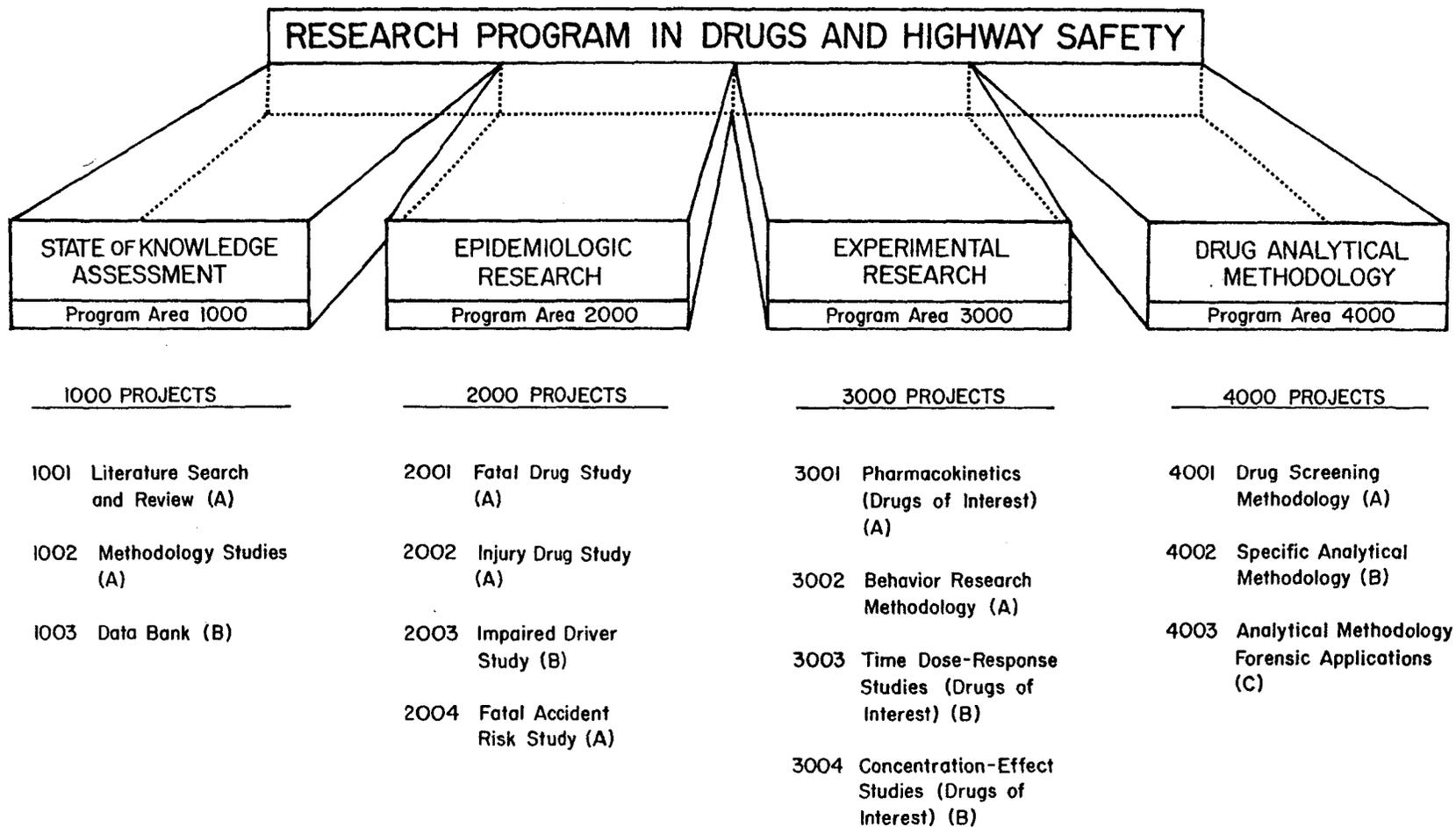


FIGURE 10-2. A PROGRAM OF RESEARCH ON DRUGS AND HIGHWAY SAFETY: PRIORITY PROJECTS

collation of available data, and dissemination of information.

By means of these projects, a continual awareness of research, both accomplished and required, can be attained. In addition to bibliographic material, data bases necessary for the development or completion of research in other program areas should be established.

The centralized storage of data would aid efforts to monitor the progress of research and would encourage the sharing of information among the groups active in research on drugs and highway safety. Projects that involve review of the state of knowledge and problems concerning methodology have somewhat higher priority, but this last-mentioned project is very important for developing a systematic program of research.

10.2.2 Epidemiologic Research (Program Area 2000). The four projects listed under Epidemiologic Research involve the direct study of drug use by drivers. The projects differ according to the population of drivers under study. The first three field surveys form an initial set which should lay the groundwork for surveys designed to assess the actual crash risk of drugs. Project 2004, for fatally injured drivers, is only one such survey. Additional studies that compare the prevalence of drugs in other accident populations with nonaccident populations would be required to determine the full extent to which drugs increase risk to highway safety. Projects 2001, 2002, and 2003 serve to indicate the need for this kind of field research.

2001 Fatal Drug Study (A). This project is a study of the incidence of drugs in fatally injured drivers. Ideally, the sample should be nationally representative. At a minimum, specimens of blood should be analyzed for the presence and amounts of drugs and metabolites. Analytical methods should be sensitive enough to detect and quantitate the levels of drugs obtained after therapeutic dosages. To the extent possible, collateral data should be collected to determine any differences between drug-involved and non-drug-involved accidents and drivers. In the program of research, this project provides one line of evidence showing the extent

of drug involvement in fatal accidents. By itself, in the absence of a comparable sample of living drivers, no estimate of actual crash risk is possible.

2002 Injury Drug Study (A). Because the involvement of drugs may vary with the type of accident under study, other populations of drivers must be studied to define the problem of drugs and driving. This project studies of drivers injured in traffic crashes, and its requirements for methodology are similar to 2001. Again, collateral data should be obtained to determine if the characteristics of accidents and drivers vary according to the involvement of drugs.

2003 Impaired Driver Study (B). A substantial population of drivers are apprehended for impaired driving. Often the use of drugs other than alcohol is suspected, especially when the level of alcohol is below that indicated by the observed degree of impairment. This project involves the study of an impaired driver population for the incidence of drugs, alone and in combination with alcohol. Like 2001 and 2002, screening for a wide range of drugs of interest in specimens of blood is required. Collateral data should be collected as available. Problems inherent in this kind of study include legal issues as well as how "impaired driving" is defined. This study would provide an indication of drug use by drivers described as impaired. Because this population of drivers is not accident-involved, and because certain types of impaired driving may not necessarily lead to accidents, findings from this kind of study are limited as far as indicating the **crash risk** of drugs. This project, while important, has somewhat lower priority.

2004 Fatal Accident Risk Study (A). This project is an epidemiologic study to assess the relative risk of fatal accidents involving drugs. Comparable samples of drivers are drawn from the population of fatally injured drivers and from the population of non-accident-involved drivers. Sample sizes sufficiently large are required for the statistical determination of fatal crash risk given the presence of a drug. Again, analytical methods to analyze blood should be sensitive enough to detect and quantitate therapeutic levels of drugs. As discussed above, similar projects for the study of other accident populations may be required to

assess adequately the actual crash risk due to drugs.

One possible facet of the above projects might be the in-depth study of accidents. The causation of traffic crashes is thought to involve a set of factors. A clinical assessment, or causal analysis, of drug-involved accidents—fatal or otherwise—could be done, for example, in a subset of cases under study. Of course, a certain level of investigation is required to estimate the significance of a drug present in any amount. Among the objectives of in-depth studies, however, would be an attempt to identify specific driver behaviors impaired at the time of the accident. This kind of study would provide a link to experimental research on the effects of drugs on behavior related to driving.

This set of projects should provide a firm basis from which (1) to initiate other projects and (2) to initiate activity in the area of countermeasures—at least preliminary efforts to identify and develop such measures as identify by this research to define the problem. These projects should also identify certain drugs for further, more intensive research, for example, behavioral studies.

10.2.3 Experimental Research (Program Area 3000). Laboratory-based research can describe how drugs affect behavior related to driving and their potential for driver impairment. The projects listed under Experimental Research represent efforts in applied research to characterize the levels of drugs in biofluids, the effects of drugs, and their variability in human subjects. Experimental research on drugs and driving is limited in that it indicates only the potential of drugs to increase crash risk. Nevertheless, because the meaning of drug levels in the blood must be established, experimentation may provide the only approach to interpreting the findings of field surveys.

Projects 3001 and 3003 represent studies on which more comprehensive efforts can be based (e.g., project 3004). Because these kinds of projects are time consuming and costly, they should follow field research that indicates which drugs should be studied. Project 3002 provides the behavioral methods to assess the effects of drugs on skills related to driving performance.

3001 Pharmacokinetics of the Drugs of Interest (A). Some knowledge of the pharmacokinetics of drugs selected for research is required to design behavioral studies that correlate the levels of drugs and their effects. Important metabolites of drugs, which are formed by the body after drug administration, should be measured as well. Information on concentrations of drugs and metabolites in body fluids should be gathered after both acute and chronic administration. This project involves the measurement of these concentrations over time and after varying amounts of drug. This project provides a reliable data base for the development of specific methods for the analysis of drugs in blood as well as other biofluids, such as saliva. This project also estimates the variability among subjects with respect to drug concentrations obtained after doses of given amounts. Project 3001 represents research preliminary to such projects as 3004.

3002 Behavioral Research Methodology (A). Methods to detect and measure changes in driving performance are required to assess the potential of drugs to increase highway safety risk. In this project, present methodology is evaluated for applied research on drugs and driving. For example, correlations between laboratory tasks and closed course driving tests could be made. The objective of this project is to develop a basic set of behavioral tests with which to assess the effects of drugs of interest. The battery of tests would be used in projects 3003 and 3004.

3003 Time-Response Studies of the Drugs of Interest (B). The time dependency of drug effects is generally understood, but may not be well defined for drugs of interest. Information concerning the duration of their impairing effects, as well as possible "hangover" effects, is important for the safe use of drugs by drivers. Applying methods that measure skills with an established relation to driving performance, this project assesses the behavioral effects of drugs over time. Time-response studies should also estimate the variability in response among subjects for the drugs of interest. The output of these studies will indicate periods after different dosages when impairing effects are observed. These times should be included in concentration-effect studies, such as project 3004.

3004 Concentration-Effect Studies of the Drugs of Interest (B). Before findings of the amounts of drugs in drivers can be meaningfully interpreted, additional research must correlate the concentrations of drugs in blood (or other biofluids) and their effects. This project applies behavioral methods related to driving performance and analytical methods to measure the concentration of drugs and metabolites in biofluids. Projects 3001, 3002, and 3003 provide the basis for this research. Project 3004 may differ, in that experimental designs that reduce variability among subjects may be required to permit use of drug levels as an independent variable. The objective of this project is to establish **threshold impairment levels** for the drugs of interest.

These projects provide information essential to the conduct, interpretation, and development of projects in other areas of the program. Projects 3001 and 3002 have highest priority. Project 3001 produces data for the design of analytical methods to detect and quantitate drugs in biofluids. Project 3002 identifies behavioral methodology for use in experimental research. Projects 3003 and 3004 have lower priority. They represent research later in the temporal span of the program and depend on the output of 3001 and 3002. Of course, some information on the pharmacokinetics of drugs and existing behavioral methods is available in the literature. Relevant data may be collected (e.g., in project 3003) to facilitate the development of research in this and other areas of the program.

10.2.4 Drug Analytical Methodology (Program Area 4000). Research in three areas of drugs and driving--epidemiology, experimentation, and if needed, countermeasures--require the analysis of biofluids for drugs and metabolites. The amount of drugs in drivers provides an objective measure of their effects on performance. The projects below satisfy requirements for methods of drug analysis for research on drugs and highway safety. Although each describes the development of analytical methods, they differ in their specific objectives to support research in other areas of the program.

4001 Drug Screening Methodology (A). Exploratory field research, as

well as epidemiologic studies of accident risk due to drugs, require methods to detect and quantitate drugs and metabolites in blood. Initially, a wide range of drugs of interest should be measured at concentrations resulting from therapeutic doses. This project fulfills the requirement for sensitive, specific methodology for the screening of biofluids for the set of drugs of interest.

4002 Specific Analytical Methodology (B). Initial field research may identify some drugs whose involvement in accident populations warrants further study, both epidemiologic and experimental. Based on knowledge of their pharmacokinetics, this project develops specific screening methods for field research and for experimental studies (e.g, projects 2004 and 3004). These methods would detect and quantitate a narrower range of drugs of interest as well as their metabolites. The objective of this project is to provide analytical methods that permit the comparison of findings of field surveys and experimental studies. For example, this project might develop methods to detect and quantitate drugs in saliva, and correlate these levels with behavioral effects found in laboratory-based tests.

4003 Analytical Methodology for Forensic Applications (C). Chemical tests used to provide evidence in legal proceedings must meet exacting standards. The forensic application of methods for drug analysis requires their evaluation and standardization. This project identifies analytical requirements to meet forensic standards and methods suitable for this application. The objective of this project is to support the identification and development of legal countermeasures that involve drug analysis. This project has a low priority because its initiation depends on results of research to define the problem of drugs and driving.

These projects support other program areas that require the analysis of biofluids for drugs. Projects such as 1001, 2001, and 3001 will specify the analytical characteristics of methods needed for research. The priority of projects in Program Area 4000 reflects the priority of research they support. Thus, screening methods for field research (4001) have higher priority than development of more specific methods (4002). As noted above, the low priority of project 4003 indicates the uncertainty of

requirements in the area of countermeasures.

The projects described above are the major elements of a program of research on drugs and highway safety. Their assigned priorities suggest a temporal order for the conduct of specific research. However, because projects in the four program areas are interrelated, their sequence depends in part on these interrelationships, which are discussed below.

10.3 Interrelationships of Research Projects

A "systematic" program of research implies rational design. The initiation of separate projects should occur in a logical sequence, depending on their objectives, their requirements for methodology and information, and their relation to other projects in the program. For example, a **methodological dependency** may arise between projects. Unless adequate methods specific to the purpose of a project are available, and unless methodological issues are resolved, projects dependent on such research have little hope of a successful outcome.

Similarly, an **informational dependency** between projects indicates the need for specific data prerequisite to the planning or design of a study. Findings generated by other projects may be required before a project can be initiated. In some cases, needed information may exist, albeit scattered throughout the literature. Here, a research project might incorporate a specific search and review of relevant documents.

Other factors may specify the order of projects in a program of research. For research on drugs and highway safety, projects to define the problem precede others to identify and develop control measures. Exploratory research may involve a series of projects to progressively define the problem in greater depth. Constraints on research--legal, political, or social--may also determine the sequence of projects.

The projects described in Section 10.2 illustrate all of these interrelationships. For example, projects in Program Area 3000 represent different levels of research. The need for analytical methods of increasing specificity orders projects in Program Area 4000. In Program Area 1000, however, projects relate to each other and to other projects in a unique fashion. This is discussed below.

10.3.1 The Interrelationship of Program Area 1000 (PA 1000) Projects.

PA 1000, State of Knowledge Assessment, contains projects of a continuous and ongoing nature. Project 1001, Literature Search and Review, maintains awareness of current research and assesses the general state of knowledge in drugs and driving. Project 1002, Methodological Studies, focuses on issues that hamper research progress or isolates for further research those issues not adequately examined. Project 1003, Data Storage, provides informational support in this and other program areas.

The interrelationship of PA 1000 projects is illustrated in Figure 10-3. While the projects may support each other, primary relationships are unidirectional. These are indicated by large arrow heads. Project 1001 identifies, evaluates, and then inputs literature and other data sources into 1002 and 1003. Project 1002 in turn utilizes both 1001 and 1003 outputs as information bases on which to conduct methodological inquiries. As noted, **secondary** relationships also exist. Once data bases become operational, specialized literature searches and review tasks may use them, perhaps via information retrieval systems. Methodological approaches to the identification and collection of literature and the establishment and maintenance of data storage units may be the result of Project 1002 activity. Such project functions are quite possible since the multidisciplinary nature of drugs and driving research gives rise to a great need for improved information utilization.

Taken together as a program area, PA 1000 projects may function generally within the program of research, or specifically in response to requirements in other program areas. For example, this report represents a general state of knowledge review which incorporates elements of all three projects. In minor or highly specialized projects, the functions of Program Area 1000 might be internalized within the scope and objectives of each project. The next subsection discusses the relationship of Program Area 1000 to the other program areas.

10.3.2 The Relationship of Program Area 1000 to Other Program Areas. As stated in Section 10.1, the function of PA 1000 is to determine

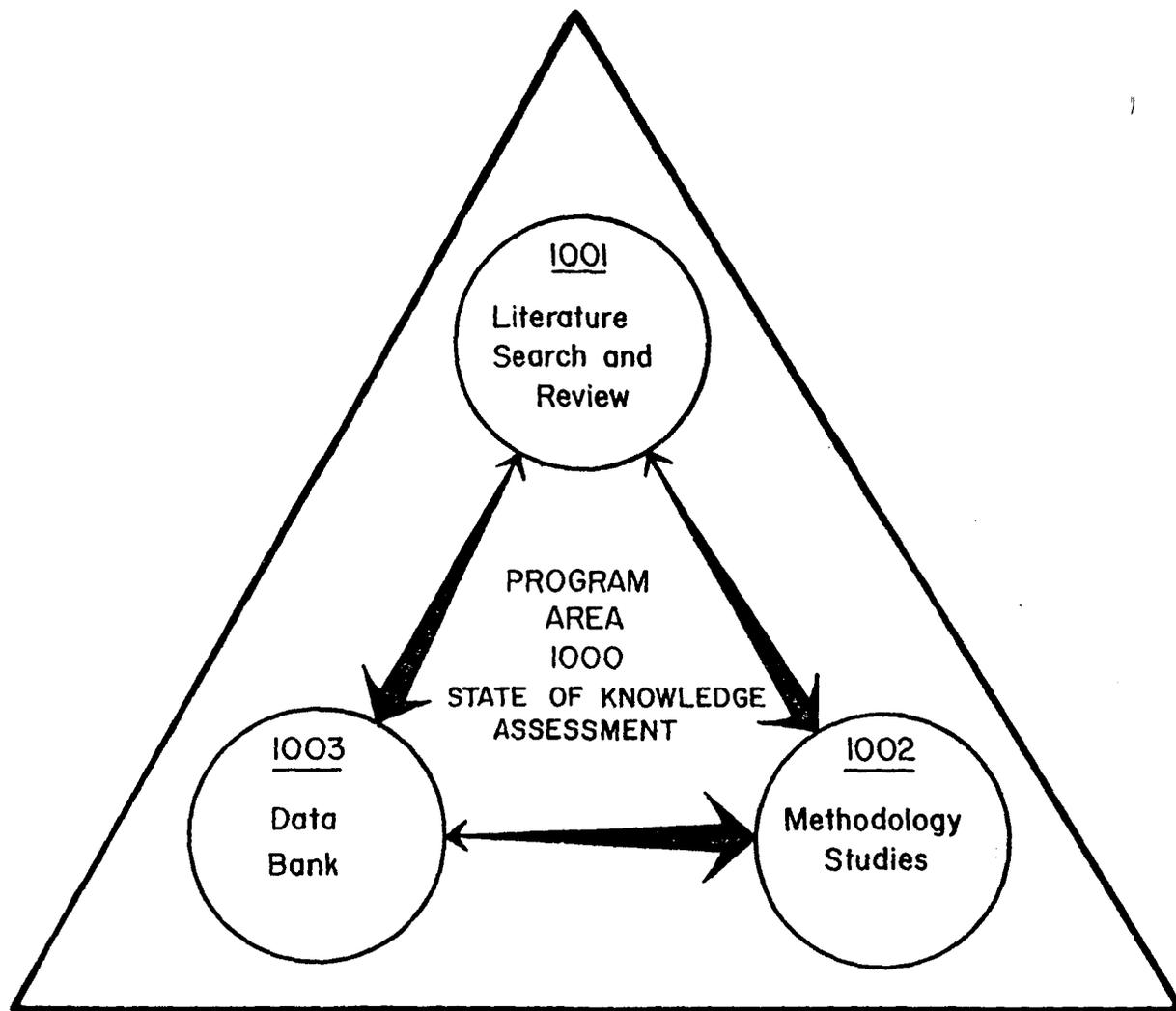


FIGURE 10-3. THE INTERRELATIONSHIP OF PROGRAM AREA 1000 PROJECTS

what has been done and **what ought to be done**. Evaluation of past and ongoing research is implied, since an uncritical examination of problem issues and study findings is unproductive. Another aspect of program function is suggested by the pivotal nature of project activity in PA 1000. Each project fulfills general program requirements (i.e., literature and problem issue review, data accumulation and storage), and may remain unattached to specific research areas. In addition, while other projects reach completion, these research efforts continue for the life of the overall program. Thus, PA 1000 provides continuity and flexibility to the research program.

Figure 10-4 depicts the functional relation of PA 1000 to the overall research program. The outer rectangle represents the "drug and driving problem"; the inner rectangle represents the research program. The project triad of PA 1000 occupies the functional center of the research program. The **scope** and **basis** of the overall program may be extended by the literature identification and data collection activities associated with PA 1000. Other program areas may be firmly established and extended from research termed "state of knowledge assessment." The distinction between research directed toward problem identification and research on countermeasures is incorporated into Figure 10-4. The output of research to define the problem is directed toward identification and development of measures to deal with any identified problem.

With the understanding that PA 1000 relates generally to each program area, and may provide specific input, informational or methodological, to almost every research project described in Section 10.2, a systematic outline of the program of research on drugs and highway safety may be presented. The interrelationship of projects from the several program areas is discussed below.

10.4 A Systematic Program of Research on Drugs and Highway Safety

The research program described in this section has been developed from the current state of knowledge in the area of drugs and driving. It reflects a systematic approach to research now required to define the problem of drugs and driving. Greatest emphasis is placed upon

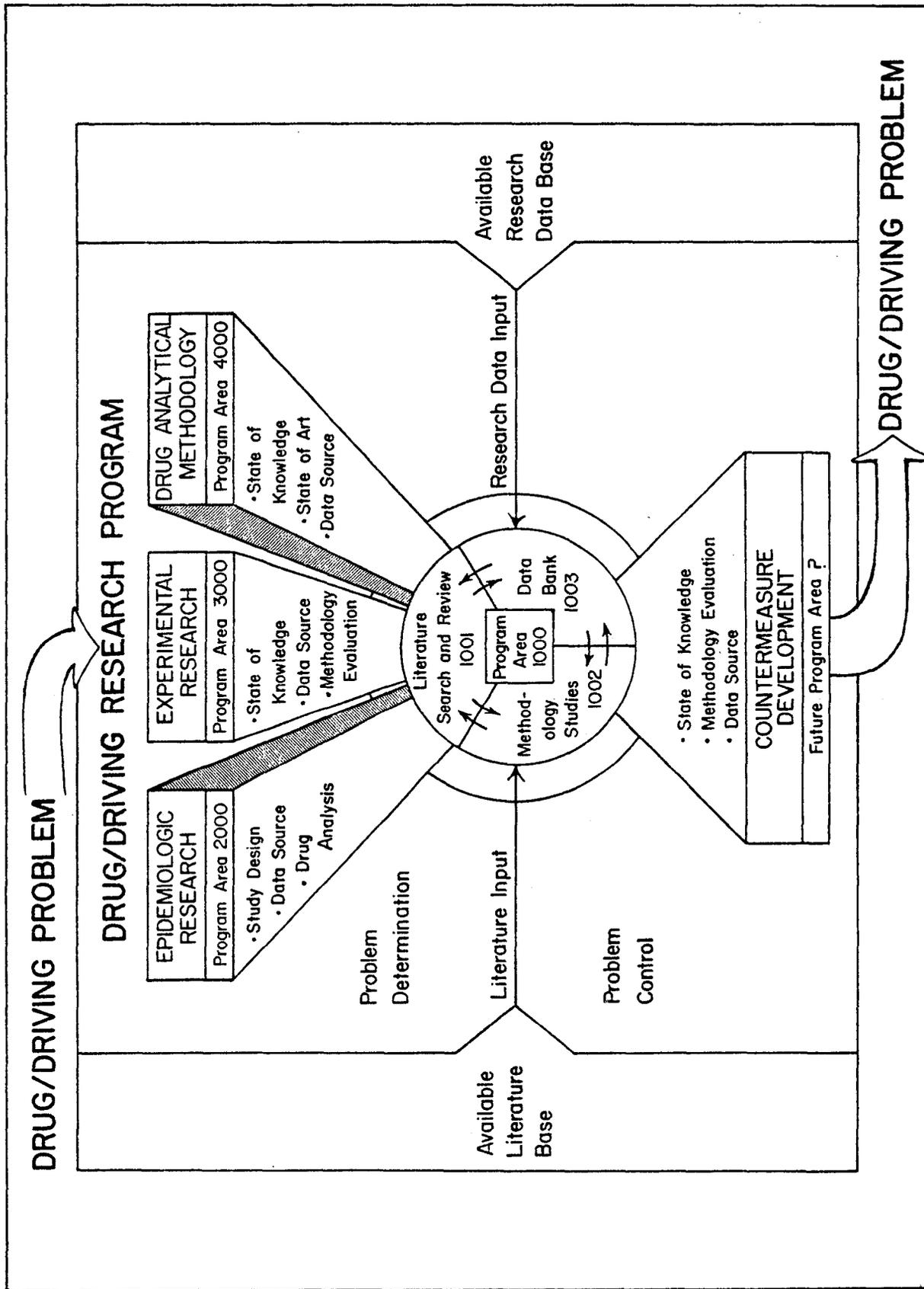


FIGURE 10-4. FUNCTIONAL RELATIONSHIP OF PROGRAM AREA 1000 AND OTHER PROGRAM AREAS

exploratory and **definitive** research projects. The types of interrelationships between projects are indicated.

Figure 10-5 presents the research program in the form of a network. The illustration depicts the relationship and dependency of research projects. While the diagram is similar in appearance to PERT (program evaluation and review technique) networks and other critical-path procedures, several distinctions should be noted. In the critical-path procedure, networks may be used in which links represent activities and **nodes** denote completed portions or milestones. The length of line connecting milestones indicates the length of time required to complete each task. In Figure 10-5, however, the arrows represent **project relationships** and the circles (or nodes) represent **project activities**. The length of arrows connecting projects does not represent time, nor is time specifically considered in the scheme. **Methodological** and **informational** dependencies are indicated by the appropriate letters (i.e., M and I). The arrows are numbered for the purpose of identification and for the convenience of later discussion. The numbers do **not** specify the numerical order of project initiation.

Program Area 1000 (PA 1000) is considered as the focus of program initiation. It provides for the review of research and assessment of methodology. Immediate information needs may be satisfied by referral to the available literature. Each program area and nearly all projects depend on research activity in PA 1000. For the sake of simplicity, only a few outputs from PA 1000 have been shown. However, whenever information needs or methodological issues arise, the program functions represented by PA 1000 are required as project inputs.

Arrows ①, ② a, and ③ join together a set of projects that constitute initial exploratory research in drugs and driving. PA 1000 provides research data and methodological studies required for the design and operation of projects 4001 and 2001. The output of project 4001, a general drug screening system, is required for the fatal drug study. Additional exploratory studies involving different driver populations (projects 2002 and 2003) also require general drug screening systems (② b and ② c). These field surveys show a temporal relationship (T) to project

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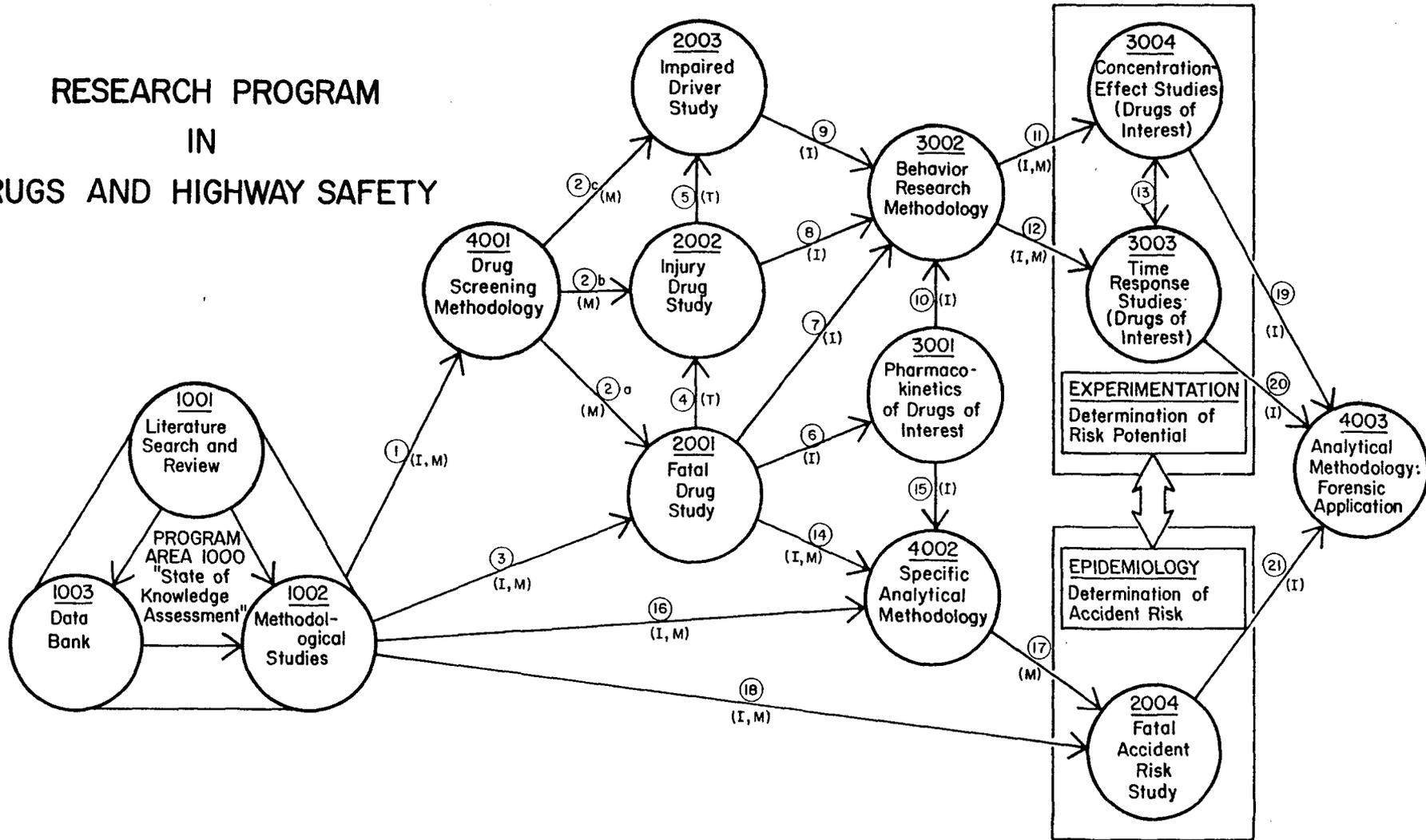


FIGURE 10-5. INTERRELATIONSHIP OF PROJECTS IN A SYSTEMATIC PROGRAM OF RESEARCH ON DRUGS AND HIGHWAY SAFETY

2001 (④ and ⑤). The main "ordering factors" are constraints on investigating the study populations and the degree of accident severity attributable to drug influence.

The informational output of the epidemiologic studies may be used to focus research activity in other program areas. The identification of "drugs of interest" (those substances whose use appears to increase the risk of traffic crash) allows concentrated efforts in program areas where comprehensive study of all drugs, or even **many** drugs, is precluded by limited resources. Thus, the development of behavior research methodology and the characterization of pharmacokinetics may be directed toward a relatively restricted set of drugs as a result of the field surveys (⑥ , ⑦ , ⑧ , ⑨). Of course, arrows could also be drawn from projects 2002 and 2003 to projects 3001 and 4002, indicating possible expansion or contraction of the set of drugs of interest over time.

Methodological studies and to a lesser extent collected research data form the cornerstone of definitive research in drugs and highway safety. Behavioral research ("Experimentation") depends greatly on the identification of methodology and study designs that would permit the determination of drug risk potential. Pharmacokinetics data are required for the design of the analytical component of drug concentration-effect research ⑩ . Reliable test methods must be available to determine the nature and degree of drug impairment in objective terms (⑪ and ⑫). The bidirectional arrow ⑬ between 3003 and 3004 indicates a close relationship of these projects. That is, both sets of data for each drug must be available and compatible for the meaningful interpretation of drug concentrations in man.

Definitive field surveys ("Epidemiology") also depend on input derived from other projects. Refined and more specific drug screening systems may be developed based on:

- drug identification and previous research experience ⑭ ;
- pharmacokinetics data ⑮ ; and
- input from literature and other research sources ⑯ .

Besides drug analytical methodology ⑰ , project 2004 requires the integration of comprehensive accident analysis. The identification and

resolution of methodological and other problem issues facing this type of investigation is represented by arrow ⑱ from PA 1000.

The double arrow linking experimentation and epidemiology indicates the close and interdependent relationship between these research approaches. The cross-utilization of research output primarily concerns validation of methodology and data interpretation. The development of drug analytical methodology suitable for forensic application (Project 4003) depends on the end results of problem determination (⑲, ⑳, and ㉑), as well as other factors. For example, the decision to develop countermeasures involving the measurement of drugs in body fluids may also be based on sociolegal and economic factors. The objective determination of accident risk and the reliability of drug concentration values as indicators of driver impairment must be established first.

Figure 10-6 depicts a temporal ordering of projects in the four program areas. The sequence of projects is presented in a vertical arrangement, proceeding from top to bottom in the chart. In Program Area 1000, the three projects are grouped, indicating their ongoing, concurrent nature. In other program areas, the temporal order of projects is generally more discrete. Horizontal relationships indicate the possibility of implementing projects from different program areas in the same time frame. Such an approach has the advantage of completing needed research more quickly in the program context. As discussed above, the temporal ordering is based on several different factors. Two factors, informational (I) and methodologic (M) interrelationships, are indicated for each project in the program area columns.

10.5 Summary

A systematic research program in drugs and highway safety has been outlined. Four program areas have been identified:

- State of Knowledge Assessment, concerning the informational and methodological requirements of other program areas;
- Epidemiologic Research, concerning exploratory and definitive research related to drug accident risk;

FIGURE 10-6. TEMPORAL ORDERING OF PROJECTS BASED ON INFORMATION (I), METHODOLOGIC (M) AND OTHER FACTORS*

PROJECTS FROM WHICH INPUTS ARE NEEDED											
PA 1000	I	M	PA 2000	I	M	PA 3000	I	M	PA 4000	I	M
1001											
1002	1001										
1003	1001	1002									
									4001	1001	1002
										1003	
			2001	1001	1002						
					4001						
			2002	1001	1002						
					4001						
			2003	1001	1002	3001	1001	1002			
					4001		1003				
							2001				
							2002				
						3002	1001	1002	4002	1001	1002
							2001			1003	4001
							2002			2001	
							2003			2002	
										3001	
			2004	1001	1002	3003	1001	1002			
					4001		1003	3002			
					4002	3004					
									4003	1001	1002
										1003	
										2004	
										3003	
										3004	

* Ordering proceeds from top to bottom of chart, horizontal lines indicate different time frames.

- Experimental Research, concerning the determination of drug potential risk and driver impairment;
- Drug Analytical Methodology, concerning the development of screening systems with detection and quantitation capabilities; and

The interrelationships of projects within these areas have been described.

APPENDIX A

TABULAR SUMMARIES OF EXPERIMENTAL
STUDIES OF DRUG EFFECTS, WITH REFERENCES

TABLE A-1
SUMMARY OF SELECTED STUDIES OF DRUG EFFECTS

Drug	Dose/Administration	Subject(s)	Experimental Design and Conditions	Tests	Reference
acetylsalicylic acid [#]	1 gr + 1 placebo - alcohol drink	50 volunteer students	independent controls design; groups matched for age, sex, weight, educational level, and living district. Placebo group, 30; drug group, 20. Double-blind conditions, 3 test times.	1. Choice Reaction Test (2 measures) 2. Coordination (2 tests, 5 separate measures)* (number of mistakes, test 2) 3. Divided Attention test (2 measures)*	(1)
alphadione [#]	85 mc1/kg intravenous anesthesia	50 volunteer students, early 20's	posttest only control group (between subjects); subjects randomly assigned to drug (4) and placebo (1) groups, 10/group. Training session provided day before test; test administered 2, 4, 6, 8 hrs. during recovery from anesthesia.	1. Sim-L-car driving simulator (12 variables measured)* (performance errors increased at 6 hours)	(2)
amobarbital [#]	265 mg	28 undergraduate students	pre- and postdrug schedules; independent control design (between subjects) with placebo.	1. Stroop Test 2. Witkin's Colored Embedded Figures Test* (broadened attention)	(3)
amobarbital [#]	100, 200 mg (at night)	10 healthy male medical students as paid volunteers, 18-20 years; 69-83 kg	2- 5 X 5 Latin squares (each treatment preceded twice by every other treatment); double-blind; random treatment allocation, with placebo and one other drug. Each subject tested five times at 14-day intervals, 9-18 hrs. after drug ingestion depending on fixed test schedule.	1. Card Sorting (13 hours post-drug) 2. Electroencephalographic Effects* (100, 200 mg)	(4)

TABLE A-1 (Continued)

Drug	Dose/Administration	Subject(s)	Experimental Design and Conditions	Tests	Reference
amobarbital [#]	150, 300, 450 mg	21 (15) healthy male student volunteers	repeated measures design (within-subject); 7 test-days, with minimum 3 days between each; double-blind, randomized treatment order included placebo, other drugs.	<ol style="list-style-type: none"> 1. Choice Reaction-Time Test (2 performance measures)* (300 mg performance significantly better than 150 mg; 450 mg impaired reaction time performance) 2. Tapping Speed* (150 mg; 450 mg) 3. Critical Flicker Fusion Frequency* (150, 450 mg) 4. Hand-coordination tests (3 performance measures)* (slightly improved by 300 mg; impaired by 450 mg) 5. Standing Steadiness* (450 mg) 6. Counting and discriminating tones* (450 mg) 	(5)
amobarbital [#]	50, 100 mg	12 healthy volunteers	balanced design, 2 six-sided Latin squares, double-blind condition, two test times, morning and afternoon, with placebo.	<ol style="list-style-type: none"> 1. Vigilance Test [tone detection]* (both doses, morning only) 2. Auditory Reaction Time Test* (100 mg morning and afternoon) 3. Short-term Memory Test* (both doses, morning only) 4. Digit Symbol Substitution Test* (both doses, morning only) 5. Tapping Test 6. Visual Search Test [random letters] 7. Subjective Evaluation* (both doses, morning) 	(6)
amobarbital [#]	100 mg, every night for 2 weeks	40 paid volunteer students (33 men, 7 women)	drugs and placebo administered double-blind in crossover design. Training on test apparatus and treatment allocation by Latin square to minimize learning effects.	<ol style="list-style-type: none"> 1. Choice Reaction-Time Test (2 performance measures) 2. Coordination (2 tests, 5 performance measures)* 3. Divided Attention task 	(7)

TABLE A-1 (Continued)

Drug	Dose/Administration	Subject(s)	Experimental Design and Conditions	Tests	Reference
amobarbital [#]	30 mg t.d.s. (5 doses prior to test)	100 (50 men, 50 women) mostly students	5 groups (10 men, 10 women) for four drugs and double-placebo. Each subject took drug and placebo on separate occasions and served as own control. Order of administration randomized.	Kinetic Visual Acuity* (improved values for male subjects)	(8)
amobarbital [#]	30 mg five times every 36 hours	80 student volunteers; 40 men, 40 women	separate double-blind cross-over designs with placebo; groups of 20 (10 men, 10 women) for drug-placebo combinations (4).	1. Actual car driving including weaving and gap estimation tasks (4 performance measures)* 2. Personality assessment*	(9,10)
benzquinamide [#]	200 mg	20 healthy young women from hospital staff	pretraining on tests, repeated measures (within-subject) design random drug condition with placebo.	1. Auditory Span* 2. Critical Flicker Fusion Frequency* 3. Coordinator Test* 4. Standing Steadiness* 5. Cancellation Test*	(11)
bromazepam [#]	9 mg	13 male volunteers 21-29 years (mean = 23) 59-82 kg (mean = 70)	Latin square design, including placebo.	1. Electroencephalogram Recording (3 variables plus frequency distribution analysis)*	(12)
bromvaletone [#]	0.6 gr with alcohol-placebo drink	220 volunteer students; 40 policemen, 37-44 years	double-blind, independent controls design (between-subjects); placebo and no treatment groups included; 20 subjects per group (all students).	1. Choice Reaction Test (2 performance measures)* (decreased reaction time) 2. Coordination tests [Tracking Performance]* (improved performance by decreasing errors) 3. Attention Test* (less correct responses in one of three time periods, 30 min.)	(13)

TABLE A-1 (Continued)

Drug	Dose/Administration	Subject(s)	Experimental Design and Conditions	Tests	Reference
bupivacaine [#]	1.3 mg/kg intramuscularly	11 healthy students, 9 men, 2 women; 21 ± 2.2 years, 70 ± 10 kg, 178 ± 8.3 cm	training period on test apparatus. Three treatments (including placebo, one other drug) administered with 1-week intervals in double-blind, crossover, randomized (Latin square) manner. Tested before (control) and 3 times after each treatment.	1. Choice Reaction-Time Test (2 performance measures)* (improved performance for both measures) 2. Coordination (2 tests, 5 performance measures)* (mistake percentage, test II) 3. Critical Flicker Fusion Frequency* 4. Visual Function tests (3)	(14)
caffeine [#]	300 mg/70 kg	university students, 18-30 years	independent control design (between-subjects) with placebo; 17 subjects per group.	"Performance measurement" tests (tests not specified, but included sensory, cognitive, and motor function tests)* (standing steadiness, eyes open test)	(15)
carbon monoxide	6-8% carboxyhemoglobin (COHb) after gaseous administration	7 paid volunteers (6 men, 1 woman) 19-27 years	training sessions preceded counterbalanced design with CO and air placebo for control condition.	1. Optical driving simulator with secondary task* (mean reaction time to speed changes, steering wheel reversals)	(16)
clobazam*	20 mg	5 healthy male subjects 24-39 years (mean = 32) 67-83 kg (mean = 72)	performance training to plateau. Four 2-day sessions, (with placebo, other drugs) separated by 4 weeks. Double-blind, random treatment assignment. Performance assessed at several time points.	1. Adaptive Tracking Test 2. Reaction time	(17)
clobazam [#]	20 mg each morning for 3 days	24 male students, 18-24 years, selected for high neuroticism	Latin square design with placebo.	1. Actual car driving (29 variables)* (more ready to brake) 2. Subjective tiredness 3. Labyrinth Test 4. Mood ratings (3 variables)* (less depressed than placebo) 5. Concentration Test (3 variables)	(18)

TABLE A-1 (Continued)

Drug	Dose/Administration	Subject(s)	Experimental Design and Conditions	Tests	Reference
clorazepate [#]	premedication: 10 mg, three times a day, for 7 days. experimental doses: 10, 20, 40 mg, acute administration.	42 healthy volunteers, 19-29 years	posttest only control group (between-subjects) with placebo; subjects randomly assigned to groups (7), 6 per group.	1. Simulated Car Driving with 3 performance measures 2. Physiological Functions	(19)
chlorimipramine [#]	10 mg three times a day for one week, then 25 mg three times a day for one week	20 healthy male students, 20-24 years, paid volunteers	drugs (2) and placebo administered double-blind in crossover design for 2 weeks each. On 14th day, effects of drugs tested in 2 kinds of learning situations; treatments administered in random order.	1. Immediate Memory Span (2 performance measures) 2. Paired Associate Learning (2 parameters)	(20)
chlordiazepoxide [#]	60 mg	20 healthy young women from hospital staff	pretraining on tests; repeated measures (within-subject) design; random drug condition with placebo.	1. Auditory Span 2. Critical Flicker Fusion Frequency* (decreased frequency) 3. Coordinator Test 4. Cancellation Test* (improved performance, decreased errors) 5. Standing Steadiness* (impaired performance)	(21)
chlordiazepoxide	20 mg	5 healthy male subjects 24-39 years (mean = 32), 67-83 kg (mean = 72)	performance training to plateau. Four 2-day sessions (with placebo, other drugs) each separated by 4 weeks. Double-blind, random treatment assignment. Performance assessed at several time points.	1. Adaptive Tracking Test 2. Reaction time*	(22)

TABLE A-1 (Continued)

Drug	Dose/Administration	Subject(s)	Experimental Design and Conditions	Tests	Reference
chlordiazepoxide [#]	20, 40 mg, with placebo-alcohol drink	university students 18-30 years	independent control design (between-subjects) with placebo; in drug interaction study.	"Performance measurement" tests (test not specified, but included sensory, cognitive, and motor function tests)* (impairment with 40 mg "consistent with the expected effects of a minor tranquilizer")	(23)
chlordiazepoxide [#]	20, 40 mg	21 male student volunteers	repeated measures design (within-subject); 7 test-days, with minimum 3 days between each; double-blind with randomized treatment order; placebo and other drugs included in study.	<ol style="list-style-type: none"> 1. Choice Reaction-Time Test (2 performance measures)* (significant dose-dependency) 2. Tapping Speed* (significant dose-dependent reduction) 3. Critical Flicker Fusion Frequency* (40 mg only) 4. Hand-Coordination tests (3 performance measures) 5. Standing Steadiness 6. Counting and discriminating tones 	(24)
chlordiazepoxide [#]	10 mg, three times per day, for 2 weeks (tested with placebo-alcohol drink)	20 male volunteer students, 20-23	double-blind, crossover design with treatments randomly allocated to subjects according to Latin square. On the 7th and 14th days of treatment, testing was repeated three times.	<ol style="list-style-type: none"> 1. Choice-Reaction-Time Test (2 performance measures) 2. Coordination (2 tests, 5 performance measures) 3. Divided Attention Task 	(25,26)
chlordiazepoxide [#]	15 mg, three times per day, 7 doses prior to testing; along with placebo-alcohol drink before test	18 paid volunteer medical or graduate students; 20-31 years; (6 female, 12 male)	double-blind, crossover design, treatments scheduled on a triplicated 6 X 6 random plan, with minimum 48 hours between testing and next treatment.	<ol style="list-style-type: none"> 1. Delayed Auditory Feedback [mental performance] 2. Pursuit Meter [attentive motor performance] (4 test patterns) 	(27)

TABLE A-1 (Continued)

Drug	Dose/Administration	Subject(s)	Experimental Design and Conditions	Tests	Reference
chlordiazepoxide [#]	10 mg five times in 36 hours	80 student volunteers, (40 men, 40 women)	separate double-blind cross-over designs with placebo; groups of 20 (10 men, 10 women) for drug-placebo combinations (4).	1. Actual car driving including weaving and gap estimation tasks (4 performance measures)* (driving time, gap estimation) 2. Personality assessment	(28,29)
chlordiazepoxide [#]	10 mg, t.d.s. (5 doses prior to test)	100 (50 men, 50 women), mostly students	5 groups (10 men, 10 women) for 4 drugs and double-placebo. Each subject served as his own control, taking drug and placebo on separate occasions. Order of administration randomized.	Kinetic Visual Acuity* (improved values for male subjects)	(30)
dexchlorpheniramine [#]	4 mg/70 kg	12 university students, 18-30 years	Latin square design with placebo [within drug interaction study].	"Performance measurement" tests (tests not specified, but included sensory, cognitive, and motor function tests)* (Vienna Determination Apparatus, standing steadiness)	(31)
dextro-amphetamine [#]	10 mg/70 kg b.w. + placebo-marijuana	healthy male medical and graduate students, 21-30 years (number unknown)	double-blind, randomized complete block design with placebo.	1. Wobble Board [standing steadiness] (4 tests)* (significantly improved performance in test 3) 2. Pursuit Meter [attentive motor performance] (4 tests) 3. Pursuit Meter [reaction time] (4 tests) 4. Pursuit Meter-fatigue (3 tests) 5. Delayed Auditory Feedback 6. Simple Reaction Time 7. Tapping Test 8. Peg Board (3 tests)	(32)

TABLE A-1 (Continued)

Drug	Dose/Administration	Subject(s)	Experimental Design and Conditions	Tests	Reference
dextro-amphetamine [#]	5, 10, 15 mg (per 70 kg b.w.)	12 healthy men, 21-30 years	double-blind, complete block design; 2 practice sessions.	1. Wobble Board [standing steadiness] (3 tests of performance)* (improved standing steadiness in test 2, dose related) 2. Pursuit Meter [attentive motor performance]* (improved performance in test 1, dose related) 3. Delayed Auditory Feedback	(33)
diazepam [#]	10 mg; 0.14 mg/kg, men; 0.18 mg/kg, women mean	270 healthy medical students 20-23 years; 195 men, 70 ± 8 kg; 75 women, 55 ± 5 kg	three groups, 65 men, 25 women for the three conditions, including placebo and one other drug. Measures taken before and twice after drug ingestion.	1. Nowlis adjective check list [mood assessment]* (inactivity) 2. Digit Symbol Test [concentration]* 3. Memory Test* (men) 4. Psychic functions* (women)	(34)
diazepam [#]	10 mg	5 healthy male subjects 24-39 years (mean = 32) 67-83 kg (mean = 72)	plateau performance training. Four 2-day sessions (with placebo, other drugs). Separated by four weeks. Double-blind, random order for drug treatment. Several times of performance assessment.	1. Adaptive Tracking Test* 2. Reaction Time*	(35)
diazepam [#]	6 mg	16 male, 16 female volunteer students and postgraduate workers 18-38 years	independent control design (between-subject); double-blind; 8 per group, random, equal-sexed distribution.	1. Reaction Time Test (with monitoring of physiological measures)* (EEG, auditory evoked response) 2. Tapping Rate 3. Symbol copying tests	(36)
diazepam [#]	10 mg, with placebo-alcohol drink	university students, 18-30 years	independent controls design (between-subject) with placebo; in drug interaction study.	"Performance measurement" tests (tests not specified, but included sensory, cognitive, and motor function tests)* ("psychomotor performance was slightly impaired")	(37)

TABLE A-1 (Continued)

Drug	Dose/Administration	Subject(s)	Experimental Design and Conditions	Tests	Reference
diazepam [#]	10 mg	13 male volunteers 21-29 years (mean = 23) 59-82 kg (mean = 70)	Latin square design including placebo.	1. Electroencephalogram Recording (3 variables plus frequency distribution analysis)* (significant changes observed)	(38)
diazepam [#]	10 mg + placebo-alcohol cocktail	8 healthy male student volunteers 24-30 years, 62-81.5 kg	randomized, complete block design with placebo treatment, blind for subjects and results recorder	1. Letter Cancellation Test (3 measures)* (reduced attempts) 2. Modified Osgood Test [mental state evaluation]* 3. Sorting Test 4. Flicker Fusion Frequency* 5. Time evaluation ability 6. Complex Coordination Test 7. Mirror Tracing Test (3 separate measures)* (increased total time)	(39)
diazepam [#]	10 mg with alcohol-placebo drink	220 volunteer students; 40 policemen, 37-44 years	double-blind, independent controls design (between-subject); placebo and no treatment groups included; 20 subjects per group (all students).	1. Choice Reaction Test (2 performance measures) 2. Coordination tests [Tracking Performance]* (improved performance by decreasing errors)	(40)
diazepam [#]	0, 5, 10, 20, 40 mg	6 healthy male volunteers, 33-48 years	familiarization with test procedure; randomized treatment, single blind. Each subject tested on 22 occasions at minimum 3 day intervals.	1. Critical Flicker Fusion Frequency* (dose dependent decrease) 2. Coordination* (20, 40 mg) 3. Modified Osgood Test [mental state evaluation]* (5 mg: alertness; 40 mg: inattention, inefficiency, lack of concentration)	(41)
diazepam	10 and 20 mg/70 kg b.w.	9 healthy male student volunteers, 24-30 years, 62-81 kg	randomized, complete block design with placebo treatment.	1. Heart rate 2. Heart rate variability 3. Galvanic skin responses (3 measures)* (amplitude increased, 10 mg; amplitude decreased, 20 mg; frequency decreased, 20 mg)	(42)

TABLE A-1 (Continued)

Drug	Dose/Administration	Subject(s)	Experimental Design and Conditions	Tests	Reference
diazepam	0, 10 mg or 20 mg	8 healthy male student volunteers, 24-29 years 62-80 kg	randomized, complete block design with amount of drug blind to subjects and recorder of results; 2 test-series times.	<ol style="list-style-type: none"> 1. Modified Osgood Test [mental state evaluation]* (relaxed, at ease, pleasant, unconcentrated inefficient, inattentive) 2. Time Evaluation Ability* (time estimated less than elapsed, 20 mg) 3. Letter Cancellation Test (3 measures)* (reduced attempts, decreased correct cancellations, 20 mg) 4. Sorting Test* (20 mg) 5. Flicker Fusion Frequency* (10, 20 mg) 6. Complex Coordination Test* (20 mg) 7. Mirror Tracing Test (3 separate measures)* (total time, 10, 20 mg; time spent correcting errors, 20 mg) 	(43)
diazepam [#]	0, 2.5, 5.0 mg	12 healthy volunteers	balanced design, 2 six-sided Latin squares double-blind conditions; 2 test times (morning, afternoon).	<ol style="list-style-type: none"> 1. Vigilance Test [tone detection]* (2.5, 5.0 mg in morning) 2. Short-Term Memory Test* (2.5, 5.0 mg in morning) 3. Auditory Reaction Time Test* (5.0 mg in morning) 4. Visual Search Test [random letters] 5. Tapping Test 6. Digit Symbol Substitution Test* (5 mg, morning) 7. Subjective evaluation* (impairment, 5 mg, morning) 	(44)
diazepam [#]	5 mg three times per day for two weeks	20 male student volunteers, 20-23 years	drugs (2) and placebo administered double-blind in crossover manner; treatment sequence allocated to subjects at random according to a Latin square design. Stable level of test performance achieved by prior training.	<ol style="list-style-type: none"> 1. Choice Reaction-Time Test (2 performance measures)* (improved reaction times) 2. Coordination (2 tests, 5 performance measures)* 3. Divided Attention Task 	(45,46)

TABLE A-1 (Continued)

Drug	Dose/Administration	Subject(s)	Experimental Design and Conditions	Tests	Reference
diazepam	5 mg, three times a day for one week	17 male college students	a double-blind, 2 group (8 diazepam, 9 placebo), before-after design was used. Data analyzed by computer.	Reading monitored by electrooculogram [continuous performance task sensitive to sedative-induced attentional deficits]* (impairment of several aspects of visual scanning)	(47)
diazepam [#]	10 mg each morning for 3 days	24 male students 18-24 years selected for high neuroticism	Latin square design with placebo; driving test 2nd day, lab tests 3rd day.	1. Actual car driving (29 variables)* (less readiness to brake) 2. Subjective tiredness 3. Labyrinth Test 4. Mood Ratings (3 variables)* (depression, activity) 5. Concentration Test (3 variables)	(48)
diazepam [#]	premedication: 5 mg, three times 7 days; experimental doses: 5, 10, 20 mg acute administration	42 healthy volunteers, 19-29 years	posttest only control group (between-subjects); with placebo; subjects randomly assigned to groups (7); 6 per group.	1. Simulated Car Driving with 3 performance measures 2. Physiological Functions* (skin conductance) (10, 20)	(49)
diazepam [#]	6 mg, three times a day, 7 doses prior to testing; placebo-alcohol drink included in procedure prior to test	18 paid volunteer medical or graduate students, aged 20-31 years (6 female, 12 male)	double-blind, crossover design, treatments scheduled on a triplicated 6 X 6 random plan, with minimum 48 hours between testing and commencement of next treatment.	1. Delayed Auditory Feedback [mental performance] (9 measures of performance) 2. Pursuit Meter [attentive motor performance] (4 test patterns)	(50)
diphenhydramine [#]	50 mg 0.71 mg/kg, men; 0.91 mg/kg, women	270 healthy medical students 20-23 years; 195 men, 70 ± 8 kg; 75 women, 55 ± 5 kg	3 groups, 65 men, 25 women for the 3 conditions, including placebo, and one other drug. Measures taken before (control values), and twice after drug ingestion.	1. Nowlis adjective check list [mood assessment]* (increased inactivity, sociability in women; euphoria, increased depressivity in men) 2. Digit Symbol Test [concentration]* (women) 3. Memory Test 4. Psychic functions* (men)	(51)

TABLE A-1 (Continued)

Drug	Dose/Administration	Subject(s)	Experimental Design and Conditions	Tests	Reference
dipiperon [#]	0, 20, 40 mg	21 male student volunteers	repeated measures design (within-subject) 7 test-days, with minimum 3 days between each; double-blind, randomized treatment order including placebo, and other drugs.	1. Choice Reaction-Time Test (2 performance measures) 2. Tapping Speed 3. Critical Flicker Fusion Frequency* 4. Hand-Coordination tests (3 performance measures) 5. Standing Steadiness 6. Counting and discriminating tones	(52)
ethinamate [#]	1 gr with alcohol-placebo drink	220 volunteer students; 40 policemen, 37-44 years	double-blind, independent controls design (between-subject); placebo and no treatment groups included; 20 subjects per group (all students).	1. Choice Reaction Test (2 performance measures) 2. Coordination tests [Tracking Performance]* (improved performance by decreasing errors) 3. Attention Test*	(53)
etidocaine [#]	2.6 mg/kg (intramuscularly)	11 healthy students, 9 men, 2 women. 21 ± 2.2 years, 70 ± 10 kg b.w. 178 ± 8.3 cm tall	training period allowed on test apparatus; 3 treatments (including placebo, one other drug) administered in double-blind, crossover, randomized (Latin square) manner, with 1-week intervals. Subjects tested before (control) and 3 times after each treatment.	1. Choice Reaction-Time Test (2 performance measures)* (improved performance, increase reaction times) 2. Coordination (2 tests, 5 performance measures)* (improved performance on test 2, lower mistake percentage) 3. Critical Flicker Fusion Frequency* 4. Visual Function tests (3)	(54)
flurazepam [#]	30 mg at night	6 healthy male subjects 24-39 years (mean = 32) 67-83 kg (mean = 72)	subjects trained to plateau level; drugs, placebo given in random order, double-blind; repeated measures design. Tests given 10, 13, 16, 19, 34 hours postdrug.	1. Adaptive Tracking* (impaired 10-16 hours) 2. Reaction Time* (increased up to 16 hours)	(55)

TABLE A-1 (Continued)

Drug	Dose/Administration	Subject(s)	Experimental Design and Conditions	Tests	Reference
flurazepam [#]	30 mg, every night for 2 weeks	40 paid volunteer students (33 men, 7 women)	drugs and placebo administered double-blind in crossover design. Training on test apparatus and treatment allocation by Latin square used to minimize learning effects.	1. Choice Reaction-Time Test (2 performance measures) 2. Coordination (2 tests, 5 performance measures)* 3. Divided Attention Task	(56)
flurazepam	15, 30 mg every night for one week	30 adult patients (twenty female, 10 male)	double-blind, crossover study. Two doses of drug and placebo treatment given in random order, each for a week's duration. Tests administered at end of the week.	1. Auditory Reaction Time 2. Tapping Rate* (30 mg) 3. Pursuit rotor* (30 mg)	(57)
flupenthixole [#]	0.5 mg, three times per day for 2 weeks; (tested with placebo-alcohol drink)	20 male volunteer students, 20-23	double-blind crossover design with treatments randomly allocated to subjects according to Latin square. On 7th and 14th days of treatment, testing was repeated three times.	1. Choice Reaction-Time Test (2 performance measures) 2. Coordination (2 tests, 5 performance measures) 3. Divided Attention Task	(58,59)
glutethimide	250 mg, every night for 2 weeks	40 paid volunteer students (33 men, 7 women)	drugs and placebo administered double-blind in crossover design. Training on test apparatus and treatment allocation by Latin square used to minimize learning effects.	1. Choice Reaction-Time Test (2 performance measures) 2. Coordination (2 tests, 5 performance measures) 3. Divided Attention Task	(60)
haloperidol [#]	0.5 mg 5 times in 36 hours	80 volunteer students, (40 men, 40 women)	separate double-blind crossover designs with placebo; groups of 20 (10 men, 10 women) for drug-placebo combinations (4).	1. Actual car driving including weaving and gap estimation tasks (4 performance measures)* (gap estimation by women) 2. Personality assessment*	(61,62)

TABLE A-1 (Continued)

Drug	Dose/Administration	Subject(s)	Experimental Design and Conditions	Tests	Reference
haloperidol [#]	0.5 mg t.d.s. (5 doses prior to test)	100 (50 men, 50 women) mostly students	5 groups (10 men, 10 women) for four drugs and double-placebo. Each subject took drug and placebo on separate occasions and served as own control. Order of administration randomized.	Kinetic Visual Acuity* (improved male performance, impaired female performance)	(63)
heptabarbital	0, 200, 300, 400 mg	seven healthy males, 24-39 years (mean = 32) 67-83 kg (mean = 72)	double-blind, repeated measures design; subjects trained to plateau level; multiple time points (10, 13, 16, 19, 34 hours postdrug. 4 experiments, each separated by four weeks.	1. Adaptive Tracking Task* (decrements in performance observed after all doses, up to 19 hours for 400 mg)	(64)
imipramine [#]	50 mg (salt)	24 healthy male volunteers 19-43 years (mean = 27.7) 58.2-97.7 kg (mean = 70.6)	double-blind three-way cross-over design with placebo and viloxazine; 6 per group in several individual studies; with several time point measures.	1. Reaction Time (two studies)* (Study 2, 7 hours) 2. Critical Flicker Frequency (two studies)	(65)
indomethacin [#]	50 mg + placebo-alcohol drink	50 volunteer students	double-blind, independent controls group; groups matched for age, sex, educational level, weight, living district. Placebo group, 30; drug group 20. 3 test times.	1. Choice Reaction Test 2. Coordination (2 tests)* 3. Divided Attention Test (2 measures)* (decreased number of total and correct responses)	(66)

TABLE A-1 (Continued)

Drug	Dose/Administration	Subject(s)	Experimental Design and Conditions	Tests	Reference
lidocaine [#]	200 mg; intramuscularly	30 healthy volunteer students	subjects randomly assigned to three test groups (2 female, 8 male subjects in each); 3 conditions including lidocaine, placebo, and one other drug. Training permitted on tests before drug administration. Measures taken before and three times after drug.	1. Choice Reaction-Time Test (2 performance measures)* (longer reaction times at 25 minutes) 2. Coordinative Skills and Driving Time 3. Divided Attention (2 performance measures) 4. Critical Flicker Fusion Frequency	(67)
lidocaine [#] (with adrenaline)	500 mg; intramuscularly	30 healthy volunteer students	subjects randomly assigned to three treatment groups (2 female, 8 male subjects) for placebo, lidocaine with adrenaline, and one other drug. Training permitted on tests before drug administration; measures taken before (control) and three times after drug.	1. Choice Reaction-Time Test (2 performance measures) 2. Coordination Skills and Driving Time 3. Divided Attention (2 performance measures)* (improved performance, increased correct responses) 4. Critical Flicker Fusion Frequency	(68)
lithium [#]	dose adjusted to give 0.75 meq/l for 2 weeks	20 male student volunteers, 20-23 years	drugs (2) and placebo administered double-blind in cross-over manner; treatment sequence allocated to subjects at random according to a Latin square design. Stable level of test performance achieved by prior training.	1. Choice Reaction-Time Test (2 performance measures)* 2. Coordination (2 tests, 5 performance measures)* 3. Divided Attention Task*	(69,70)
marijuana	not controlled	40 male volunteers 18-23 years (mean = 20.4)	4 groups of 10, classed as naive (control group), former smokers, habitual smokers (placebo), habitual smokers.	1. One-hole Test* 2. Rotary Pursuit Test (2 performance measures)*	(71)

TABLE A-1 (Continued)

Drug	Dose/Administration	Subject(s)	Experimental Design and Conditions	Tests	Reference
marijuana	not controlled	10 healthy male volunteers, 21-29 years occasional users of marijuana (1-2 per week or less)	each subject given marijuana and placebo according to cross-over design, 3 days apart.	<ol style="list-style-type: none"> 1. Continuous Performance Test ["A-X" task] (3 performance measures) 2. Time Estimation Test 3. Automated Digit Symbol Substitution Test (general index of performance provided by stated formula)* 	(72)
marijuana [#]	25 mcg/kg delta-9-THC (via smoking)	12 healthy male volunteers, 22-30 years, all had experienced smoking marijuana at least once previously	drug or placebo administered double-blind with treatments assigned to each subject according to randomized complete block design. Drug (2) and placebo (2) treatments given at weekly intervals. Practice sessions held for procedure familiarization.	<ol style="list-style-type: none"> 1. Modified Pursuit Meter [attentive motor performance] 2. Wobble Board [standing steadiness]* 3. Delayed Auditory Feedback [mental performance]* (impaired performance in 2 of 5 tests) 4. Manual Coordination* (impaired 1 of 5 task measures) 	(73)
marijuana [#]	25 mcg/kg THC + placebo-dextroamphetamine	healthy male medical and graduate students 21-30 years	double-blind, randomized complete block design with placebo inclusion.	<ol style="list-style-type: none"> 1. Wobble Board [standing steadiness] (4 tests)*(in 3 of 4 tests) 2. Pursuit Meter [attentive motor performance] (4 tests)* 3. Pursuit Meter (reaction time (4 tests)* (significant increase only for test 1)) 4. Pursuit Meter-Fatigue [attentive motor performance] (3 tests)*(increased scores in 2 of 3 tests) 5. Delayed Auditory Feedback 6. Simple Reaction Time 7. Tapping Test 8. Peg Board (3 tests)* 	(74)

TABLE A-1 (Continued)

Drug	Dose/Administration	Subject(s)	Experimental Design and Conditions	Tests	Reference
marijuana	0, 50, 100, 200 mcg THC per kg b.w. (via smoking)	23 social users of marijuana, 21-32 years (mean = 24)	4 X 4 Latin square design with placebo	1. Film projection driving simulator 2. Heart Rate* (50, 100, 200) 3. Visual Subsidiary Task* (50, 100, 200)	(75,76)
marijuana	70, 130, 190, 250 mcg/kg delta-9-THC (via smoking)	5 paid volunteers, 4 male and 1 female, 21-32 years, occasional users of marijuana (average twice a week)	Longitudinal repeated-measurements design with placebo and no-smoking conditions. Six experimental conditions replicated 4 times for each subject. Treatment Sequence determined by modified Latin squares design, with minimum 3 days interval between sessions and with double-blind and standard smoking conditions.	1. Simple Reaction Time (2 performance measures)* 2. Complex Reaction Time (2 performance measures)* 3. Temporal Judgment (2 performance measures)* (biphase dose effect observed) 4. Digit Symbol Substitution Test [psychomotor learning]* 5. Work Association Test*	(77)
marijuana	0, 50, 200 mcg THC per kg b.w. (via smoking)	10 male social users of marijuana 21-26 years (mean = 23.8)	repeated-measure design with placebo comparison	1. Driving film visual scanning situation in driving simulator 2. Subsidiary Task 3. Pulse Rate (8 performance measures)	(78)
marijuana	50, 100, 200 mcg delta-9-THC/kg b.w.	23 male college students 21-32 years (mean = 24) occasional marijuana users	one training and 5 experimental sessions administered in 5 X 5 Latin square design, including no-treatment and placebo conditions. Double-blind procedure.	1. Auditory Signal Detection - concentrated attention* 2. Auditory Signal Detection - divided attention*	(79)
delta-9-tetrahydrocannabinol	0, 25 mcg/kg (via smoking)	24 healthy male medical students; 21-24 years; all has smoked marijuana at least once previously	double-blind, Latin square design; treatments assigned to minimize order and learning effects; practice sessions held. Drug (2) and placebo (2) treatments given at weekly intervals.	1. Wobble Board [standing steadiness]* 2. Modified Pursuit Meter [attentive motor performance]* 3. Delayed Auditory Feedback [mental performance]* 4. Manual Coordination*	(80)

TABLE A-1 (Continued)

Drug	Dose/Administration	Subject(s)	Experimental Design and Conditions	Tests	Reference
delta-9-tetrahydrocannabinol	0.2, 0.4, 0.6 mg/kg, p.o.	20 volunteers, 21-34 years (10 men, 10 women); 10 "occasional users" of marijuana (twice a month or less); 10 frequent users (twice a week or more often)	2 groups, 5 men, 5 women, balanced for age, education level, intelligence and weight, differing only in marijuana use. Four sessions, including placebo, separated by 1-week intervals sequence randomized under double-blind conditions and standard testing procedures.	1. Color-Number Matching 2. Spiral After effect 3. Critical Flicker Fusion Frequency 4. Reaction Time* 5. Dot tests 6. Rhythm tests 7. Finger Oscillation Test 8. Halstead Category Test 9. Tactual Performance Test 10. Trail Making Test	(81)
delta-8-tetrahydrocannabinol	8.3 or 20.7 mg delta-8-THC (via smoking)	6 male casual marijuana smokers	3 test sessions: open-placebo; 2 double-blind, rotated among subjects 1 week apart. 2 subjects received 21 mg delta-8-THC (open session); measurements obtained 8 times within 5 hours.	1. Heart rate* (increased) 2. Respiration [not reported] 3. Electrocardiogram [not reported] 4. Critical Flicker-Fusion* 5. Two-Choice Reaction Time* 6. Vernier visual acuity (KVAT) [not reported]	(82)
meclastine [#]	1 mg with placebo-alcohol drink	60 university students 18-30 years	independent control design (between-subjects); with placebo; in drug interaction study; 20 subjects per group.	"Performance measurement" tests (tests not specified, but included sensory, cognitive, and motor function tests)	(83)
meprobamate	800 mg twice daily for one week	33 paid volunteer students (30 male, 3 female)	double-blind, crossover design with pretesting included. Tests administered 5 occasions in total.	1. Visual Threshold 2. Auditory Threshold 3. Digit Span Test 4. Digit Symbol Test	(84)
meprobamate [#]	800 mg twice daily for 21 or 28 days	51 university students men and women	double-blind, repeated-measures design.	51 behavioral variables including driving skills, visual acuity, steadiness, tapping rate, characteristic tempos, perception tests, kinesthetic figural after-effects plus personality variables determination "no adverse effects"	(85)

TABLE A-1 (Continued)

Drug	Dose/Administration	Subject(s)	Experimental Design and Conditions	Tests	Reference
meprobamate [#]	1,600 mg/day for 21 days	32 (15 men, 17 women) including 23 anxiety neurotic patients, 9 normal subjects	repeated-measures design with placebo comparison.	1. Driving Simulation("Auto Trainer")* (high speed reaction time) 2. Vision Tests 3. Kinesthetic Figural After-Effect 4. Tempos and Time Estimations* (improved) 5. Attention Span (Digit span) 6. Muscular Persistence 7. Anxiety Condition* (decreased anxiety and symptoms)	(86)
methamphetamine [#]	10 mg	28 undergraduate students	pre- and post-drug schedules; independent control design (between-subjects) with placebo.	1. Stroop Test* (narrowed focus of attention) 2. Witkin's Coloured Embedded Figures Test	(87)
methamphetamine [#]	15 mg/150 lb b.w.	36 healthy male students, paid volunteers in early 20's	repeated measures design (within-subject); treatment position and sequence balanced; tests occupied standard position within longer battery; 3 test-days at two-weekly intervals; double-blind with placebo and another drug.	1. Modified Stroop Test 2. Running Memory Span Test	(88)
methaqualone hydrochloride [#]	400 mg at night	6 healthy male subjects 24-39 years (mean = 32); 67-83 kg (mean = 72)	training to plateau performance; placebo, drugs given in random order, double-blind, repeated measures design. Tests given 10, 13, 16, 19, 34 hours after drug.	1. Adaptive Tracking* (enhanced performance at 34 hours only) 2. Reaction Time* (decreased at 19 hours only)	(89)
methaqualone/diphenhydramine	250 mg (methaqualone) 25 mg (diphenhydramine) [combination drug] every night for 2 weeks	40 paid volunteer students (33 men, 7 women)	drugs and placebo administered double-blind in crossover design. Training on test apparatus and treatment allocation by Latin square to minimize learning effects.	1. Choice Reaction-Time Test (2 performance measures) 2. Coordination (2 tests, 5 performance measures) 3. Divided Attention Task	(90)

TABLE A-1 (Continued)

Drug	Dose/Administration	Subject(s)	Experimental Design and Conditions	Tests	Reference
methohexital [#]	2.0 mg/kg (intra-venous anesthesia)	50 volunteer students, in early 20's	posttest only control group (between-subjects); subjects randomly assigned to drug (4) and control (1) groups, 10 per group. Training session preceded test day; test administered 2, 4, 6, 8 hours after anesthesia.	1. Sim-L-car driving simulator (12 variables measured)*	(91)
methylperone [#]	0, 10, 25, 50 mg	6 healthy male volunteers, 33-48 years	familiarization with test procedure; randomized treatment, single blind. Each subject tested on 22 occasions at minimum 3 day intervals.	1. Critical Flicker Fusion Frequency* (decreased in dose dependent fashion) 2. Coordination* (50 mg) 3. Modified Osgood Test [mental state evaluation]* (sedation after 50 mg dose)	(92)
6-(4-methyl-1-piperazinyl)morphanthridine (PLP) [#]	10 mg (every night for 2 weeks)	17 male, 3 female volunteer students 20-25 years	drugs (2) and placebo administered double-blind in cross-over manner; treatment sequence randomly allocated.	1. Choice Reaction-Time Test (2 performance variables) 2. Coordination (2 tests, 5 performance variables)* (increased mistakes in tests 1 and 2, longer driving times in test 2) 3. Divided Attention Task	(93)
nitrazepam [#]	5, 10 mg (at night)	10 healthy male paid volunteer medical students 18-20 years and 69-83 kg	2- 5 X 5 Latin squares, (each treatment preceded twice by every other treatment); double-blind, random treatment allocation with placebo and one other drug. Each subject tested five times at 14-day intervals, 9-18 hours after drug ingestion depending on fixed test schedule.	1. Card sorting (13 hour post-drug)* (5, 10 mg) 2. Electroencephalographic Effects* (5, 10 mg)	(94)

TABLE A-1 (Continued)

Drug	Dose/Administration	Subject(s)	Experimental Design and Conditions	Tests	Reference
nitrazepam [#]	10 mg at night	6 healthy male subjects 24-39 years (mean = 32) 67-83 kg (mean = 72)	subjects trained to plateau level; drugs, placebo given in random order, double-blind; repeated-measures design. Tests given 10, 13, 16, 19, 34 hours postdrug.	1. Adaptive Tracking* (impaired 10-19 hours, enhanced 34 hours) 2. Reaction Time* (increased up to 16 hours and 34 hours)	(95)
nitrazepam [#]	(a) 10 mg with alcohol-placebo drink (b) 5 mg, with alcohol-placebo drink	(a) 220 volunteer students (b) 40 policemen (37-44 years)	double-blind, independent controls design (between-subject) age variable uncontrolled; placebo and no treatment groups included; 20 subjects per group; control groups all students.*	1. Choice Reaction Test (2 performance measures)* (reaction times and accuracy in older subjects, 5 mg) [†] 2. Coordination tests [Tracking Performance]	(96)
nitrazepam [#]	10 mg (every night for 2 weeks)	17 male, 3 female volunteer students 20-25 years	drugs (2) and placebo administered double-blind in cross-over manner; treatment sequence randomly allocated.	1. Choice Reaction-Time Test (2 performance variables) 2. Coordination (2 tests, 5 performance variables)* (test 1: increased % mistakes; test 2: decreased total mistakes, increased driving time) 3. Divided Attention Task*	(97)
nortriptyline [#]	10 mg three times a day for one week, then 20 mg three times a day for one week	20 healthy male students, 20-24 years, paid volunteers	drugs (2) and placebo administered double-blind in cross-over design for 2 weeks each. On 14th day, effects of drugs tested in 2 kinds of learning situations; treatments given in random order.	1. Immediate Memory Span (2 performance measures) 2. Paired Associate Learning (2 parameters)	(98)
oxazepam [#]	0, 10, 20, 40 mg	6 healthy male volunteers, 33-48 years	familiarization with test procedure; randomized treatment, single blind. Each subject tested on 22 occasions at minimum 3 day intervals.	1. Critical Flicker Fusion Frequency* (dose dependent decrease) 2. Coordination* (40 mg) 3. Modified Osgood Test [mental state evaluation]* (10 mg: alertness; 20 mg: pleasant; 40 mg: sedation)	(99)

TABLE A-1 (Continued)

Drug	Dose/Administration	Subject(s)	Experimental Design and Conditions	Tests	Reference
pentobarbital [#]	200 mg at night	6 healthy male subjects 24-39 years (mean = 32); 67-83 kg (mean = 72)	training to plateau performance; placebo, drugs, in random order, double-blind, repeated-measures design. Tests given 10, 13, 16, 19, 34 hours after drug.	1. Adaptive Tracking* (impaired 10-19 hours, enhanced at 34 hours) Reaction Time*	(100)
pentobarbital [#]	100 mg/150 lb b.w.	36 healthy male students; paid volunteers; early 20's	repeated-measures design (within-subject), treatment position and sequence balanced; tests occupied standard position within longer battery; 3 test-days at 2-weekly intervals, double-blind with placebo and one other drug.	1. Modified Stroop Test 2. Running Memory Span Test	(101)
pentobarbital [#]	200 mg at night	6 healthy male subjects 24-39 years (mean = 32); 67-83 kg (mean = 72)	subjects trained to plateau level; drugs, placebo given in random order, double-blind; repeated-measures design. Tests given 10, 13, 16, 19, 34 hours postdrug.	1. Adaptive Tracking* (impaired 10-19 hours, enhanced 34 hours) 2. Reaction Time* (increased 10-16 hours, 34 hours)	(102)
phenylbutazone [#]	200 mg and placebo-alcohol drink	50 volunteer students	double-blind conditions; independent control groups, matched for age, sex, weight, education level, living district. Placebo group, 30; drug group, 20, 3 test times.	1. Choice Reaction Test 2. Coordination (2 tests)* 3. Divided Attention Test (2 measures)* (decreased number of total and correct responses)	(103)
prochlorperazine [#]	10 mg twice daily for 21 or 28 days	51 university students men and women	double-blind, repeated-measures design	51 behavioral variables including driving skills, visual acuity, steadiness, tapping rate, characteristic tempos, perception tests, kinesthetic figural after-effects plus determination of personality variables "no adverse effects"	(104)

TABLE A-1 (Continued)

Drug	Dose/Administration	Subject(s)	Experimental Design and Conditions	Tests	Reference
propanidid [#]	6.6 mg/kg (intravenous anesthesia)	50 volunteer students, early 20's	posttest only control group (between-subjects); subjects randomly assigned to drug (4) and control (1) groups, 10 groups; training session provided day before test; test administered 2, 4, 6, 8 hours during recovery from anesthesia.	1. Sim-L-car driving simulator (12 variables measured)	(105)
propranolol [#]	120 mg (both racemic [Inderal] and (+)-isomer tested at this dose)	16 male, 16 female volunteer students and postgraduate workers, 18-38 years, selected for stress susceptibility	independent control design, (between-subject; double-blind; 8 per group with random, equal-sexed distribution.	1. Reaction Time Test (with monitoring of physiological measures)* (decreased pulse rate) 2. Tapping Rate 3. Symbol Copying tests	(106)
secobarbital [#]	150 mg/70 kg	12 healthy male volunteers, 22-30 years, with marijuana experience	drug (2) or placebo (2) administered double-blind with treatments assigned to each subject according to randomized complete block design. Practice session held for procedure familiarization. Treatments given at weekly intervals.	1. Modified Pursuit Meter [attentive motor performance] 2. Wobble Board [standing steadiness]* (decreased performance in 1 of 4 test measures) 3. Delayed Auditory Feedback [mental performance]* [decreased performance in 2 of 5 test measures] 4. Manual Coordination* (decreased performance in 3 of 5 task measures)	(107)

TABLE A-1 (Continued)

Drug	Dose/Administration	Subject(s)	Experimental Design and Conditions	Tests	Reference
thiopental [#]	6.0 mg/kg (intra-venous anesthesia)	50 volunteer students, early 20's	posttest only control group (between-subjects); subjects randomly assigned to drug (4) and control (1) groups, 10 per group. Training session preceded test day; test administered during recovery from anesthesia at 2, 4, 6, 8 hours.	1. Sim-L-car driving simulator (12 variables measured)*	(108)
Tranquil ^{R#}	5 tablets per day (containing approximately 1.5 gr bromide salts) for 21 days	32 (15 men, 17 women) including 23 anxiety neurotic patients, 9 normal subjects	repeated-measures design with placebo comparison	1. Driving Simulation ("Auto Trainer")* (high speed reaction time) 2. Vision Tests* (near acuity) 3. Kinesthetic Figural After-Effect 4. Tempos and Time Estimations 5. Attention Span [Digit Span] 6. Muscular Persistence 7. Anxiety Condition* (decreased symptoms)	(109)
trifluoperazine [#]	2 mg 5 times every 36 hours	80 student volunteers, (40 men, 40 women)	separate double-blind cross-over designs with placebo; groups of 20 (10 men, 10 women) for drug-placebo combinations (4)	1. Actual car driving including weaving and gap estimation tasks (4 performance measures)* (driving time) 2. Personality Assessment*	(110,111)
trifluoperazine [#]	2 mg, t.d.s. (5 doses prior to test)	100 (50 men, 50 women), mostly students	5 groups (10 men, 10 women) for four drugs and double-placebo. Each subject took drug and placebo on separate occasions and served as own control.. Order of administration randomized.	Kinetic Visual Acuity*	(112)
viloxazine hydrochloride [#]	100 mg (base)	24 healthy male volunteers 19-43 years (mean 27.7) 58.2-97.7 kg (mean = 70.6)	double-blind three-way cross-over design with placebo and imipramine; 6 per group in several time point measures.	1. Reaction Time (2 studies) 2. Critical Flicker Frequency (2 studies)* (Study 2, 5 hours)	(113)

TABLE A-2

SUMMARY OF SELECTED STUDIES OF THE COMBINED EFFECTS OF DRUGS

Drug Combination (Dose)	Control Conditions	Results of Drug Combination	Reference
<u>acetylsalicylic Acid</u> (1 g)	<u>alcohol</u> (0.5 g/kg)	placebo + placebo (no drug) alcohol + placebo placebo + acetylsalicylic acid	No interaction observed. (114)
<u>amobarbital</u> (100 mg, every night for 2 weeks)	<u>alcohol</u> (0.5 g/kg, adminis- tered on morning of 7th and 14th days)	placebo + placebo (no drug) alcohol + placebo placebo + amobarbital	Enhanced impairment of eye-hand coordination but not attention or reactive skills. (115)
<u>bromvaletone</u> (0.6 g; administered evening preceding test day)	<u>alcohol</u> (0.5 g/kg; adminis- tered on test day, approximately 9 hours after drug)	placebo + placebo (no drug) alcohol + placebo placebo + bromvaletone	"Relatively strong" interaction with alcohol on attention, "perhaps due to toxic metabolites." (116)
<u>caffeine</u> (300 mg/70 kg)	<u>alcohol</u> (0.75 g/kg)	placebo + placebo (no drug) alcohol + placebo placebo + caffeine	No effect on BAC; improved reaction time, but not perceptual or motor functions. (117)
<u>chlordiazepoxide</u> (a. 20 mg, b. 40 mg; 1 hour prior to alcohol)	<u>alcohol</u> (a. 0.75 g/kg; b. 0.54 g/kg)	placebo + placebo (no drug) alcohol + placebo placebo + chlordiazepoxide	a. "Synergism" observed only in manual dexterity test among unspecified sensory, cognitive, and motor function tests. b. Antagonism of some but not all effects of alcohol (0.54 g/kg). (118)
<u>chlordiazepoxide</u> (10 mg, t.i.d. for 2 weeks)	<u>alcohol</u> (0.5 g/kg; adminis- tered on 7th and 14th days with 10 mg chlordiazepoxide)	placebo + placebo (no drug) alcohol + placebo placebo + chlordiazepoxide	Subjects unable to compensate for impaired coordination; impaired attention; increased anxiety in normal subjects. (119,120)

TABLE A-2 (Continued)

Drug Combination (Dose)	Control Conditions	Results of Drug Combination	Reference
<u>chlordiazepoxide</u> (15 mg, t.i.d. for 2 days and morning of test day)	<u>alcohol</u> (45 ml ethanol/68 kg b.w. with 15 mg chlordiazepoxide on test day)	placebo + placebo (no drug) alcohol + placebo placebo + chlordiazepoxide	No appreciable additive effect was evident. (121)
<u>chlorimipramine</u> (10 mg, t.i.d. for 7 days, then 25 mg t.i.d. for 7 days)	<u>alcohol</u> (0.5 g/kg; administered on morning of 14th day with chlorimipramine)	placebo + placebo (no drug) alcohol + placebo placebo + chlorimipramine	Chlorimipramine antagonized the alcohol-induced impairment of memory. (122)
<u>codeine (as ACC)</u> (30 mg)	<u>alcohol</u> (0.60 g/kg, with additional doses of 0.10 g/kg at 90, 150 minutes to maintain 0.06 g/100 ml BAC)	placebo + placebo (no drug) alcohol + placebo	Significant additional impairment (response time) corresponding approximately to Canadian presumptive limit (0.08 g/100 ml BAC) (123)
<u>dexchlorpheniramine</u> (4 mg/70 kg, 1 hour prior to alcohol)	<u>alcohol</u> (0.75 g/kg)	placebo + placebo (no drug) alcohol + placebo placebo + dexchlorpheniramine	No effect on BAC; in almost all tests, drug delayed recovery time from alcohol-induced impairment. (124)
<u>diazepam</u> (5 mg)	<u>alcohol</u> (0.60 g/kg, with additional doses of 0.10 g/kg at 90, 150 minutes to maintain 0.06 g/100 ml BAC)	placebo + placebo (no drug) alcohol + placebo	Significant additional impairment (response time) corresponding approximately to Canadian presumptive limit (0.08 g/100 ml BAC). (125)
<u>diazepam</u> (10 mg)	<u>alcohol</u> (0.78 ml 96% ethanol per kg)	placebo + placebo (no drug) alcohol + placebo placebo + diazepam	Reduced heart rate variability in subjects at rest, but not in stimulated subjects; other autonomic nervous indicators were not affected. (126)

TABLE A-2 (Continued)

Drug Combination (Dose)	Control Conditions	Results of Drug Combination	Reference
diazepam (10 mg; administered evening preceding test day)	alcohol (0.5 g/kg; adminis- tered on test day, approximately 9 hours after drug)	placebo + placebo (no drug) alcohol + placebo placebo + diazepam	Additive effects with alcohol on reactive and coordinative skills of subjects. (127)
diazepam (10 mg)	alcohol (0.78 ml 96% ethanol per kg)	placebo + placebo (no drug) alcohol + placebo placebo + diazepam	Increased detrimental effects on mental and psychomotor performance. (128)
diazepam (a. 10 mg; b. 10 mg; 1 hour prior to alcohol)	alcohol (a. 0.75 g/kg, b. 0.54 g/kg)	placebo + placebo (no drug) alcohol + placebo placebo + chlordiazepoxide	a. Alcohol impairment enhanced by diazepam ("synergistic" interaction). (129) b. Alcohol impairment enhanced by diazepam ("synergistic" interaction).
diazepam (a. 5, 10, 20, or 40 mg administered simulta- neously with alcohol; b. 20 mg administered 90 minutes before alco- hol.	alcohol (0.5 ml/kg b.w.)	placebo + placebo (no drug) alcohol + placebo placebo + diazepam	a. "Synergistic" effects seen with 10, 20 mg on CFFF; enhanced impairment of coordination ability: 20, 40 mg; increased lack of alertness, 20 mg. (130) b. Increased impairment compared to diazepam only, but less than simultaneous administration.
diazepam (6 mg, t.i.d. for 2 days and morning of test day)	alcohol (45 ml ethanol/68 kg b.w., administered with 6 mg diazepam on test day)	placebo + placebo (no drug) alcohol + placebo placebo + diazepam	No appreciable additive effect was evident; "synergistic" effect found in one of the tests. (131)
diazepam (5 mg, t.i.d. for 2 weeks)	alcohol (0.5 g/kg adminis- tered on 7th and 14th days with 5 mg diazepam)	placebo + placebo (no drug) alcohol + placebo placebo + diazepam	Combined effects of drugs "particularly serious" on psychomotor performance; marked impairment of information retrieval and response orientation. (132,133)

TABLE A-2 (Continued)

Drug Combination (Dose)	Control Conditions	Results of Drug Combination	Reference
<u>diphenhydramine</u> (50 mg)	<u>alcohol</u> (0.60 g/kg, with additional doses of 0.10 g/kg at 90, 150 minutes to maintain 0.06 g/100 ml BAC)	placebo + placebo (no drug) alcohol + placebo	Significant additional impairment (response time) corresponding approximately to the Canadian presumptive limit 0.08 g/100 ml BAC. (134)
<u>ethinamate</u> (1 gr; administered evening preceding test day)	<u>alcohol</u> (0.5 g/kg; administered on test day, approximately 9 hours after drug)	placebo + placebo (no drug) alcohol + placebo placebo + ethinamate	Only "very mild" interaction with alcohol. (135)
<u>flupenthixole</u> (0.5 mg, t.i.d. for 2 weeks)	<u>alcohol</u> (0.5 g/kg; administered on 7th and 14th days with 0.5 mg flupenthixole)	placebo + placebo (no drug) alcohol + placebo placebo + flupenthixole	Combination deleterious for human psychomotor skills. (136,137)
<u>flurazepam</u> (30 mg, every night for 2 weeks)	<u>alcohol</u> (0.5 g/kg; administered on morning of 7th and 14th days)	placebo + placebo (no drug) alcohol + placebo placebo + flurazepam	Significantly impaired psychomotor performance but not attention or reactive skills. (138)
<u>fructose</u> (1.2 g/kg)	<u>alcohol</u> (0.75 g/kg) [?]	placebo + placebo (no drug) alcohol + placebo	Slightly lower blood alcohol levels (attributed to delayed absorption); correlated with slight improvement in function tests. (139)
<u>fructose</u> (a. 1 g/kg simultaneously with alcohol on evening preceding test day; b. 0.5 g/kg on test day 9 hours post-alcohol)	<u>alcohol</u> (1.75 g/kg; administered on evening preceding test day)	water (no drug) alcohol only	a. Monosaccharide decreased mistakes compared to alcohol only group in choice reaction test. b. Decreased mistakes compared to alcohol, but impaired coordinative skills in hangover phase. (140)

TABLE A-2 (Continued)

Drug Combination (Dose)	Control Conditions	Results of Drug Combination	Reference
<u>glutethimide</u> (250 mg, every night for 2 weeks)	<u>alcohol</u> (0.5 g/kg; adminis- tered on morning of 7th and 14th days)	placebo + placebo (no drug) alcohol + placebo placebo + glutethimide	No significant interaction. (141)
<u>glucose</u> (a. 1 g/kg simultaneous- ly with alcohol on evening preceding test day; b. 0.5 g/kg on test day 9 hours post- alcohol)	<u>alcohol</u> (1.75 g/kg; adminis- tered on evening preceding test day)	water (no drug) alcohol only	a. Monosacharide decreased mistakes compared to alcohol only group in choice reaction test. b. Decreased mistakes compared to alcohol but impaired coordinative skills in hangover phase. (142)
<u>dextrose [d-Glucose]</u> (1.2 g/kg)	<u>alcohol</u> (0.75 g/kg) [?]	placebo + placebo (no drug) alcohol + placebo	Slightly lower blood alcohol levels (attributed to delayed absorption); correlated with slight improvement in function tests. (143)
<u>imipramine Hydrochloride</u> (50 mg salt)	<u>alcohol</u> (15 ml "whisky")	no drug pretest alcohol + placebo post test [double-blind 3-way crossover study, n=6]	Imipramine "potentiated" effects of small doses of alcohol on reaction time. (144)
<u>indomethacin</u> (50 mg)	<u>alcohol</u> (0.5 g/kg)	placebo + placebo (no drug) alcohol + placebo placebo + indomethacin	Less impairment after combination. (145)
<u>lithium</u> (0.75 meqw/liter for two weeks; drug adminis- tered with alcohol on days 7 and 14)	<u>alcohol</u> (0.5 g/kg)	placebo + placebo (no drug) alcohol + placebo placebo + lithium	Effects similar to alcohol alone on coordination; slight antagonism found in attention tests; improved reactive skills. (146,147)
<u>marijuana</u> (cigarette containing 21 mcg delta-9-THC/kg b.w.; via smoking)	<u>alcohol</u> (.03% BAC; .03 g/ 100 ml blood)	placebo + placebo (no drug) alcohol + placebo placebo + marijuana	Significant impairment as indicated by test parameters; appeared similar to low alcohol-only dose in some cases, and to low marijuana-only dose in others. (148)

TABLE A-2 (Continued)

Drug Combination (Dose)	Control Conditions	Results of Drug Combination	Reference	
marijuana (1.5 gr of 1.1% THC [by weight] via smoking at 90 minutes after alcohol, 0.5 gr at 150 minutes)	alcohol (0.60 g/kg with ad- ditional doses of 0.10 g/kg at 90, 150 minutes to maintain 0.06 g/100 ml BAC)	placebo + placebo (no drug) alcohol + placebo	Significant additional impairment (response time) corresponding approximately to Canadian presumptive limit (0.08 g/100 ml BAC).	(149)
marijuana (25 mcg/kg THC)	dextroamphetamine (10 mg/70 kg, admin- istered 1-1/2 hours before marijuana smoking)	placebo + placebo (no drug) marijuana + placebo placebo + dextroamphetamine	No significant interaction on psychomotor performance.	(150)
marijuana (25 mcg/kg THC)	secobarbital (150 mg/70 kg, admin- istered 50 minutes before marijuana smoking)	placebo + placebo (no drug) marijuana + placebo placebo + secobarbital	No significant interaction on motor coordination, manual coordination, and mental performance; simple "additive decrements in motor and mental performance results."	(151)
delta-9-tetrahydrocan- nabinol (25 mcg/kg THC)	cannabidiol (CBD) (150 mcg/kg CBD)	placebo + placebo (no drug) THC + placebo placebo + CBD	Psychomotor impairment due to THC was not significantly altered by simultaneous administration of CBD, but a trend indicating a decrease in THC-like effects was observed.	(152)
meclozine (1 mg, 1 hour prior to alcohol)	alcohol (0.54 g/kg)	placebo + placebo (no drug) alcohol + placebo placebo + meclastine	No effect on BAC; no significant modification of alcohol- induced impairment of psychomotor performance.	(153)
meprobamate (7, 14, 21, 28 mg/kg)	alcohol (0.25, 0.50, 0.75, 1.0 g/kg)	placebo + placebo (no drug) alcohol + placebo placebo + meprobamate	Worst performance occurred after higher doses of drugs in combination; impossible to characterize results of drug combinations as additive, potentiative, synergistic, or antagonistic.	(154,155)

TABLE A-2 (Continued)

Drug Combination (Dose)	Control Conditions	Results of Drug Combination	Reference
<u>methaqualone- diphenhydramine</u> (250 mg - 25 mg, every night for 2 weeks)	alcohol (0.5 g/kg; adminis- tered on morning of 7th and 14th days)	placebo + placebo (no drug) alcohol + placebo placebo + methaqualone- diphenhydramine	No significant interaction. (156)
<u>methylperone</u> (a. 10, 25, or 50 mg administered simultane- ously with alcohol; b. 25 mg administered 150 minutes before alcohol)	alcohol (0.5 ml/kg b.w.)	placebo + placebo (no drug) alcohol + placebo placebo + methylperone	a. No alcohol enhancement of depressive effects (CFFF, coordination, mood). b. Slightly less effect compared to simultaneous administration. (157)
<u>6-(4-Methy-1-piperazin- yl)-morphanthridine (PLP)</u> (10 mg every night for 2 weeks)	alcohol (0.5 g/kg, on morning of 7th and 14th day of treatment)	placebo + placebo (no drug) alcohol + placebo placebo + PLP	Enhanced impairment observed 30 minutes following morning administration of alcohol. (158)
<u>nitrazepam</u> (a. 5 mg, b. 10 mg; administered evening preceding test day)	alcohol (0.5 g/kg; adminis- tered on test day approximately 9 hours after drug)	placebo + placebo (no drug) alcohol + placebo placebo + nitrazepam	a. Significant additive effects in older subjects (com- pared to young subjects in control group). b. Slightly enhanced alcohol-induced impairment of attention, but not reactive or coordinative skills in young subjects. (159)
<u>nitrazepam</u> (10 mg every night for 2 weeks)	alcohol (0.5 g/kg, on morning of 7th and 14th day of treatment)	placebo + placebo (no drug) alcohol + placebo placebo + nitrazepam	Enhanced impairment observed. (160)
<u>nortriptyline hydrochloride</u> (10 mg, t.i.d. for 7 days, then 20 mg, t.i.d. for 7 days)	alcohol (0.5 g/kg; adminis- tered on morning of 14th day with nor- triptyline)	placebo + placebo (no drug) alcohol + placebo placebo + nortriptyline	Significantly increased errors in paired associate learning test, but not memory test, compared to double- placebo group only. (161)

TABLE A-2 (Continued)

Drug Combination (Dose)	Control Conditions	Results of Drug Combination	Reference
<u>oxazepam</u> (a. 10, 20, or 40 mg administered simultaneously with alcohol; b. 40 mg administered 150 minutes before alcohol)	<u>alcohol</u> (0.5 ml/kg b.w.)	placebo + placebo (no drug) alcohol + placebo placebo + oxazepam	a. Alcohol significantly enhanced depressive CFFF effect 10 mg, but did not alter coordination or mood ratings. b. Significantly less pronounced effect than simultaneous administration. (162)
<u>phenobarbital</u> (32 mg)	<u>alcohol</u> (0.60 g/kg, with additional doses of 0.10 g/kg at 90, 150 minutes to maintain 0.06 g/100 ml BAC)	placebo + placebo (no drug) alcohol + placebo	Significant additional impairment (response time) corresponding approximately to Canadian presumptive limit (0.08 g/100 ml BAC). (163)
<u>phenylbutazone</u> (200 mg)	<u>alcohol</u> (0.5 g/kg)	placebo + placebo (no drug) alcohol + placebo placebo + phenylbutazone	Combined effects were "very deleterious" on attention and coordinative skills. (164)
<u>viloxazine hydrochloride</u> (100 mg base)	<u>alcohol</u> (15 ml "whisky")	no drug pretest alcohol + placebo posttest [double-blind 3-way crossover study, n=6]	Viloxazine did not "potentiate" effects of small doses of alcohol on reaction time. (165)

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APPENDIX B

RELATIONSHIPS BETWEEN THE CONCENTRATIONS OF
DRUGS IN BIOFLUIDS AND THEIR EFFECTS:
THE STATE OF KNOWLEDGE

RELATIONSHIPS BETWEEN THE CONCENTRATIONS OF DRUGS IN
BIOFLUIDS AND THEIR EFFECTS:
THE STATE OF KNOWLEDGE

The basic purpose of research on drugs and highway safety is to define the role of drugs in the causation of traffic crashes. This report has stressed the need for an adequate definition of the problem with studies using epidemiologic and experimental approaches. The definition of any problem proceeds from reliable, objective measures of variables chosen for its study. Before the relationship between drugs and highway safety can be defined, such measures must be identified to describe the effects of drugs on driving performance--both in the field and in the laboratory. One such measure, common to both epidemiology and experimentation in drugs and driving, is the concentration of drug present in biofluids.

This report has emphasized that the **presence** of drugs in biofluids does not in itself suffice as a measure of their effects. Qualitative findings of the incidence of drugs in populations of drivers, therefore, do not describe the degree of their influence on measures of driving performance. The concentration of drug (or drugs) present, expressed as units of mass per unit volume of blood or other body fluid (e.g., 0.05 mg/ml), may indicate the degree of effect. So the quantitative determination of drugs in biofluids is essential to any program to define the problem of drugs and driving.

This appendix concerns research to relate the concentration of drugs in biofluids to their effects on measures of human performance. Three main topics are discussed. The first topic is the relevance of these kinds of studies to drug and driving research. The second topic, the requirement for methodology to analyze biofluids for drugs, develops from the first. The last topic is the state of knowledge of relationships between the levels of drugs in biofluids and their effects. A review of the literature includes effects on human performance related to driving itself as well as

effects on other behavioral and clinical variables.

B.1 Drug Concentration as a Measure of Drug Effect

The influence of the alcohol-highway safety experience is pervasive in any discussion of drugs (other than alcohol alone) and highway safety, but it may be strongest where the significance of drug levels is considered. Not only is ethanol in the form of alcoholic beverages the most widely and frequently used drug, but it was for ethanol that blood concentrations were established in law as an objective measure of driver impairment.

The general acceptance of drug levels in blood as a measure of effect stems from basic principles of pharmacology (Fingl and Woodbury 1975). Just as the blood carries oxygen to the tissues, so the blood transports drugs to their sites of action. Drug effects, whether cellular or behavioral, are believed to result from the interaction of the drug with tissue receptors. Two assumptions are made: (1) that a drug's effects at the cellular level in an organism are proportional to its concentration at the site(s) of action; and (2) that the concentration of drug in the blood relates directly to the drug's concentration at its site of action. For the most part, the physical sites of drug action remain uncharacterized, and except for such global localizations as the "central nervous system," unspecified as well. In addition, since no drug has only one effect, more than one type of action may be presupposed for all drugs. In man, the sites of drug action are inaccessible to direct study. Thus, drug concentration in the blood remains the closest, **directly measurable** chemical correlate of drug effect.

A drug's concentration in body fluids other than blood may also be used as chemical correlates of its effects. Often mentioned in this regard is saliva, which can be obtained from research subjects by noninvasive techniques, an advantage in both epidemiologic and experimental studies. For other body fluids (including breath) to replace blood as the preferred specimen, one of two basic requirements must be met:

1. A drug's concentration in the body fluid must be directly proportional to its concentration in blood; or

2. A drug's concentration in the body fluid must be as (or more) highly correlated with the magnitude of the drug's behavioral effects over the time course of its action.

The measurement of alcohol (i.e., ethyl alcohol, ethanol) in breath illustrates this point. Because of its *chemical properties*, alcohol diffuses across small blood vessels and enters the alveoli, the smallest air cells in the lung. Because of its rate of diffusion and its volatility, alcohol equilibrates rapidly between blood and air, and the concentration of alcohol in the exhaled deep lung air is directly proportional to its concentration in the blood passing through the lung. This physiological fact became the basis for breath testing devices that measure (indirectly) the concentration of alcohol in the blood.

Few other drugs of interest in highway safety possess the physiochemical properties of alcohol. It is unlikely that concentrations of many other drugs will be so easily detected and quantified in breath. Ongoing research has been studying other body fluids—in particular, saliva (Mucklow et al. 1978)—for their usefulness in estimating the blood concentrations of some drugs. But until one or other of the two requirements above are satisfied, blood remains the specimen of choice for indicating influence of drugs on behavior. One of the problems in the area of research, however, is that even blood concentrations of drugs other than alcohol may not be good chemical correlates of their behavioral effects.

Nevertheless, in a legal sense, alcohol has become the prototypic drug. Significant precedents were set when blood-alcohol concentration (BAC), as determined by chemical tests, was made legally admissible as evidence of driver impairment. Later, the concept of the **presumptive limit** was introduced. In 1956, the National Safety Council Committee on Alcohol and Drugs (then named the Committee on Tests for Intoxication), recommended that the Uniform Vehicle Code be revised to state that, if a person's BAC were 0.15% w/v or more, that person would be presumed to have been under the influence of intoxicating liquor. Under this presumption, the burden of proof shifts to the defendant, who may then introduce evidence to support a contention that he was not, in fact,

"under the influence." In 1960, the Committee recommended the presumptive limit for alcohol be reduced to 0.10% w/v; in 1971, "the Committee took the position that 'a concentration of 80 milligrams of ethanol per 100 milliliters of whole blood (0.08 percent w/v) in any driver of a motor vehicle is indicative of impairment in his driving performance'" (National Safety Council 1978, p.19). (Earlier, Utah had lowered its presumptive limit to 0.08% w/v; most states still have a presumptive limit of 0.10% w/v.)

Some states have passed "per se" laws, which make it illegal to drive with a BAC exceeding a statutory limit, e.g., 0.10% w/v. The U.S. Department of Transportation's 1968 report to Congress on alcohol and highway safety discussed the advantages of this approach:

Such a statute eliminates the concepts of intoxication or impairment of driving ability altogether. Once the prohibited blood alcohol concentration has been competently put into evidence, the defense lawyer may only attach the correctness of the evidence, and should seldom succeed where the system employed has been carefully established. Overly sympathetic juries can be restrained by strict instructions to convict if the laboratory evidence is found to be valid. Trials can be shorter, saving the resources of police who would otherwise act as witnesses, and of the courts themselves. (U.S. Department of Transportation 1968, p.122)

Ten states, led by Nebraska, have "per se" laws.

Throughout the United States, therefore, BAC has been established as legal evidence of driving impairment. Apart from its establishment in law, the relationship of BAC and driving impairment was secured in the public mind by the results of experimental and epidemiological studies. This relationship is not exact due to operation of such modifying variables as driver skill, physiological tolerance, and environmental factors. However, continued support has been forthcoming to justify the establishment of a given BAC as indicative of driver impairment (e.g., Evans et al. 1974).

Nevertheless, alcohol may be a special if not unique drug in the

pharmacological sense. Ethyl alcohol is a small, simple molecule. It is absorbed from the digestive tract rapidly and is evenly distributed in the total body water at equilibrium. It is primarily eliminated by metabolism in the liver. Moreover, "it has been repeatedly demonstrated that there is a close correlation between the concentration of ethanol in the central nervous system and the qualitative and quantitative effects of alcohol on the body. Essentially the same correlation exists between the concentration of alcohol in other body fluids and its effect on the brain" (Forney and Forney 1975).

In contrast, it is recognized that there are literally hundreds of drugs that may have detrimental effects on driving. These drugs represent dozens of diverse chemical structures with distinct pharmacological properties and innumerable physiological, psychophysical, and psychological effects. Few if any drugs behave as simply in the human body as does ethanol. Generally absorbed, they distribute differently in the body tissues than ethanol does. They too are metabolized by the liver, but, unlike alcohol, are eliminated mostly by urinary excretion.

Curry (1975) discussed the effects of drugs and their quantitation in body fluids. He summarized the consequences of differences between alcohol and other drugs:

In the clinical interpretation of the effect of a drug on a person, three separate relationships may be considered. Firstly, there is the relationship between dose and effect; generally speaking, a small dose will not kill the person; a large dose will. Secondly, there is the relationship between the dose and the level of the drug in the blood. This is a relationship which applies in some cases but not in others. Finally, there is the relationship between the level of drug in the blood and the effect; again this relationship does not hold in a large number of cases. Because most of these relations hold for alcohol, it is very tempting for the layman or the lawyer to believe that the same criteria hold for other drugs, but it must be emphasized that generally that is not so.

Scientists and doctors have produced statistical evidence in

relation to the absorption, distribution, systematic circulation and excretion of alcohol, which allows valid conclusions to be drawn and allows those responsible for traffic safety to take effective action. As far as drugs are concerned, the picture is highly complex and each individual drug must be considered separately. It is necessary to show that there is some relationship between concentrations of a particular drug in body fluids and accident involvement. Whether one measures blood or urine concentrations, there are analytical difficulties which are far more intense than those met in the case of alcohol, and clearly breath analyses are out of the question. How the body deals with drugs must be viewed not as an overall concept, but each drug must be looked at individually. (p. 479-80.)

The aim is to describe quantitatively a drug's effect in terms of its concentration in, for example, the blood. Most commonly this requires an experimental approach where the concentration of drug becomes an independent variable. Essential for such studies is the analysis of biofluids to measure actual concentrations attained after given doses of a drug. The relevance of this approach to research in highway safety is discussed below.

B.2 Applications in Highway Safety of Knowledge of Relationships Between the Concentration and Effect of Drugs

Information about the relationship between drug concentration and effect is required for determining the role of drugs in traffic crashes. This information would also be needed for establishing objective legal criteria of driver impairment by drugs other than alcohol alone. Three general areas require the measurement of drug effects in terms of drug levels in the blood:

- epidemiology,
- experimentation, and
- countermeasures.

Table B-1 summarizes the information needs and utilization of data

establishing drug concentration-effect relationships.

Epidemiology in drugs and driving involves identifying significant accident risk factors. Actual accident risk due to the use of drugs by drivers can be established from studies in which the body fluids of accident- and non-accident-involved drivers are examined for the presence of drugs. Limited research funds combined with the relatively low incidence of drugs other than alcohol may preclude the classical approach in epidemiology: establishing statistical overrepresentation as a precise, quantitative indicator of increased accident risk due to any one drug. Increased reliance on the known significance of drug levels in blood may be required to adequately assess the influence of particular drugs in traffic crashes.

How various drugs are used may also be indicated by drug-concentration data obtained in field surveys. The specification of target groups for countermeasure activity may also result from epidemiological research. Correct data interpretation based on threshold values for drug impairment or toxicity could lead to identification of high-risk drug user groups, including those evidencing multiple drug ingestion.

Experimental research in drugs and highway safety seeks to identify drugs with high potential for increased accident risk. Ideally, efforts made in this research area result in drug concentration-effect relationships described in terms of behavior functions important in the real-life driving situation. Short of this, estimates of risk potential might be made, for example, on the basis of values analogous to the "therapeutic index" of drugs. The precise definition of therapeutic index is given below:

$$\text{Therapeutic Index (TI)} = \frac{LD_{50}}{ED_{50}}$$

where LD_{50} is a dose of drug that results in the death of 50% of an animal test group; and ED_{50} is a dose that results in the production of (desired) drug effects in 50% of a comparable animal test group. Since this sort of determination is performed in species other than man, such as

TABLE B-1

THE MEANING OF DRUG LEVELS IN BIOFLUIDS:
 INFORMATION NEEDED IN RESEARCH ON DRUGS AND HIGHWAY SAFETY

Area of Highway Safety	Information Needs	Information Utilization
Epidemiological Research	Threshold values for driver impairment by drugs.	Identification of drugs as risk factors in traffic crash causation.
Experimental Research	Drug concentration-effect relationships in terms of relevant behavior measures; estimates of accident risk in terms of relative drug concentration.	Identification of drugs with high potential risk.
Countermeasures	Threshold values for driver impairment by drugs.	Citation of drivers for driving under the influence of drugs.

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the rat or dog, the therapeutic index is necessarily approximate for humans beings. However, the higher this ratio, the safer a drug is considered for use. A similar approach may be taken in experimental research directed specifically toward the determination of threshold impairment values for drugs:

$$\text{Driver Impairment Index} = \frac{\text{threshold drug concentration for behavior impairment}}{\text{threshold drug concentration for therapeutic effects}}$$

Performance impairment may occur at drug concentration greater than (ratio greater than 1.0), equal to (ratio = 1.0), or below (ratio less than 1.0) concentrations required for therapeutic effects. The lower this ratio for a drug, the more likely the drug has a potential to increase the risk of traffic crash. Preliminary data indicating concentration-effect relationships for various drugs of interest are required in this approach to determine drug risk potential. Experiments to establish the range of threshold impairment should be designed to include the concentration of drugs in biofluids as independent variables.

In order to **develop drug countermeasures** based on the detection and quantitation of drugs in body fluids, criteria of impairment must be specified. Statutes that proscribe driving under the influence of drugs may require the legal establishment of threshold drug concentrations demonstrated to produce driver impairment. Scientific data resulting from experimental or epidemiologic research may provide the basis for this countermeasure approach. Whatever the source of data, accurate knowledge of drug concentration-effect relationships and the possible influence of background variables (e.g., presence of alcohol or medical condition) is needed prior to implementing these kinds of countermeasures. Another prerequisite is methodology to detect and quantify drugs in biofluids. The role of drug analysis in determining the influence of drugs in highway traffic crashes is discussed in the following subsection.

B.3 Application of Drug Analytical Methodology in Drugs and Highway Safety

The research requirements in highway safety for drug analytical methodology vary with the intended application. Three major areas that involve the analysis of body fluids for drugs are:

- Epidemiological Research
- Experimental Research
- Countermeasure Research

Table B-2 summarizes the types of methodology required and the information output resulting from the application.

Epidemiological research requires development and use of drug screening systems to determine the nature and extent of drug use by drivers. Such systems used for exploratory research must be capable of detecting, identifying, and quantifying a wide range of drugs of interest and their principal metabolites. The need for accurate, quantitative data requires use of confirmatory methods developed to measure particular drugs and their metabolites. In some cases, such as those of cocaine and heroin, metabolite determination may be required to detect use of the parent substance. Analytical methods are also required to confirm nonspecific, drug-positive results, especially those resulting from immunological techniques.

Requirements of experimental research on drug effects reflect the laboratory control of variables related to the type and amount of drug present in body fluid samples. In general, reliable, sensitive methods, usually developed specifically for the drug under study, are used. The simultaneous detection and quantitation of both the drug and its important metabolites may require highly specialized procedures. For pharmacokinetic studies, especially after acute dosage with therapeutic amounts of drugs, quantitative techniques described as "ultrasensitive" are often needed.

Countermeasure research involves the identification, development, demonstration, evaluation, and implementation of programs designed to deal with an identified problem. Countermeasure programs, whether legal or informational, will undoubtedly require improved analytical capability. To detect most drugs that can impair driving may require screening systems similar to that described for epidemiological purposes.

TABLE B-2

REQUIREMENTS FOR ANALYTICAL METHODOLOGY IN RESEARCH ON DRUGS AND HIGHWAY SAFETY

Area of Highway Safety	Methodology Requirements	Information Output
Epidemiological Research	General drug screening systems utilizing reliable techniques with adequate sensitivity for a broad range of drugs and their metabolites in biological fluids.	Prevalence of drugs in drivers.
Experimental Research	Quantitative-confirmatory methods for specific drugs detected in body fluids.	Type and amount of drugs present in drivers.
Experimental Research	Specific and ultrasensitive methods with excellent reliability for the determination of specific drugs and their metabolites.	Drug concentration-effect relationships in behavior studies.
Countermeasures	(Limited) drug screening capability with sensitivity requirements stipulated by presumptive limits.	Pharmacokinetic data Drug metabolite pattern identification.
Countermeasures	Quantitative confirmatory methods which meet established forensic standards.	Evaluative data on countermeasure effectiveness. Legal evidence of driver impairment by drugs.

Alternatively, the analyzing of body fluids for drugs may be limited to a group of designated drugs, corresponding to the focus of the countermeasure effort. Should presumptive limits be established for some drugs, the methods chosen for drug analysis will have to meet forensic standards for reliability and precision.

B.4 Experimental Determination of Drug Concentration-Effect Relationships

The experimental literature on the relationships between the concentration of drugs in biofluids and their effects includes both animal and, to a much lesser extent, human studies. We are, of course, interested in measures of human performance related to highway safety, so the latter group of studies is the basis for this review. But many of the principles applied in human studies flow from an understanding obtained with animals. In particular, many of the variables known to influence concentration-effect relationships have been identified through studies with animals.

The experimental determination of drug concentration-effect relationships is beset by the phenomenon of intersubject variability. Both fundamental parameters--drug concentration in blood and the behavioral measure itself--vary considerably after administration of a single, standard dose of drug to a group of subjects. This problem is not confined to behavioral pharmacology but is also found in clinical studies. Variability in the concentration-effect relationship for a given drug is a source of concern for those in applied fields who desire to use objective measures of drug effects. If necessary in highway safety, the development of legal countermeasures would depend on the identification of reliable indices of driver impairment due to drugs. The indices may be behavioral or chemical, of course.

In contrast to alcohol, the relation of concentration to effect for other drugs is relatively complex. In this subsection, variables that influence drug concentration-effect relationships are identified. General patterns in the time-based relation of blood concentration to effect intensity are then described.

B.4.1 Background Variables Influencing the Experimental Determination of Drug Concentration-Effect Relationships. Many variables that can influence drug concentration-effect relationships have been identified (Sellers 1975a; Fingl and Woodbury 1975; Sellers 1975b; Curry 1975; Jusko 1975; Curry 1974; Glassman and Perel 1974). Some experimental sources of statistical variance are summarized in Table B-3. The variables are typed according to general classifications. Although termed "variables," many of these factors lie well beyond systematic variation in the experimental setting. Even a casual glance at Table B-3 will confirm that the range of variables alone defies complete experimental control. They range from the molecular (sites of drug action, metabolism) to the social (subject interactions), and from the physical (drug measurement, extraction efficiency) to the psychological (personality, motivation). While distinctions have been made, the variables cannot be considered separate and noninteractive. For example, many pharmacokinetic parameters are altered by physiologic and pharmacologic factors, such as the physicochemical nature of the drug and the medical condition of the subject (Fingl and Woodbury 1975; Jusko 1975).

The nature and number of variables present great difficulties in experimental determination of concentration-effect relationships. First, it is not known a priori which of the variables will significantly influence the results of the experiment. This will depend on the drug and the effect under study. As noted previously in this report, the determination of drug concentrations in the experimental study of behavioral effects has been exceptional rather than the rule. This has resulted in a current lack of information on which to base the design of future experiments along these lines. Second, many of the variables operate indeterminately in the real world, where the experimental results must be applied. As a consequence, the laboratory simulation of real-world events or processes presents a fundamental dilemma. If strong, active variables are not controlled, the precision of behavioral testing may decrease, rendering insignificant the behavioral changes produced by a drug in a group of subjects. Conversely, "the effect of controlling extraneous or irrelevant

TABLE B-3
 VARIABLES THAT CAN INFLUENCE THE EXPERIMENTAL DETERMINATION
 OF DRUG CONCENTRATION EFFECT RELATIONSHIPS

Classification	Type of Variable	Specific Example
DRUG	Physicochemical properties	Partition coefficient
	Dosage form	Bioavailability
	Chemical structure	Susceptibility to biotransformation Receptor affinity
PHARMACOKINETICS	Absorption	Route of drug administration Gastric contents (and rate of emptying)
	Distribution	Volume of distribution Serum protein and tissue binding and storage Enterohepatic circulation Localization of active drug
	Biotransformation	Impaired hepatic function Rate of active metabolite formation First-pass metabolism
	Elimination	Rate of excretion of drug or active metabolites Daily fluctuations
SUBJECT: Physiological	Biological variation	Metabolic differences (genetic, environmental) Hyperreactivity (or hyporeactivity)

TABLE B-3 (Continued)

Classification	Type of Variable	Specific Example
SUBJECT: Physiological	Physical characteristics	Body weight Age Sex
	Medical condition	Clinical diagnosis
	Physiological state	Acid-base status Fatigue Sleep deprivation Tolerance (due to prior drug use, e.g., alcohol) Adaptation (due to repeated drug tests)
SUBJECT: Psychological	Personal characteristics	Education level Attitude
	Personality	Risk-taking Placebo reactance
	Motivation	Ability to compensate for drug effect
EXPERIMENTAL	Test characteristics	Cognitive complexity <u>Sensitivity</u> (to specific drug's effect) <u>Specificity</u> (for a given drug effect)

TABLE B-3 (Continued)

Classification	Type of Variable	Specific Examples
EXPERIMENTAL	Design of experiment	Mode of drug administration (acute v. chronic) Time of testing Drug dosage Setting Subject interactions Body fluid sampling (site, time)
	Behavioral phenomena	State-dependent learning Practice effects Acute tolerance
ANALYTICAL	Drug concentration	Total, bound or free drug in blood Metabolite or other chemical interference
	Test procedure	Method of body fluid sampling Extraction efficiency
	Test characteristics	Accuracy Precision Specificity "Appropriateness" of internal standard
	Laboratory performance	Skill of technician Performance variation

variables in the laboratory is to increase the precision of an experiment but at the risk of discovering effects so small that they are of no practical importance" (Chapanis 1967, p. 557). Thus, concentration-effect relationships cannot be easily determined in the laboratory setting due to intersubject variability and cannot be readily extrapolated to the context of real-world driver impairment.

B.4.2 General Drug Concentration-Effect Relationships. Despite the possible action and interaction of background variables, attempts have been made to characterize concentration-effect relationships for psychoactive drugs. Curry (1974) has described some general relationships that can result from the combined features of drug, effect (and its measurement), and disease state (when studied):

They can occur as direct relationships, with changes in effect exactly following changes in concentrations. Other types--indirect relationships--can involve peaking of the effect **before** the peak in concentration is reached. This will occur when, soon after dosing, the drug is localized preferentially in that area of the body where the sites of action are, the blood samples being collected from another area. It will also occur if the drug effect is a function of the rate of rise of the concentration at its site of action, rather than of absolute concentration, or if compensatory reflexes act rapidly to reverse the effect of the drug, or if other forms of tolerance act equally rapidly. A third type of relationship involves the **peak effect occurring after** the peak concentration in plasma. This occurs when a drug is carried relatively slowly to its site of action, or when the effect is mediated by an active metabolite, or when the recorded effect is not the primary pharmacologic effect, being instead an observable result linked to the primary effect by a chain reaction requiring several hours or days to transmit the signal. (p. 192-3.)

To these relationships may be added others:

- nonmonotonic relationships, where the primary effect is

reversed with increasing blood concentration (e.g., Ashford and Carpenter 1975; Asburg 1974),

- qualitative changes in drug effect with increasing blood concentrations (Fingl and Woodbury 1975), and
- inverse linear relations (Kragh-Sorensen, Asbert, and Eggert-Hansen 1973).

The **types** of concentration-effect relationships may vary within a single therapeutic class of drugs. Glassman and Perel (1974) reviewed four separate studies that attempted to relate plasma levels of tricyclic antidepressants to clinical outcome. In each of the four studies, a different relationship was found. The authors attributed these results to two underlying methodologic problems: the apparent discrepancies may have been due to "heterogeneity of the depressive population" (subject characteristics) and "individual variability in plasma protein binding" (pharmacokinetics). These were clinical studies, in which the outcome variables may be far removed from the drug's primary effects. But in many ways, analogous methodologic issues apply to the investigation of drug-involved accidents. Some outcome variables (driver error, culpability) along with their attendant factors (like information processing) are often as difficult to measure as certain clinical conditions, such as depression. Thus, the analogy to disease in the epidemiology of drug-involvement in highway safety may not be far removed. Certainly, this seems to be the case in characterizing the influence of drugs in accident causation.

This section has described the **general** nature of drug concentration-effect relationships. In general, they are not as direct as they are for alcohol and are subject to considerable variation. The following subsection briefly reviews experimental and epidemiological studies in which "drug concentration" in body fluids was related to outcome variables.

B.5 "Drug Concentration" as a Parameter in the Correlation of Drug Presence with Observed Effect(s)

Reports in which relevant aspects of human performance are correlated with drug concentration measurements range from those in

which drug levels were determined incidentally and only approximately at the time of behavioral testing, to those in which careful and frequent measures of both drug levels and behavioral parameters were obtained. Rarely, a study has been performed solely to evaluate the **applicability** of drug-concentration data to the **assessment** of drug effects. Unfortunately, most studies of this latter type are clinical in nature, and often relate only very indirectly to driver behavior and driving performance. However, they do provide some indication of how useful drug concentration data can be in respect to tests of drug effects.

B.5.1 Experimental Studies. The most useful reports in the literature are studies that attempt to characterize a drug's concentration-effect relationship in behavioral terms related to the driving task. However, like most behavioral drug research, the behavioral measures utilized have been rarely evaluated for their degree of relevance to real-world driving performance, and the results obtained are only indicative, not definitive. On the other hand, the type or reliability of a concentration-effect relationship for a given drug can be established, often for several measures of behavior simultaneously.

The most prevalent and **least** useful studies determine drug concentrations in subjects more or less while measuring drug effects on behavior. Many of these studies report the effects of chronic administration of drugs along with weekly determinations of serum drug concentrations (Horns, Rado, and Goldstein 1975; Saario and Linnoila 1976; Linnoila et al. 1975; Linnoila, Saario, and Maki 1974; Saario, Linnoila, and Maki 1975). Such studies may be useful for indicating the effects of drug cumulation, if present, as well as differences in the effects of acutely and chronically administered drugs. For example, in one study, increases in the plasma level of chlordiazepoxide and its active metabolite after two weeks' treatment were associated with increased subjective reports of impaired performance and evidence for compensation in a coordination task (Linnoila et al. 1975). In the same study, it was found that **chronically** administered flupenthioxole did not impair performance on a divided attention task, while in a previous study using the same test system, **acute** doses of flupenthioxole **did** impair performance (Linnoila

1973b). Chronic administration of nitrazepam, a benzodiazepine hypnotic that was shown to accumulate significantly in the serum of subjects, resulted in decreased coordination and attention (Saario, Linnoila, and Maki 1975), whereas acute doses nitrazepam impaired only attention (Linnoila 1973a). The primary emphasis in this type of study is clearly on the behavioral effects of the drugs, and not the correlation of drug concentrations with human performance measures. At best, they provide a rough estimate of the drug levels attained during chronic administration and intersubject variability, along with measures of the drug's effects.

Studies have been reported in which two or three serial determinations of drug concentrations in blood were made in conjunction with behavioral testing after acute drug administration (Korttila 1974; Korttila, Hakkinen, and Linnoila 1975; Linnoila, Seppala, and Mattila 1974; Haffner et al. 1973; Morland et al. 1974). Correlations between drug concentration and effect have also been attempted when two or more doses of the same drug are used in a study (Haffner et al. 1973; Borland and Nicholson 1974). For diazepam, where small numbers of subjects were used and large interindividual differences in drug concentration resulted from the administration of a fixed dose, meaningful concentration-effect correlations could not be made (Haffner et al. 1973; Morland et al. 1974). The short-term effects of local anesthetics were correlated with blood levels following intramuscular administration, but such relationships can be questioned in light of known arterial-venous blood differences in drug concentration (Korttila 1974; Korttila, Hakkinen, and Linnoila 1975). For antipyretic analgesics, comparisons at three time points led to the conclusion that "generally, the strongest impairment of performance after phenylbutazone or indomethacin coincided with the highest serum levels of these drugs" (Linnoila, Seppala, and Mattila 1974, p. 483). Borland and Nicholson (1974) studied the residual effects of heptabarbitalone (200, 300, and 400 mg) in seven subjects:

The dose related effects of impaired performance and persistence of impaired performance suggest that adaptive tracking is a valuable technique in the determination of the residual effects of hypnotics. Though performance measures

and blood heptabarbital concentrations for each dose gave a relationship between decrement in performance and blood concentration ($P = 0.01$), this relation **did not apply** to individual blood levels and individual performance measures. This could indicate that blood levels of heptabarbital do not provide a means of predicting performance decrements. (p. 214, emphasis added.)

More intensive investigations are illustrated by the following studies of psychoactive drugs.

In a study of acutely administered diazepam and its clinical effects (including coordination, mental arithmetic, and sleepiness), it was demonstrated that the **clinical** effects and serum concentrations ran parallel. Although the sample was small and the variations of individual response and drug levels were great, the results indicated that the functional impairment caused by diazepam is absent at serum levels below 400 ng/ml (Hillestad et al. 1974). On continuous administration of diazepam, the concomitant cumulation of effect and serum levels was shown. However, **tolerance** was seen to develop, since serum levels above 400 ng/ml caused **less marked deterioration** of mental and physical functions (Hillestad, Hansen, and Melsom 1974).

Critical flicker-fusion (CFF), two-choice reaction time (RT), heart rate (HR), and vernier visual acuity were measures of psychomotor performance taken during a study of the pharmacokinetics of delta-8-tetrahydrocannabinol (Agurell et al. 1976). Delta-8-THC is a synthetic isomer of delta-9-THC, the primary active constituent in marijuana. Whereas HR correlated well with plasma levels, the performance measures did not. The authors suggested that the receptors corresponding to these effects might be located in respective "shallow" and "deep" compartments, in the pharmacokinetic sense. The authors stated that these and other results have indicated that if the effects of delta-8-THC and delta-9-THC are similar (as other studies have suggested [Jarbe and Henriksson 1974]), then "the plasma level of THC is not an entirely relevant parameter for estimating the degree of impairment in performance" (Agurell et al. 1976, p. 60).

In contrast, while absolute levels of the hallucinogen N,N-dimethyltryptamine (DMT) in blood and urine were quite small and variable between individuals (10-150 ng/ml after intramuscular administration of 0.7 mg/kg), the time course of blood levels and subjective ratings of effect agreed very well. Even though intraindividual correlations between concentration and effect were better than between subjects, the time course of both parameters was similar for all (Kaplan et al. 1974).

This group of studies, while less than definitive because of the limited number of drugs studied, does illustrate three important points. First, the infrequent determination of drug levels yields, at best, only an indication of whether there is a concentration-effect correlation for the drug. The time-course of the relationship remains indeterminate. Second, the use of small numbers of subjects with infrequent sampling tends to produce results where the intersubject variability is so great that any concentration-effect correlation is of borderline significance, if any judgment can be made at all. Certainly, little or no characterization of the drug's concentration-effect relationship can result from such a study. Third, the potential impact of this experimental design on research aims becomes evident. This point is further discussed below.

In the studies described, two questions are implicit, and sometimes explicit:

- Does Drug X at the dose(s) employed produce significant behavioral effects?
- For Drug X, what is the relationship between its blood concentration and its behavioral effect(s)?

The oft chosen experimental approach--behavioral testing shortly after acute or chronic drug administration--may result in significant effects. However, with infrequent determinations of drug concentrations, definitive answers to the second question are not forthcoming. The importance of early and frequent measurements of drug concentration in such experiments has been pointed out by Sellers (1975a). With regard to the phenomenon of acute tolerance--greater effects in a subject when the concentration of a drug is rising than when it is falling--Sellers (1975a)

also recommends testing of each subject at several times in conjunction with determinations of drug concentrations:

Few studies have examined the relation of serum drug concentration and the development of acute tolerance. Such studies seem essential as part of acute and chronic studies for without them there is no way of determining how much inter-individual response is related to the rate of rise of serum drug concentration or to differences in 'end organ' responsiveness and adaptation. (p. 289.)

This data would also apply to the development of guidelines for the time a patient must wait to drive after needed medication.

The effect of experimental design on the accomplishment of research aims stems mainly from the use of "drug dose" as an independent variable in the study of drug effects (question one above). Drug studies are most often performed using a balanced experimental design with the amount of drug administered under experimental control. This is accomplished by using one or more fixed doses of drug, usually in the therapeutic range. As noted above, intersubject differences tend to produce wide variations in the plasma levels of the drug. This situation, combined with the use of a limited number of subjects, frustrates these attempts to determine concentration-effect relationships (question two above).

The presence of several objectives that must be considered simultaneously requires prioritization of objectives in terms of experimental design, as Ashford and Carpenter (1975) have demonstrated. In the context of studying drug interactions, they suggested that the most appropriate approach is sequential experimentation. At the initial stage, the most important objective would seem to be the determination of whether a suspected drug has significant behavioral effects at commonly used doses. Once this aim has been satisfied, researchers might proceed to characterize the concentration-effect relationship in terms of the testing system. Alternatively, they might choose to generate a behaviorally significant concentration range by "titrating" each subject in a group until all were affected to criterion. In either case, it appears that the divergent aims represented by the assessment of behavioral

effects and drug concentration-effect relationships might be better satisfied by separate experiments, with specific designs that yield the desired information.

B.5.2 Epidemiological Studies. The limited number of epidemiological studies has provided few data with which to describe a relationship between drug levels and accident involvement. However, useful information and important, if tentative, implications have been obtained from several efforts in the United States.

Glauz and Blackburn (1975) studied drug use among drivers selected from the living driver population at the approximate locations of recent fatal crashes. The survey procedure consisted of stopping randomly selected motorists, conducting an interview, and requesting breath, urine, blood, and lip swab samples. The body fluid samples were screened for forty-one drugs by thin-layer chromatography. During confirmation by gas-liquid chromatography, quantitative determinations were performed.

Earlier, the same performing organization, Midwest Research Institute, conducted a study of fatally injured drivers (Lin et al. 1975) in which drugs were identified and quantitated in blood, urine, and bile. In this study, an incidence of positive drug findings of 13.09% in the urine and 4% in the blood was reported. The analytical methods employed were the same as indicated above. Under Contract No. DOT-HS-119-3-627, detailed statistical analyses were performed for drugs that:

- a. were reconfirmed in blood at any measurable amount; and
- b. were present in the urine or bile at a concentration of 1.0 mcg/ml or greater.

It was considered desirable to compare the drug findings in the two studies in order to make inferences concerning the relative probability of fatal accident involvement. However, since so few of the living drivers tested met the above criteria for inclusion in the statistical workup, two categories were defined. "Level A" category was as described above for the fatal study, while "Total" included also those instances in which lesser amounts of drug were found in the urine. To ensure comparability, the data from the fatal study were reexamined and retabulated more

inclusively.

In comparing living and fatally injured drivers at "Level A," a higher percentage of fatally injured drivers were included, compared to living drivers. Sedative-hypnotic agents predominated here, as they did at all drug levels. A test of statistical significance was used to show that fatally injured drivers were more likely to have been taking drugs than were living drivers. Thus, the relative chance of a fatally injured driver's evidencing use of any of the forty-one drugs was estimated to be 3.87 times that of the average driver.

The small sample size precluded extensive analysis of the effect of the amount of drug on the relative chance of being fatally injured. An intermediate group was defined on the basis of drug levels in body fluids. "Level B" included drivers in whom no drugs were detected in the blood and less than 1.0 mcg/ml were confirmed in the urine. The relative chance of being fatally injured was in the order of "Level A" (5.16) being greater than "Level B" (3.71) which was greater than 1. A third group, defined as those drivers in whom any drugs were detected in the blood, was given an even greater chance of being fatally injured. However, in a test of these limited findings, it was found that there was no significant effect of drug amount on the chances of being fatally injured.

Such analyses were most limited, of course, by the nature and paucity of data. Data interpretation was also complicated by the substantial percentage (58%) of fatally injured drivers who had consumed alcohol. However, the presence or absence of alcohol was not related to the presence or absence of other drugs and did not differ significantly from the total group. In the living driver sample, little difference was found in the alcohol consumption between users and nonusers of drugs. Evidently, the lack of positive drug finds did not permit the determination of relative chances of being fatally injured after the combined use of two (or more) drugs.

Garriott and Latman (1976) conducted a study in which drivers arrested for intoxication were tested for the incidence of drugs. The population consisted of individuals whose degree of intoxication was greater than that indicated by alcohol breath analysis, or for whom other evidence of

drug use was present at the time of arrest. Each subject was asked to submit a blood sample and was charged with driving under the influence of drugs. With a few exceptions, samples referred for analysis contained less than 0.10% w/v alcohol in the blood.

Within the constraints of original case reporting, full descriptions of each case were presented (Garriott and Latman 1976). Sedative-hypnotic drugs also accounted for the greatest percentage of drug finds in this study. From the blood concentrations the authors concluded "in most cases that the drugs were being taken in doses greater than therapeutic ones, and, if obtained by legitimate prescription, were not taken as prescribed . . . in addition, the high incidence of drugs found in combination with alcohol tends to point toward abuse . . ." (Garriott and Latman 1976, p. 403). No further analysis of drug concentration data was presented in this report.

Garriott et al. (1977) also conducted a study of the incidence of drugs and alcohol in fatally injured motor vehicle drivers. The total sample consisted of all fatalities associated with motor vehicle accidents, including drivers, passengers, and pedestrians. Excluded were those for whom no blood specimens were obtained upon arrival at the hospital and who lived at least twenty-four hours after the accident. Children under fifteen years were also excluded. The analytical procedures were the same as used in the earlier study of intoxicated drivers, described above.

Of the 127 drivers, drugs were detected in 18% and ethyl alcohol in 61%. Alcohol alone was detected in 52%; other drugs were detected in 9%; and both alcohol and other drugs were found in 9% of the drivers. Statistics used to compare at-fault drivers with those not at fault suggested "strongly" that the presence of drugs, alcohol, or both contributes to causation of accidents. Of the twenty-two pedestrians killed in the accidents, eighteen had drugs or alcohol present.

The results of our study seem to indicate that psychoactive drugs are a significant contributory factor to motor vehicle accidents. These drugs may be present alone or associated with alcohol. In the former instance, most such individuals have drug concentrations indicative of drug abuse, while in

the latter instance, the majority of drivers had therapeutic concentrations of drugs in the presence of alcohol. (Garriott et al. 1977, p. 388.)

The authors also suggested that in those drivers having both drugs and alcohol in their blood, the combination appeared to have induced a state of intoxication contributing to the accidents. They acknowledged that the amount of alcohol alone in most cases would be sufficient to explain the accidents. However, they considered significant the fact the diazepam, a drug experimentally shown to interact significantly with alcohol, was present in seven of the twelve drivers who had both alcohol and drugs.

The "additive" effects of drugs to driver impairment by alcohol was also suggested by Finkle's study (Finkle 1969) of drugs in drinking drivers. In fact, "only six percent of those cases in which a clearly significant amount of drug was detected were negative for alcohol" (p. 182). The levels of drugs present strongly implicated drug abuse as a factor in these cases.

Thus, the findings of field studies suggest that the problem of drugs and driving may have two major components: one in which driver impairment is caused by drugs alone, and another, perhaps of greater proportion, in which drugs with alcohol contribute to accident causation. It is significant that nonmedical drug use itself is strongly associated with the concurrent use of alcohol (O'Donnell et al. 1976). However, controlled field studies with larger samples and comprehensive, sensitive analytical methods are required to confirm and extend these findings.

B.6 Summary

The need for objective measures of drug effects requires that drug concentration-effect relationships be established. The development of threshold values for impairment depends to a great extent on the method of data generation. Research requirements in three main areas of research--epidemiology, experimentation, and countermeasures--call for assessment of drug effects in terms of drug concentration and require quantitative determination of drugs and metabolites in body fluids.

A review of research on concentration-effect relationships for

psychoactive drugs reveals that few, if any, have been defined and sufficiently characterized. That "drug concentration" has not been established as a reliable indicator of drug effects is the general impression gained from the clinical, pharmacological, and behavioral literature. For example, while there is a growing body of pharmacokinetic information, there is a paucity of data relating known drug effects to drug concentrations in body fluids. This may be due to the sheer diversity and number of drugs, the insufficient availability or use of modern analytical tools in those laboratories studying drug effects, or the lack of research interest or support.

Experimental and epidemiological outcome variables have been both expressed and discussed as a function of drug concentration in body fluids. Important questions must be answered before this practice can be given full confidence:

- What is the range of variation for the general (driving) population in terms of drug concentration in the blood and drug effect for individual drugs?
- How reliable are concentrations in body fluids for indicating the impairing effects of individual drugs?
- What are the factors which significantly alter the concentration-effect relationship for a given drug?
- To what extent may an experimentally established relationship between drug concentration and effects on driving-related performance measures be extrapolated to the real-world driver population?

The application of laboratory findings to real-world situations is difficult in the best of circumstances. This problem, combined with the lack of data relating drug concentration to effects on driving performance variables, leads to the conclusion that no valid data are available that would permit determination of accident risk in terms of drug concentration other than for alcohol. Furthermore, until the utility and reliability of drug concentration data are established for assessing effects of drugs on human performance, the application potential of drug concentration data to areas of concern in traffic safety will remain

minimal.

Efforts to maximize the meaningfulness of drug concentrations in the body fluids of accident-involved or intoxicated drivers should be encouraged and supported. The development of mathematical models for drug combinations (Ashford and Cobby 1974) and the computerization of pharmacokinetic data (Atkins 1976; Sheiner, Melmon, and Rosenberg 1974) may provide advances toward the goal of using "drug concentration" as an objective measure of driver impairment.

Basic information related to the pharmacokinetics of drugs, particularly the time-dependent, relative concentrations of individual drugs and their metabolites, is required. For example, the concentration patterns of drug metabolites over time might be used to determine the time of ingestion, the type of drug use, and the degree of effect that might be expected at the time of accident-involvement. Such data, where available, should be gathered into a central store for use in developing the necessary methodology required to analyze blood specimens following drug detection and identification.

Current limitations on drug measurement methods result in part from insufficient knowledge of the metabolism and pharmacokinetics of behavior-modifying drugs.

These data and required experimental research to quantitate the influence of drugs on driver behavior constitute the greatest needs concerning the relationship between drug concentration in body fluids and the influence of drugs on traffic crashes.

APPENDIX C

METHODOLOGY FOR THE ANALYSIS OF
BIOFLUIDS FOR DRUGS:
THE STATE OF THE ART

METHODOLOGY FOR THE ANALYSIS OF BIOFLUIDS FOR DRUGS: THE STATE OF THE ART

In highway safety research, analyses of biofluids for drugs are required in the general areas of epidemiology, experimentation, and, possibly, countermeasures. The development of programs in the area of countermeasures, however, depends on the nature and extent of the problem of drugs and driving. This appendix presents a review of the state of the art in methodology to detect the presence and to measure the amounts of drugs and their metabolites in biofluids.

The following topics are covered:

- Factors in Assessing the State of the Art in Methodology for Drug Analysis
- A Review of Past Evaluations of Methodology for Drug Analysis
- Methodology for the Screening of Biofluids for Drugs
- Methodology for Determining the Amounts of Drugs in Biofluids
- The Selection and Evaluation of Laboratories

Because epidemiologic research has high priority in the near term, the discussion reflects most the requirements of field surveys that analyze biofluids to determine the incidence of drugs among drivers.

C.1 Factors in Assessing the State of the Art in Methodology for Drug Analysis

A review of methodology for drug analysis is needed to determine how well the state of the art compares to requirements in highway safety research. In assessing the state of the art, several factors must be considered. This subsection discusses these factors.

Two distinct ways of assessing the state of the art are possible. They stem from basic research and the application of its fruits to practical

problems. One way to assess the state of the art examines present technology for drug analysis. The other way emphasizes methodology, for example, comparing specific methods. In fact, since methods are based on techniques, the latter approach is not wholly exclusive of the former. Both are needed here to address the concerns of highway safety research.

Methodology for drug analysis is based on various techniques, each of which has different analytical characteristics and each of which is in a different stage of development. The application of technology to the determination of drugs in biofluids may be well established, as in gas chromatography, or in the early stages of testing, as for "high pressure liquid chromatography." However, certain methods may be well developed for the assay of some drugs, but not for others. Immunochemical methods are a case in point. The availability of techniques is also an important factor. Even a highly developed technique, if it is restricted to only a few centers, may not fulfill the requirements of highway safety research.

How a technique or method is to be applied greatly influences an assessment of both technology and methodology. For example, the requirements for the screening of drugs and for measuring their amounts differ very much. The reader should realize, too, that analyses of biofluids for drugs are performed in many fields of research for many purposes. These applications vary greatly, and this variance is reflected in the development of specific methods. The approaches used, the techniques adapted, the methods chosen, all depend on the nature of their application.

In general, several methods are available for the analysis of any given drug. Several techniques may be applicable to the problems of detection and quantification in body fluids. Thus, which method is the "method of choice" often depends on the purpose for its original development. In some cases, assays are developed to detect only gross amounts of drug in body fluids. Other methods may be applicable to one specific fluid, such as urine. Intermethod comparison is important for the selection of user-oriented methodology. For some drugs, development of methods better suited for specific purposes may be indicated.

The biofluids to be analyzed and the drug or drugs to be measured are factors in the development of techniques and methods. Their application for purposes other than originally intended also depends on these factors. A method developed for analyzing urine may not be appropriate for analyzing blood. The sensitivity, specificity, and other analytical characteristics will vary, depending on the analyzed drug, its chemical properties, metabolite presence, and other factors. For example, gas chromatography-mass spectrometry-computer (GC-MS-COM) systems allow ultrasensitive and specific assays. Yet, if a particular drug elutes poorly from the chromatographic column, the technique may be inadequate, or less useful than some other method. This holds true for different methods based on the same technique. In the case of gas chromatography (GC), selective GC-detectors have been developed which are quite sensitive. However, if that type of detector does not respond well to the compound of interest, the method may be less useful than another CG method using the more standard flame ionization detection, a more "universal" detector.

Therefore, the specific aims of methods reported in the literature may significantly influence the overall assessment of the state of the art. In general, the more specific an analytical method becomes for a given drug, the more likely it is to have superior analytical characteristics, thus becoming a "method of choice" for the drug. However, as a method gains specificity, it is likely to lose applicability to other drugs of interest, or to different body fluids. A striking example is the immunoassay for drugs. Although absolute specificity for a single compound is not achieved, each immunoassay can detect chemical compounds with very closely related structures. Methods developed to determine simultaneously a given drug and (some of) its metabolites also have very circumscribed applications, restricted often even to a particular body fluid.

The state of knowledge in drug metabolism and pharmacokinetics is also a factor in the assessment of drug analytical methodology. The identification of drug metabolites and the knowledge of typical blood concentrations both of the parent drug and its principal metabolites

permit the specification of analytical requirements. Analytical requirements form an important basis on which to assess drug analysis methods. Insufficient knowledge in drug metabolism and pharmacokinetics may limit the assessment of drug analytical methodology. For example, specificity in drug measurement is important in drug analysis. The influence of metabolites on the qualitative identification and quantitative determination of drugs is well known. Misidentification and inaccurate quantitations may result when metabolites interfere with measurement of the parent compound. The possibility of metabolite interference may influence the choice of methods, since some analytical variables (e.g., light absorption) may be nonspecific. The meaning of blood concentration data resulting from the use of drug analysis methods is also rendered uncertain. This has serious consequences: "Analytical methods are invariably based on choosing some set of parameters which are to be correctly, accurately, and precisely measured. If these parameters are insufficiently understood so as to be unmeaningful, the analysis itself cannot be any more meaningful" (Bosin 1977, p. 142).

Thus, several factors influence the review and evaluation of analytical methodology in drug analysis:

- the intended application area of user groups;
- the state of the art in technique development, including demonstration of general reliability;
- the applicability of a technique or method to user problem area, including ability to detect drugs in biological liquids;
- the analytical requirements (e.g., sensitivity, specificity, range of drugs detected) desired by user;
- the state of knowledge in intermethod comparison for drugs of interest; and
- the availability to user groups, including factors such as cost, training personnel required, and geographical distribution of technique.

These factors are critical to decisions concerning the type and degree of potential involvement of analytical methodology in such highway safety

projects as field surveys. The same points apply to the evaluation of analytical capability as a basis for laboratory selection for the drug analysis phase of epidemiological research.

C.2 A Review of Past Evaluations of Methodology for Drug Analysis

Past evaluations of analytical methodology in the highway safety context can be briefly reviewed in light of these considerations. There have been few attempts to discuss the state of knowledge in analytical methodology regarding specific research concerns of drugs and highway safety. Many reviewers in the drugs and driving area have focused solely on overall progress towards determination of drug influence on traffic accidents. Evaluations of drug assay techniques have been made in passing, either presuming consensus or deferring to more detailed, technical evaluations elsewhere. In one area, epidemiological research, criticisms of the screening systems employed to detect drugs in body fluids are invariably offered, but no review of this problem area appears to have been written. Most remarks concerning drug analysis have been general, and are not illuminating for decision-makers who must design future projects in this area.

Basically, deficiencies in the epidemiological (Joscelyn and Maickel 1977a; California Highway Patrol 1974; Kapur 1975; Silverstone 1974) and experimental (Sellers 1975a) literature have been ascribed both to the analytical techniques employed and to their lack of use. Past research efforts have been hampered by methods deemed inadequate to describe fully the nature and extent of drug involvement in traffic crashes. The cost, complexity, and limited availability of certain techniques have been cited as important factors. The situation appears the reverse for experimental research. In concluding that serum concentrations are better predictors of drug effect than dose for many drugs, Sellers (1975b) pointed out that:

The vast majority of studies of drug effects on driving skills have failed to include concurrent measurements of plasma drug concentrations. The predictable result, because the relation of dose to concentration is so variable, is a literature

of confusing, contradictory, and often uninterpretable results. Sufficiently sensitive and specific assays for many drugs are now available, and future experimental studies of drug effects on driving skills should include such analysis. (p. 290.)

Despite their being "an integral part of studies of drugs and driving skills," Sellers also considered that "the widespread, intelligent application and appropriate interpretation of serum concentration measurements of psychoactive drugs in driving skill studies will be difficult and expensive" (Sellers 1975b, p. 291).

The California Highway Patrol (CHP) conducted a feasibility study for establishing presumptive limits for drugs (California Highway Patrol 1974). The report (January 1974) contained a chapter devoted to the forensic analysis of drugs in blood and urine. In this section, the analytical support capability was studied for laws requiring forensic-grade qualitative and quantitative drug analyses. Requirements included the following:

- reliable chemical tests;
- adequately trained personnel;
- sensitive, accurate instruments;
- adequate funds;
- development of methods to process large numbers of samples from time of arrest to courtroom with minimum number of errors.

Evidence of drug involvement would necessarily have to measure up to legal standards. Expert witnesses in analytical methodology would be required to establish the reliability and validity of the chemical tests employed. Technicians would have to be certified. Rigid controls were considered essential to support the programs and laws requiring forensic work.

In assessing the state of the art regarding this application of analytical methodology, the CHP concluded that both testing methods and trained personnel were lacking.

Current analytical capability is a major deficiency in the problem of drug identification. Many drugs cannot be determined in blood or urine by current methods—particularly

the hallucinogens. Very few drugs can be determined in blood on a routine basis. Quantitation of drug levels is by and large omitted because of excessive cost and because of lack of standards for interpreting drug levels. (California Highway Patrol 1974, p. 81-2.)

Drug analyses for traffic cases at that time were handled by several types of laboratories, including coroner, state and local criminalistics, and private laboratories. Choice of method was based primarily on available funds, expertise of staff, available space, equipment, and, perhaps, work load. Also variable was the range of drugs tested. No standardization of methodology was evident, and California had not appraised any of the methods in use, unlike the controls placed on alcohol analysis. The most serious problem was seen to be the lack of properly trained personnel to conduct drug analyses.

In a brief overview of techniques used to determine drugs in body fluids, the advantages of several methods were described and their cost estimated. Although costs of a drug analysis support effort were not detailed, the CHP indicated that the cost could be high in terms of benefit to highway safety.

A recent research review completed by Joscelyn and Maickel (1977a) also discussed the detection and measurement of drugs in the context of highway safety. The authors pointed out that, despite technological advances in analytical chemistry, such as GC-MS and immunoassay techniques, development and application of methods to define the problem of drugs and driving lagged considerably. Technical difficulties of measuring extremely small amounts of drugs in complex biological liquids present significant methodological problems. Legal and practical constraints associated with the solution of the drug and driving problem itself also contributed to analytical insufficiency. Thus, methodological problems had a dual nature. Basic research-oriented issues were presented along with questions concerning the optimum service utilization of analytical methodology (Bosin 1977). In consequence, "limitations of drug detection and measurement techniques place constraints on the interpretation of the results of existing research. These same limitations

constitute practical constraints for the development of countermeasure programs" (Joscelyn and Maickel 1977a, p. 35).

A recent symposium on drugs and driving devoted a working session to the discussion of analytical methodology in drugs and driving (Bosin 1977). The state of the art in drug analyses was explored and difficulties in assessing the available methodology were underscored. Primarily, the state of methodological development was found to vary greatly according to the drug or drug class under consideration. The need to specify a listing of problem drugs was recognized. In addition, it was necessary to specify the lower limits of drug detection required of analytical methods. The lack of organization and centralization of the extant literature was considered to be another hindrance to the adequate description of the state of the art in analytical methodology.

Joscelyn and Maickel (1977a) concluded:

While it is obvious that the process of detection and measurement of drugs in biological samples is critical to effective solution of the drug/driving problem, it should be equally obvious that the current "state-of-the-art" with regard to analytical methodology is far from satisfactory. Within the constraints and limitations imposed by demands for chemical accuracy, legal requirements, and pharmacological significance, present day technology is—at best—inconsistently satisfactory. For some drugs, such as ethanol, a variety of simple, inexpensive, and highly reliable analytical procedures are available, utilizing samples of breath or blood. Indeed, hand-held instruments for quantitative analysis of breath ethanol make sure measurements hardly more difficult than statistical analyses with a pocket computer.

For virtually all other drugs, however, analytical procedures are limited to samples of blood; technological development has only reached the state of instrumentation requiring 25-50 square feet and having initial costs exceeding \$25,000 per unit; and, in most instances, a considerable amount of unit chemistry is involved, demanding expenditure

of time and availability of facilities. (p. 42.)

In summary, it is evident that development of drug screening methodology and the designing of adequate screening systems is required for epidemiologic research. Quantitative and confirmatory methods are also needed, and must be well characterized for the purposes of accuracy and reliability. More specific and sensitive methods are necessary for experimental research in drug effects. Countermeasure analytical requirements reflect the need for efficient drug screening coupled with methods meeting strict forensic standards. Factors pertaining to the application area and specific use of analytical methodology greatly influence the overall assessment of the state of the art. Recent reviews of drug analyses from the highway safety viewpoint have emphasized deficiencies perceived in the development, availability, and utilization of techniques and methods. Evaluations differ according to the types of drugs and the purpose of analysis.

In the following section, research issues associated with drug screening in body fluids are discussed. Techniques used in drug detection and analysis of body fluid samples are reviewed from the highway safety perspective. Applications of analytical methodology to drug analysis are illustrated with examples selected from the literature.

C.3 Methodology for the Screening of Biofluids for Drugs

From the standpoint of highway safety research, drug screening methodology is of foremost importance. Field surveys and the chemical testing of impaired drivers depend on analysis of body fluids. The problems faced are familiar to toxicologists: there is a wide range of possible drugs and metabolites, and, usually, it is not known or suspected which drug or drugs are present, if any. Procedures similar to those of analytical toxicology must be adopted, therefore, and optimized for the special requirements of highway safety concerns.

According to Sunshine (1975, p. 391), most systematic analyses have several distinct phases:

- **separation** of the drug from its biological matrix;
- **isolation** of the agent, its metabolites, or both;

- **identification** of the isolation material; and
- **quantitation** of identified material.

Each drug, even those structurally related, has different chemical properties, giving rise to a host of factors that necessitate special methods for **optimal** analysis. For any drug, it can be assumed that there is an optimum procedure, or "method of choice," which includes most if not all of the above analytical steps. However, in drug screening, such constraints as time, amount of sample, and laboratory capability require that **general** methods be developed which, while not optimal for any drug, are sufficient for user demands.

Analytical factors in screening methodology include the following:

- range of drugs detected,
- extraction efficiency,
- detection sensitivity,
- specificity in qualitative identification, and
- quantitative accuracy.

The greater the range of drugs, the less efficient separation methods will be for many of those drugs included. To avoid lower extraction yields, several separation procedures could be used on divided samples from a single specimen. Alternatively, techniques requiring no separation step, e.g., immunoassays, could be used for some drugs. Time of analysis and screening costs are increased, however. Use of less than optimal separation techniques also lowers detection sensitivity for all drugs. To what extent this is acceptable depends on the objective of the screening program.

Several types of drug screening systems have been reported. Applications have included the following:

- drug overdose victims (hospital toxicology unit);
- poisoning, drug-involved deaths (coroner);
- illicit street drug samples (forensic toxicology);
- urine screening (methadone maintenance programs);
- drug abuse screening (military personnel); and
- general drug screening (highway safety).

For each of these applications, different user requirements shape the

resultant screening system. For example, in treating drug overdose victims, qualitative and quantitative information is required. Rapidity of analysis is of greater importance than detection sensitivity in the design of analysis procedures. Drugs responsible for a patient's condition will be present in sufficient amounts to warrant less efficient but more rapid separation techniques.

The analysis of street drug samples requires qualitative identification up to forensic standards. The available time for analysis and amount of sample compensate for the rigorous testing. Urine screening, whether for methadone patients or for persons investigated for drug abuse, reflects the need for qualitative data pertaining to a restricted set of drugs. In the case of poisoning or drug-involved death, the information required is both qualitative and quantitative. Further, tissue concentrations of the identified agents must be measured to determine their causative role.

Drug screening methodology required for field surveys in the area of highway safety is most similar to that of the coroner. Even here, there are important differences. The coroner has available to him greater amounts and more types of tissue and body fluid samples than can be obtained by researchers, especially from the living driver population. The presence of drug containers or other evidence of drug use may indicate specific tests to the coroner. Such information is exceptional in highway safety.

Drug screening systems developed for highway safety research must adhere to the most exacting requirements relative to the other applications described:

- limited types and amounts of biological samples;
- wide range of drugs for analysis;
- drug detection sensitivity to therapeutic levels;
- qualitative identification, including drug metabolites; and
- accurate quantitative determination, preferably in the blood, for subsequent data interpretation.

The need for blood concentration data on drug-involved accidents has already been emphasized. This requirement is similar to that in the clinical evaluation of drug-overdose cases. Here, however, the screening

system must also be able to detect therapeutic levels of drugs for comparison purposes. These two requirements, drug detection sensitivity and drug concentration data in the blood, uniquely characterize the drug screening approach necessary for highway safety purposes. Unfortunately, few comprehensive screening systems have yet been designed for such applications.

The state of knowledge regarding drug screening methodology encompasses all aspects of drug analysis, from sample collection to techniques in quantitative determination. In the following subsections, information needs will be outlined by a brief review of major areas of concern in general drug screening. Introductory discussions concerning the basic steps and analytical characteristics of drug determination in biological fluids are available (Joscelyn and Maickel 1977a; Sunshine 1975; Robinson 1976; Maickel 1977).

C.3.1 Separation Techniques in Drug Screening. The development of efficient extraction techniques applicable to a wide range of drugs in body fluids is a specific requirement for field surveys. Despite the dramatic advances in laboratory instrumentation, comparatively little effort has been devoted to sample preparation procedures (Tompsett 1968; Maickel 1978; Hackett, Dusei, and McDonald 1976). Yet, unless a drug can be separated from the normal constituents of a biological fluid in sufficient quantity, many of these techniques are of little value. When the separation of a wide range of drugs is required, the dearth of research becomes a serious deficiency.

The objectives embodied in any drug screen generally specify the body fluid to be analyzed. In drug overdose cases, plasma levels of drugs are most valuable. The detection of drug abuse usually centers on urinalysis. In highway safety research both qualitative and quantitative data are required. It is well known that drugs and metabolites are concentrated in the urine. In addition, the urine presents a simpler solution from which to extract many drugs. Difficulties remain, however. Urine levels of most drugs do not accurately reflect either blood concentrations or pharmacological effect. Data reflecting blood levels of drugs can be

better interpreted in this regard. However, as in the case of many psychoactive drugs, blood levels may be so low as to remain undetected in a general drug screen, particularly by systems unable to detect therapeutic levels in plasma. Sunshine (1975) has described a compromise that may be of great value in the design of general drug screening procedures. Although taken from a slightly different context, the approach has application in this regard.

The volume of urine and/or stomach content available is usually larger than the volume of available blood; hence, they are specimens of choice for a qualitative analysis. Blood samples should be reserved for confirmation and quantitative analysis. Another reason for preferring urine for the first probe is that many substances, particularly the organic bases, are present in such low concentration in blood that they might not be found unless they were the specific target of the analysis. (p. 391.)

Of course, some drugs for which analysis is desired may not appear in the urine except in metabolized forms. Hence, it is essential to have general screening capability directed at metabolites of these drugs as well. The assembling and integration of pharmacokinetic and metabolic data for "drugs of interest" is required prior to the design of a general drug screen.

Other considerations interpose between sample collection and initial separation procedures. Adjustment of sample pH prior to extraction, protein precipitation techniques, and the reduction of glassware adsorption of drugs must be considered (Maickel 1978; Mussini, Marcucci, and Garattini 1975). In a general drug screen, however, a measure appropriate to one class of drugs may interfere with the determination of another. For example, recovery of the butyrophenone groups (major tranquilizers) will be enhanced by protein precipitation. However, the recovery of benzodiazepines (minor tranquilizers) would be decreased (Mussini, Marcucci, and Garattini 1975). Sample splitting for the purpose of two or more treatments can be considered, depending on the screening procedure and the type of drugs selected for analysis. These analytical factors must be included in the application of drug screening methodology.

Information pertaining to the behavior of drugs in body fluids such as urine and blood should be gathered from the literature and summarized for use in the design and comprehensive drug screens.

General reviews have dealt with the principles, applications, and developments in drug separation procedures (Maickel 1978; Marshman 1974; Mussini, Marcucci, and Garattini 1975). Several techniques can be employed:

- liquid-liquid extraction,
- chromatography (column, paper, thin-layer, and gas chromatography),
- distillation,
- molecular sieves (gels, resins), and
- ion exchange.

Of these, extraction of drugs by organic solvents and resins has been used most. Chromatographic techniques such as thin-layer chromatography are more often used as **isolation** procedures following initial "clean-up" steps (Sunshine 1975, p. 392).

Several general methods for drug extraction have been reported (Sine et al. 1972; Hackett, Dusci, and McDonald 1976; Warfield 1973; Finkle, Cherry, and Taylor 1971; Foerster and Mason 1974; Mule et al. 1971). Most often, an extraction procedure that differentially separates acidic, neutral, and basic drugs is developed (Sine et al. 1972; Hackett, Dusci, and McDonald 1976; Finkle, Cherry, and Taylor 1971; Foerster and Mason 1974). The absorption of drugs by Amberlite XAD-2 resin has also been investigated for its application to drug detection in the urine (Mule et al. 1971). The latter technique is subject to several major difficulties including variability in recovery values (Maickel 1978; Lin et al. 1975).

The incidence of drugs in drivers has been investigated utilizing two of the above techniques in whole and in part. Woodhouse (1974) studied the incidence of drugs in a group of drivers using the resin absorption technique. Garriott and Latman (1976) utilized n-butyl chloride as an extractant for alkaline drug screening, one part of their overall scheme. Only in the latter study could therapeutic levels of most drugs be detected in the blood.

The development of separation methodology and its evaluation for use in epidemiological research remains a significant research issue. The specification of a restricted list of drugs and the detection limits for their serum concentration would simplify this task.

C.3.2 Isolation Techniques in Drug Screening. Following separation of the drug from its biological matrix, isolation steps are usually taken prior to quantitative analysis. This is especially true if the biological extract is complex, or if a detector is relatively nonspecific, e.g., a flame ionization detector on a gas chromatograph. In the latter case, only retention time data serves to identify the isolated substance. Separation steps are often not required in immunoassay procedures, where the antibody is a specific "detector" for a given drug or closely related structure. For quantitation of a specific chemical moiety, however, isolation techniques would have to be used.

Isolation procedures are usually based on chromatographic techniques:

- column chromatography,
- paper chromatography,
- thin-layer chromatography (TLC),
- gas-liquid chromatography (GLC),
- high pressure liquid chromatography (HPLC), and
- gel permeation chromatography.

These techniques have been briefly described elsewhere in the highway safety literature (Maickel 1977).

Depending on the purpose of analysis, analytical characteristics such as sensitivity and specificity may take precedence in the design of a general drug screen. Then, the type of detector and its ability to identify drugs become important considerations in the selection of isolation techniques. For example, most detectors currently used in HPLC are based on the absorption of light in the visible or ultraviolet (UV) regions of the spectrum (Parris 1976). Detection sensitivity in the HPLC analyses of body-fluid constituents is weak, particularly where the compound has poor UV absorbance (Reid 1976b). Where detection of a wide range of drugs in low concentrations is desired, HPLC methods based on UV detection would

not be methods of choice.

For purposes of drug screening, the specific and sensitive detection of a wide variety of drugs in a wide range of concentrations depends on the **generality** of the isolation technique chosen.

Perhaps one of the greatest problems in the development of procedures for use in the toxicological or forensic laboratory is the difficulty associated with isolation procedures. A specific process that will work well for urine will fail miserably when applied to blood; an extraction process that is suitable for use with GLC may be totally useless for TLC or vice versa; a deproteinization procedure that works well for an acidic compound may yield erratic results with another; the same organic solvent or inorganic acid obtained from two different suppliers may contain quite different impurities. Nevertheless, in searching for the **ONE** simple and generally useful procedure for drug identification that would be applicable to virtually **ANY** drug and **EVERY** type of biological sample, it becomes apparent that there probably is no such process! (Maickel 1978, p. 198.)

General procedures based on the isolation techniques outlined above have been developed. A review of the analytical literature confirms the brief evaluation offered by Sunshine (1975):

Isolation of the drug from concomitantly extracted "normal" materials is usually carried out by chromatography. Paper was originally preferred, but in the last decade this technique has yielded to thin-layer films. Both of these methods are yielding to gas chromatography. Many factors will govern the method of choice--expense, experience, ease with instruments, and personnel available, to mention but a few. (p. 392.)

It may be added that the type of detector available or required greatly influences the choice of isolation technique. The advent of low-cost quadrupole mass spectrometers has contributed tremendously to the potential usefulness of gas chromatography, especially in general drug screening (Finkle, Cherry, and Taylor 1971; Bonnicksen 1975; Finkle 1975).

However, even more common than screening methods based on a single technique are those that employ several techniques to detect and to identify drugs. The use of parallel isolation procedures can enhance the generality of a screening system. Thus, different detectors with complementary analytical characteristics with respect to a group of drugs may be used. This approach is often necessary since commonly used drugs are more easily detected by separate methods. These principles were used by Garriott and Latman (1976) in their study of drugs in drivers arrested for "driving under the influence." The continued development of immunochemical assays for drug detection promises to support screening systems, e.g., in the identification of marijuana constituents.

C.3.3 Qualitative Identification of Drugs. The identification of drug substances follows their isolation from the biological extract. The chemical or electronic detection of the isolated material permits tentative identification in a well-characterized analytical system. The specificity and selectivity of a given drug screen is primarily a function of the isolation and detection techniques. Many of the chromatographic techniques feature "on-line" detectors. Particularly well-suited for on-line detection techniques is gas-liquid chromatography (GLC). Numerous detectors have been developed for GLC, including the interfaced mass spectrometer.

The applicability of available detectors depends on the isolation system employed. Indeed, for the most part, detection techniques can only be discussed in conjunction with isolation procedures. The technical convenience of on-line detection and identification capability cannot be underestimated. Each type of detector, however, will vary in complexity, sensitivity, reliability, and cost. As indicated above for general extraction procedures, no technique yet developed can adequately determine the entire range of possible drugs in a body fluid sample. Even relatively universal detectors, like the mass spectrometer or GC-flame ionization detectors, are limited by the isolation systems used to deliver substances for analysis.

The following subsections review the analytical **techniques** used to

detect and identify drugs. Of primary interest are those suitable for use in general drug screening, alone or in conjunction with other techniques.

C.3.3.1 Thin-Layer Chromatography (TLC). In addition to its uses in sample clean-up procedures, TLC systems have been developed for the combined isolation and detection of drugs in body fluids (e.g., Sunshine 1975; Kaistha, Tadrus, and Janda 1975; Jain et al. 1975). Spraying and dipping techniques are used extensively for the detection (visualization) or chromatographic zones. Kaistha, Tadrus, and Janda (1975) have described the advantages of TLC in relation to other techniques:

Although many methods for detecting commonly abused drugs are available, they vary greatly in their suitability for use in large-scale urine monitoring programs. Some of the present methods, such as immunoassay techniques, are very sensitive but prohibitive in cost, and usually selective in the drugs that they are able to test. Although radioimmunoassay, free radical assay technique and hemagglutination inhibition test[s] have a sensitivity at nanogram levels for the detection of morphine and structurally related narcotics, the chances of cross-reactivity with other drugs are enhanced at this sensitivity level. Enzyme multiplied immunoassay technique, the sensitivity of which is the same as that of thin-layer chromatography (TLC), requires individual testing of each drug in a urine specimen, and a urine specimen to be tested for morphine, methadone, amphetamine, barbiturates and cocaine metabolites will cost US \$2.50-3.85, depending upon the volume of reagents purchased. Furthermore, antibodies have not yet been developed to test for other drugs of abuse such as methylphenidate (Ritaline), phenmetrazine (Preludin) and phencyclidine (PCP) or for drugs used in the treatment of heroin addicts such as acetylmethadol and naltrexone. At present, the only suitable technique that has the versatility for testing an entire array of drugs of abuse in one run is TLC. Even this technique varies considerably in the

extraction and detection procedures from laboratory to laboratory. The extraction of drugs from a urine specimen is a necessary prerequisite to TLC. The superiority of a reported TLC technique as applied to the detection of drugs in a biological fluid can be attributed to the efficiency of the pre-chromatographic extraction step and the specificity and the sensitivity of the detection techniques used. The results of surveys by the Center for Disease Control definitely demonstrated that the use of TLC as a general approach to the identification of drugs of abuse has the highest proficiency. The only other technique that can permit simultaneous screening of a mixture of drugs is gas-liquid chromatography (GLC), but it has [the] inherent disadvantage of running a single specimen at a time; thus, it becomes time consuming and more expensive than TLC. GLC is useful when the analysis of an unconscious patient's physiological fluids for a particular drug is required. (p. 360.)

The simplicity, rapidity, and economic aspects of TLC seem particularly well suited to applications such as drug abuse prevention and treatment programs. The large sample volumes and qualitative drug testing are characteristic of these applications. However, most TLC systems currently available for drug detection are designed specifically for urinalysis. At best, they are only semiquantitative. They require greater sample volumes to compensate for their inherent lower sensitivity. Use of TLC systems seems restricted to preliminary identification of drug substances. Even the use of several solvent systems (Jain et al. 1975) is considered insufficient for the more rigorous applications in the area of countermeasures, for example. Recent developments (Zweig and Sherma 1976), such as "programmed multiple development" (Jupille and Perry 1976) and TLC-densitometry techniques (Faber 1976), while not yet applied to this area, do not seem sufficient to meet the general drug screening requirements of highway safety research. This is particularly so where blood concentrations of psychoactive drugs are required.

C.3.3.2 Liquid Chromatography. The technical advances in liquid chromatography have paralleled the increasing interest in drug analysis (Walton 1976). Preliminary among them are the developments associated with "high pressure liquid chromatography (HPLC)" (Lawrence and Frei 1976; Veening 1975). Currently, the main advantage of HPLC lies in its separation characteristics and chromatographic conditions. It can isolate thermally unstable and nonvolatile compounds while operating at or near room temperature, and is thus widely viewed as complementary to gas chromatography (GC) (Parris 1976; Veening 1975; Wheals 1976). Like gas chromatographic techniques, HPLC combines continuous separation with on-line detection of eluting material. Unlike GC, however, detectors of sufficient sensitivity and selectivity are not in common use with instrumental liquid chromatography (Reid 1976b). While new detector systems compatible with HPLC units are being developed, the ultraviolet (UV) absorption detection remains most frequently used (Walton 1976). A review of recent developments and applications of UV spectrometry in drug analysis is available (Hummel and Kaufman 1976).

The applicability of currently available HPLC techniques to drug analysis in biological fluids does not seem great. Despite ongoing work in chemical derivation to enhance detector response to drugs (Lawrence and Frei 1976), HPLC remains a separation method that supports GC methods. In discussing the forensic aspects of HPLC, Wheals (1976) evaluated the technique for its application potential:

The current status of HPLC in the Metropolitan Police Laboratory is that it is a well established method being used routinely for a number of analyses to which it is particularly well suited. However, the importance of qualitative analysis in forensic drug work means that HPLC, which is particularly advantageous where quantitation is required, is considerably less important than TLC. Similarly, there seems little possibility that HPLC will oust GC in areas where the latter technique performs adequately. (p. 104.)

The same laboratory has reported the separation of a wide range of

drugs by HPLC (Jane 1975). The application was limited to illicit drug samples and was not used for the purpose of detecting drugs in body fluids. Nevertheless, recent use of HPLC has been increasing by about thirty percent per year, according to Robinson (1979). Although the present state of the art in drug analyses by HPLC does not appear to meet requirements in highway safety research for general drug screening, undoubtedly its role as a support technique for a limited set of drugs will shortly be defined.

C.3.3.3 Gas-Liquid Chromatography (GLC). GLC techniques applied to general drug screening have won increasing acceptance. Its principal advantage over TLC rests in the variety and sensitivity of detectors that can be placed on-line with the vapor phase effluent.

Devices commonly applied to the analysis of drugs include flame ionization, nitrogen-phosphorus, electron capture, and mass spectrometer detectors. Of these, the flame ionization detector (FID) is most widely available. It possesses excellent sensitivity, a wide linear dynamic range, and responds to all organic compounds (Marshman 1974; Millard 1976). Element-selective detectors have also been developed and marketed (Cram and Juvet 1976). "Selective detectors are often more susceptible to variations in operating parameters than . . . the FID. They are usually inferior to an FID in their linearity of response and may require a considerable amount of calibration" (Adlard 1975, p. 14). For example, "the main disadvantages of the ECD [electron capture detector] are its susceptibility to contamination, its relatively small linear range, and the unpredictability of its response" (Adlard 1975, p. 32).

Selective detectors are, in most cases, more sensitive than the FID (Marshman 1974; Millard 1976). By their very nature, though, they do not respond to drug substances that do not possess the appropriate chemical prerequisites. This is a **disadvantage** in drug screening, particularly with the ECD. The nitrogen selective detector, on the other hand, has greater application, since most drugs have a nitrogen atom within their structure. Screening for drugs in the blood of drivers has been performed utilizing a GC-system with the nitrogen detector (Moller, Witzmann, and

Tausch 1973). Selective detectors can be used in a screening system, however, when used for a subset of drugs of interest (e.g., Peat and Kopjak 1979).

The detector that has captured the greatest attention is by far the mass spectrometer (MS). The advent of GC-MS instruments presented the analytical world with the combined capability of GC separation with MS sensitivity and structural specificity. The quantitative potential of GC was enhanced by several orders of magnitude (Millard 1976). Drug identification was advanced from reliance on relative retention time data to mass spectral characterization of the eluting material. In the screening of unknown samples, a peak obtained by the more conventional GC peaks has to be subjected to additional work for confirmation. As Finkle et al. (Finkle, Cherry, and Taylor 1971) stated, "GC/MS offers the most applicable technique available. It is direct, very fast, very sensitive and provides a result which puts identification beyond dispute" (p. 419).

Developments in the computer-assisted operation of "low-cost," commercial GC/MS instruments (GC-MS-COM) have further extended the analytical power of this tool. Karasek (1973) has described its impact on GC/MS:

For the analysis of organic compounds, particularly when in complex mixtures and in trace concentrations, an integrated gas chromatograph/mass spectrometer/computer system gives the ultimate in speed, accuracy and broad capability. With its ability to produce, store and replot several hundred 3- to 5-second mass spectra sequentially taken as a chromatogram evolves, such a system can detect and identify components in a mixture present in only 10^{-9} gram quantities. Through a Teletype, the analyst can ask the computer to plot out the chromatogram, mass spectra that have been stripped of background and normalized, mass chromatograms of each m/e value, and to execute a library search to identify the most likely compound producing a given mass spectrum. All these data are meaningful to an analyst, and through examination and interpretation of the plotted data he can achieve almost

unbelievable analytical results. (p. 40.)

To complement the computer capability, "libraries" of mass spectral data for drugs and metabolites have been developed, such as that of Finkle et al. (Finkle, Foltz, and Taylor 1974). The reference spectra in combination with known GC-retention times serve to identify unknown drugs and metabolites beyond the need for confirmatory procedures. Other developments have extended the potential of this technique for general drug screening. For example, several ionization techniques have been developed, some of which lead to simpler and more drug-specific spectra, important to low-resolution mass spectrometry (Milne and Lacey 1974; Smith 1975). The use of stable isotopes and other internal standards has facilitated quantification of detected compounds (Millard 1976; Horning et al. 1973). The field of mass spectrometry, including technical advances and applications, has been reviewed by Burlingame, Kimble, and Derrick (1976).

As Burlingame, Burlingame, Kimble, and Derrick (1976) observed, "mass spectrometry has never been a field driven by commercially available instrumentation" (p. 370R). The relatively high cost of GC-MS-COM systems has restricted their availability and widespread use, despite their well-recognized applicability to drug screening problems (Bonnichsen 1975; Finkle, Foltz, and Taylor 1974; Parris 1976). Nevertheless, emergency toxicological and other clinical applications have been reported (Horning et al. 1973; Costello et al. 1974). Finkle (1975) has evaluated the use of GC-MS for measurement of drugs in drivers:

GC-MS coupled to a data system or computer is the only method which can provide a legally tenable analysis of a blood sample for a broad range of drugs, rapidly, and specifically. It should be realized that it is not a panacea and there is still [1974] no ideal method for the detection of either cannabinoids or LSD in circulatory system samples. In general, drugs which are chemically weak acids or neutral occur in micrograms/milliliter concentrations and are not difficult to assay by common techniques, but basic drugs which are the largest group, and include common

tranquillizers, stimulants and psychoactive agents occur at nanograms/milliliter and less, and require GC-MS techniques.

(p. 609.)

Thus, while universal use of GC-MS equipment seems unlikely in the near future, limited applications of GC-MS-COM instruments, such as in field surveys, seem most attractive. The development and use of well-characterized GC procedures in a GC-MS with an interactive data system should be carried out for the purposes of highway safety research. GC-MS techniques in conjunction with other, more specific methods, such as radioimmunoassay and spectrophotofluorometry (Section C.3.3.4), appear to provide the best approach to **general** drug screening.

C.3.3.4 Specific Screening Methodology. In the broad-based approach to drug screening, techniques that detect a wide range of drugs are usually selected. Generally speaking, the amount of labor and other cost factors associated with drug analysis rise in direct proportion to the number of different operations that must be performed on each sample. The number of tests that can be run is also limited by the volume of sample available and the work load, or "sample throughput."

Nevertheless, in keeping with the realization that no **universal** general screening technique yet exists, sometimes it is advantageous to include specific tests in a screening system. The detection of important drugs that occur below the limits of sensitivity of the drug screen or that are not isolated by the separation technique used are cases in point. Often, the inclusion of more specific screening methods may free the general screen from certain analytical compromises that would decrease the overall sensitivity of the method, thus lowering its efficiency. Two quite different methodologies may be mentioned in this regard. Spectrophotofluorometry and immunoassay techniques have been extensively used in the screening of body fluids for drugs, both clinically and in drug abuse prevention.

A luminescence technique, spectrophotofluorometry involves "the activation of a molecule with incident radiation of a discrete wave length that will be selectively absorbed. The activated molecule, in the process

of decaying from the excited state to the lower energy ground state, then emits radiation of a longer wavelength than can be measured and used to quantitatively determine the compound" (Maickel 1977, p. 122). The fluorescent determination of drugs is subject to numerous interferences, but a number of sensitive and specific assays have been developed (Bridges 1976; Flourescence News 1971). In one application, a fluorometric assay for morphine was included in a mass drug screening program (Santinga 1971). The application of fluorescence measurements to drug detection and screening has been recently reviewed by Marshman (1974).

The immunochemical methods are characterized by their use of antibodies obtained from the antisera of animals injected with drug-attached antigens (haptens).

The basic principles involved in immunoassay procedures, whether fluorescent or radiolabeled, are relatively simple. One needs to produce the specific antibody, then react it with the appropriate hapten and isolate the product. A form of isotope dilution procedure is used. Labeled and unlabeled antigens (or haptens) compete for their specific antibody. (Maickel 1977, p. 125.)

The several immunochemical techniques, including basic theory and their applications, have been extensively reviewed (Lin et al. 1975; Wisdom 1976; Landon 1976; Scharpe et al. 1976; Cleeland et al. 1976; Butler 1977). In reviewing immunoassays for the detection of drugs in drivers, Forney and Sunshine (1975) compared four techniques commercially available for drugs of abuse (morphine; methadone; amphetamine; barbiturates; and a cocaine metabolite, benzoyl ecgonine):

- Free Radical Assay Technique (FRAT)
- Enzyme Multiplied Immunoassay Technique (EMIT)
- Radioimmunoassay (RIA)
- Hemagglutination Inhibition (HI)

The assay systems differed in cost, equipment requirements, sensitivity, and quantitation capability.

Immunological assays are a valuable addition to the analytical armamentarium for the detection of drugs of abuse in

biological systems. The high sensitivity and specificity which immunoassays provide eliminate the need for prior extraction and concentration of drug from the sample. Radio-immunoassay is the most sensitive of the assay techniques and can be used to obtain quantitative results by diluting positive samples. If the capability of performing rapid single sample analyses is required, two systems, FRAT and EMIT, are available. Both provide good sensitivity and precision. The hemagglutination inhibition assay can be employed at a very low cost for capital equipment. Each immunoassay, therefore, has its own advantages and limitations. The particular method best suited for application in any particular institution is determined by the number of samples to be analyzed per day, the sensitivity and accuracy needed, turn-around time requirements as well as money available for hardware and reagents. In an immunoassay, few things can produce a false negative result. **Immunoassays can save a great deal of time in situations where a large percentage of all samples are negative.** However, those samples indicated to be positive require further analysis using non-immunological methods such as thin-layer chromatography, gas-liquid chromatography, fluorometry or spectrometry. (Forney and Sunshine 1975, p. 617., emphasis added).

Mule, Bastos, and Jukofsky (1974) reached similar conclusions in their evaluation of immunoassay methods, comparing them to fluorometric and TLC procedures. The use of automated radioimmunoassay systems (Brooker, Terasaki, and Price 1976) is of further advantage to drug screening, especially in mass drug abuse screening programs (Sulkowski et al. 1975). While most often used for urinalysis, immunotechniques are available for applications where drug detections in blood must be performed.

The convenience, timesaving, and cost-saving aspects of the immunotechniques are not to be had without difficulty. The immunoassay methodology is in a relatively early developmental stage. For example,

the specificity of many immunoassay procedures is in serious question. Antibodies may be formed to rather narrow structural specifications, but these are not absolute. Metabolites, compounds formed in the body from the parent drug, may remain long after a drug has ceased to have effect. In many cases, the metabolites, though inactive, may differ only slightly from the original drug and interact significantly with the immunoassay. Specific antibodies are available for only a limited number of drugs (albeit those commonly used and misused), and for virtually no metabolites. The application of such techniques to drugs in the blood are often seriously limited, and their ability to serve as quantitative systems is minimal.

C.3.4 Drug Screening Systems. As indicated above, general drug screening may rely on several analytical techniques for efficient and sensitive drug detection in body fluids. Along with the increased use of drugs, interest in the development of screening systems has grown. Drug screening itself has been centered mainly in the related areas of toxicology: clinical, forensic, and analytical. Specific applications include emergency drug overdose cases, drug abuse detection, and investigation of deaths due to poisoning. Recently, field surveys of the incidence of drugs in drivers, both living and fatally injured, have employed drug screening systems (see below).

Table C-1 presents capsule summaries of the techniques employed in various types of drug screens. These selected studies do not exhaust those published in the literature. The screening systems included here may be considered representative of those that use two or more techniques to accomplish analytical objectives.

In the review of studies presented in Table C-1, the main factors that appeared to influence the selection of primary identification techniques were **sample throughput** (or caseload) and the **cost of drug analysis**. For example, in mass screening for drug use, TLC is favored over GLC, since many samples can be tested simultaneously. Objectives in drug screening directed the choice of biofluids for analysis and established the levels of sensitivity required. Urine is usually favored for large-scale,

TABLE C-1
GENERAL DRUG SCREENING SYSTEMS

Application	Body Fluid	Primary Detection Technique (Specific Drugs Identified)	Secondary Methods for Qualitative Confirmation	Reference(s)
Analytical Toxicology	urine	EMIT (opiates, barbiturates, cocaine, amphetamines, and methadone)	TLC, GLC, GC/MS	(Curtis and Pate1 1975)
	serum	TLC		
Analytical Toxicology	blood; urine	GC (basic drugs, acidic drugs, alcohol) UV (basic drugs, acidic drugs) TLC (basic drugs, acidic drugs) EMIT, RIA (basic drugs)		(Bastos and Galante 1976)
Analytical Toxicology	blood; urine	TLC GLC (amphetamine)	GLC Spectrophotometry (barbiturates)	(Robinson and Holder 1974)
Analytical Toxicology	(aqueous solutions)	GLC UV (86 drugs; several extraction systems)		(Hackett, Dusci, and McDonald 1976)
Clinical Toxicology	serum	GLC UV (barbiturates) TLC (carbarnates)	GLC	(Foerster and Mason 1974)
Drug Abuse Detection	urine	GLC Spectrophotofluorometry (morphine)	GLC	(Santinga and Dominguez 1972)
Drug Abuse Detection	urine	TLC Spectrophotofluorometry (morphine)	GLC	(Mule 1971)

TABLE C-1 (Continued)

Application	Body Fluid	Primary Detection Technique (Specific Drugs Identified)	Secondary Methods for Qualitative Confirmation	Reference(s)
Drug Abuse Detection	urine	Drug Extraction by Resin Technique TLC Spectrophotofluorometry (morphine)		(Mule et al. 1971)
Drug Abuse Detection	urine	TLC	RIA (morphine) GLC (barbiturates, amphetamines, methadone, cocaine)	(Roerig et al. 1975)
Drug Abuse Detection	urine	TLC GLC (Amphetamines, methylphenidate)		(Peat 1976)
Drug Abuse Detection	urine	Drug Extraction by Resin Technique HI (hemagglutination inhibition) (opiates, methadone, barbiturates) Spectrophotofluorimetry (phenothiazines) TZC (amphetamine)	TLC, GLC	(Alexander 1976)
Emergency Toxicology	serum; urine	TLC (hypnotic/tranquilizer screen) UV (barbiturates) Colorimetry (salicylate, phenothiazines) EMIT (opiates, amphetamines)	GLC	(Walberg, Lundberg, and Pantlik 1974)
Field Survey (Drugs in Drivers)	blood	GC (basic drugs, alcohol) UV (acidic and neutral drugs; weak bases) TLC (carbarnates)		(Garriott and Latman 1976; Garriott et al. 1977)
Field Survey (Drugs in Drivers)	urine; blood	TLC	TLC, GC, (GC/MS)	(Glauz and Blackburn 1975; Lin et al. 1975)

qualitative drug detection; in contrast, blood is chosen for analysis in clinical settings, where more meaningful, quantitative results are required.

The analytical methodology selected for a secondary or support role confirms results obtained by primary screening techniques. In screening applications where only the identity of the drug was required, additional tests were made using different techniques for **qualitative confirmation** of the preliminary find. In most drug analyses, the use of chromatographic techniques requires confirmation, usually with a different chemical test. This is not the case, however, in laboratories using GC-MS-COM systems (Costello et al. 1974). Thus, while using only a single technique, the screen provides enough information, both chemical and structural, to obviate the necessity for additional testing. To illustrate this point, it has been estimated that there is only one chance in a million that four ions selected as diagnostic of a particular compound have been formed by some other compound with exactly the same retention time (Millard 1976). Though less sensitive when monitoring all ions, the GC-MS-COM system has even less chance of misidentifying a chemical substance.

Drug and driving studies that employed general drug screening techniques have differed greatly. Woodhouse (1974) and Glauz and Blackburn (1975) report the incidence of drugs in drivers fatally injured and living, respectively. An extraction method with XAD-2 resin preceded detection by TLC and confirmation by TLC and GLC. In addition, quantitation capability was provided by GLC. A "swab test" for marijuana was included in both studies. Garriott and co-workers (Garriott and Latman 1976; Garriott et al. 1977), performing separate studies of fatally injured and intoxicated drivers, used several screening procedures for the detection of drugs in blood. Basic drugs, including synthetic narcotics, tranquilizers, antihistamines, and amphetamines, were detected and quantitated by gas chromatography. The screen for acidic and neutral drugs, including barbiturates, carbamates, and weak bases such as diazepam and methaqualone, was based on an ultraviolet spectrometric procedure. The latter screen also utilized TLC and GLC. Special procedures for the determination of blood alcohol and carboxyhemoglobin

(blood levels of carbon monoxide) were also included. These procedures were considerably more sensitive and more suited for measurements of plasma drug concentrations than those indicated for TLC above. Of the two analytical systems, the one developed by Garriott (1977) appears more adequate for application in future field surveys. The incorporation of other specific tests, e.g., for marijuana use, would be required. However, the full and detailed evaluation of any system designed for broad-based drug screening, using authentic and "spiked" body fluid samples, is essential prior to its implementation.

C.4 Methodology for Determining the Amount of Drugs in Biofluids

A review of separate methods for determination of drugs in body fluids is beyond the scope of this report. Indeed, summarizing the literature on quantitative drug analysis is a difficult task in itself. Extensive bibliographies of recent references have been compiled (Miller, Spiehler, and Keller 1972; Journal of Chromatographic Science 1972; Journal of Chromatographic Science 1974), and many of the entries represent single drug methods. With the advance of technology, new analytical systems become available, invariably followed by publication of a spate of new applications in the area of drug analysis. Unfortunately, few of the reports detail the **analytical characteristics** of these methods. To evaluate a method for potential use or to assess the validity of analytical data resulting from its use, information **must** be available on its sensitivity, specificity, reliability, validity, technical complexity, assay time, cost, and other factors associated with applicability and availability. Few of the reports provide these data (e.g., Brooker, Terasaki, and Price 1976; Sulkowski et al. 1975). The characteristics of an acceptable analytical procedure have been outlined and described previously (Maickel 1977; Curry 1975).

The current state of the art of drug analytical methodology appears quite adequate for the quantitative determination of most drugs in biological samples. The constituents of marijuana and some hallucinogens are notable exceptions. However, the detection and quantitation of cannabinoids (Willette 1976) and LSD (Christie, White, and Wiles 1976) are

active research areas, and methods suitable for the purpose of highway safety field research will almost certainly be forthcoming. Collections of evaluated analytical methods (Sunshine 1975; Pesez and Bartos 1974; American Association of Clinical Chemists) and other information related to drug analysis (Florey 1976; Reid 1976a) provide excellent resources for both experimental and epidemiological research in highway safety. Reviews of methods used to detect, identify, and quantitate major drug groups have been published in special issues of the Journal of Chromatographic Science (1972; 1974).

The selection of methods either to confirm or to quantitate drugs detected during initial screening relates directly to **general analytical strategy** (Reid 1976b). Specific extraction methods as well as separate analytical techniques may be required for different drugs. The sensitivity limits of the quantitative determination should be at least an order of magnitude lower than detection limits to ensure accurate results. Analytical requirements such as the specificity and sensitivity of the analysis **interact** with other factors, including the body fluid tested and the availability of techniques. To determine which reliable method should be chosen, each factor must be considered in light of the analytical problem as a whole. The minimum levels of detection for drugs designated as "of interest" must be established prior to selection of sample preparation and detection techniques, as well as quantitative-confirmatory methods. To aid in this process, useful compilations of therapeutic and toxic levels of drugs in the blood have been published (Baselt, Wright, and Cravey 1975; Sine et al. 1972; Sellers 1975a; Sunshine 1975; Winek 1976; Baselt and Cravey 1977).

The selection and application of reliable methods usually falls to the analyst. For the varied needs of clinical and forensic toxicology, there are dedicated laboratories in hospitals as well as laboratories maintained by local, state, or federal authorities. Independent laboratories or those associated with universities may also perform drug analyses. For the purposes of highway safety research, the selection and evaluation of **laboratories** may be of greater interest than the specific methods used for drug detection and quantitation. Certainly, lower costs would result

from utilizing laboratories already active in the field and avoiding the costs of buying equipment and developing methodology.

In the following section, research issues involved in the selection and evaluation of laboratories are reviewed. The state of knowledge regarding quality control and proficiency testing is illustrated with examples taken from the literature. Information needs concerning laboratory performance evaluation as a highway safety research requirement are specified.

C.5 The Selection and Evaluation of Laboratories

As indicated above, only reliable, valid methods should be considered in the design of screening systems for determining drug use among drivers. The identification and experimental comparison of several suitable methods may be required. Varied problems in the detection, identification, and quantification of drugs, from initial sample collection to data calculation, must be identified and resolved. These are **intralaboratory** concerns and have to do with:

- the reliability and validity of selected methodology;
- the accuracy and precision of the applied methods; and
- the significance of data derived from their use.

In addition to the fundamental analytical factors, there are human factors involved. As Jones (1974) has observed:

The degree of excellence of results from a toxicology laboratory is directly proportional to the skills of its technical staff, regardless of the multiplicity of available sophisticated instrumentation. In order to assure the user of reliable and valid results, a performance evaluation system should be an integral part of the procedural operation. This can be achieved by the use of quality control and proficiency testing programs. (p. 254.)

Thus, both the evaluation of methods **proposed** for drug screening and the proficiency testing of laboratories engaged in drug analysis are important requirements for highway safety research.

Interlaboratory factors may enter into consideration either during a laboratory selection process or during an ongoing study involving drug

analysis. By way of illustration, several laboratories may be considered for the task of analyzing body fluid samples collected in a field survey. Their ability to obtain reliable and valid data must be assessed in terms of laboratory facilities and the availability of qualified personnel, in addition to the analytical scheme proposed for drug analysis. For large studies, or where widely separated geographical areas are sampled, several laboratories may be required. In this situation, adequate but different methods may be used for determination of the same drugs. In lengthy studies, continuous monitoring of performance may be required. Interlaboratory measures must be instituted to ensure quality control and comparable results.

Jones (1974) has defined **quality control** as "an in-house program utilizing the inclusion of standards on a day-to-day or run-by-run basis" (p. 255). She advocates blind samples subjected to the normal routine, and the proficiency testing of laboratories engaged in drug analysis to minimize intralaboratory variation. The use of adequate standards becomes a requirement. The availability of reference standards is not general, and the need for drug and metabolite standards has been cited, previously (Josceelyn and Maickel 1977a, p. 42). The use of internal standards in many analytical procedures has become widespread, but certain pitfalls, such as the use of chemically dissimilar internal standards, must be avoided (Curry 1975). The standards must be added early in the analytical procedure so that each step in the method is covered (Jones 1974; Curry 1975), and so that losses due to extraction may be accounted for in each sample. This becomes important when an extraction method with variable efficiency is used, such as the resin method employed by Woodhouse (1974). Aspects of quality control in a toxicology laboratory engaged in qualitative and quantitative analysis have been discussed also by Kapur and McLaughlin (1975).

The intralaboratory procedures at best ensure the reliability, or precision, of the results. To establish the accuracy of data obtained by a given laboratory with its preferred methods, additional procedures have to be used.

This phase of performance evaluation is termed **proficiency**

testing. It is best effected by obtaining standards from without-the-house so that results can be compared to those from other laboratories. (Jones 1974, p. 255.)

In proficiency testing, the ability of the analysts and hence the laboratory itself is being tested. Frank (1975), in a report of proficiency testing in forensic drug chemistry, emphasized the need to obtain as much information as possible with which to evaluate technical performance.

Our experiences showed that the most critical factor is to limit as much as possible the variables in order to properly identify specific problem areas that may exist, such as malfunctioning instruments, decomposition of standard, or poor analytical technique. It is most important that any specific problem be identified in order to take corrective action to eliminate inconsistent or improper results, should they occur. (Frank 1975, p. 16.)

However, factors beyond analytical performance may significantly influence the results of proficiency testing. Past attempts to test laboratory performance have received criticism since no in-depth research has been conducted into the variables that may affect prepared standards and, therefore, the "objective" values of drug concentration (Jones 1974).

Kelly and Sunshine (1976) have outlined requirements for the reliable and valid testing of laboratory performance:

Interpreting the results obtained by laboratories on outside check samples demands the prior validation of a critical series of assumptions regarding the samples themselves: (a) The stated amount of a pure drug was added to the samples initially. (b) This amount was not altered by later processing of the samples (i.e., by lyophilization, the addition of preservatives, or the biological medium) before they were shipped to the participating laboratories. (c) The drug components of the samples are stable under the conditions encountered during shipment and storage before analysis. (d) All compounds are quickly and completely solubilized by the addition of diluent to a lyophilized preparation. (e) The

artificial sample behaves as does a genuine one with respect to the extraction of each component and contains no nondrug substances that may interfere with the analysis.

The usual method for verifying that these assumptions hold is to employ reference laboratories, which also analyze the samples. Their results should agree closely with the expected values for samples that have been processed in a manner similar to that used by the participating laboratories. (Kelly and Sunshine 1976, p. 1413.)

The need for accurate drug analysis both within the clinical context and between forensic and toxicological laboratories has been increasingly recognized (Jones 1974). Proficiency testing programs have ranged from small, voluntary efforts among several laboratories (Spiehler et al. 1975) to more extensive efforts mounted by federal agencies (Dinovo and Gottschalk 1976; Frank 1975).

At the behest of the National Institute on Drug Abuse, Dinovo and Gottschalk (1976) conducted a brief proficiency testing survey of nine collaborating laboratories engaged in a study of drug-related deaths (Wilde 1976). The possible influence of different laboratory procedures, thoroughness of screening, and limits of detection on the toxicological results and their interpretation was of concern in this national study. They found "startling" interlaboratory differences in accuracy and precision of detection of drugs. They concluded that the observed variations in toxicological proficiency may introduce a significant source of error in drug-death statistics and in epidemiological deductions based on these statistics. Kelly and Sunshine (1976), however, have pointed out several questions raised by the proficiency testing procedure itself, and emphasized the continuing need to develop a well-conceived program for this purpose. In addition, they suggested criteria for the proficiency testing of laboratories engaged in drug analysis.

A "self-evaluation assistance program" was conducted by the Center for Disease Control in the area of clinical toxicology (Mather 1973). Public health, forensic, private, and hospital laboratories participated in the study. Sellers (1975a), in presenting quantitative results obtained for

the "unknown" sample containing phenobarbital, termed the range of results "astonishing."

The forensic science program of the Drug Enforcement Administration undertook a program of proficiency testing to ensure the accuracy of information generated by its field laboratories. As reported by Frank (1975):

The objective of the program was to determine if any significant differences existed between laboratories and between methods in regard to the following parameters:

1. **Consistency** in the results of the two trials by the same scientist.
2. **Accuracy** of the qualitative and quantitative results.
3. **Bias** in consistency of over- or under-estimating quantitative results.
4. **Variability** in the aggregate scatter of results within a given laboratory and within a given method. (p. 8-9.)

Based upon the results of the study using a sample of homogeneous material containing 33.3% cocaine hydrochloride mixed with procaine and mannitol, the conclusion was drawn that no significant problems existed with either the laboratories or the methods being used. It must be noted that the detection and quantitation of drugs in biological liquids was not tested in this program.

Recently, a national survey (Simpson and Heayn 1975) was conducted of laboratory testing agencies in Canada that do alcohol and other drug analyses on victims of motor vehicle accidents. Its purpose was to examine practices and procedures that would affect the reliability and comparability of information relating to alcohol and drug involvement in traffic fatalities, since such data were used extensively for policymaking, information programs, and education purposes. The Traffic Injury Research Foundation, the principal source of statistics on alcohol involvement in traffic fatalities in Canada, developed survey instruments and conducted on-site visits to the laboratory testing agencies.

Technical portions of responses to the survey were evaluated by a panel of toxicologists nominated by the Canadian Society of Forensic

Science. Results showed there was considerable uniformity in the practices of laboratories, but substantial discrepancies existed in many analytical areas. In particular, it was noted that more information on drug involvement in traffic fatalities could and should be obtained by these laboratories.

The elements of laboratory performance evaluation, **quality control** and **proficiency testing**, have been reviewed. Examples from the literature demonstrate that the determination of drugs in "unknown" body fluid samples is not straightforward, and that there are considerable differences between laboratories performing this type of analysis. The results of such surveys indicate the necessity of including performance evaluation measures in any study of the incidence of drugs in drivers. While adequate methods exist for the detection, identification, and quantitation of drugs, their application in field surveys must be monitored to ensure the reliability, validity, and (if two or more laboratories are engaged) the comparability of results. Standardized methods from the collection of samples to the calculation of data should be required where possible to minimize interlaboratory variation. Quality control and proficiency testing procedures are needed for inclusion in the experimental design of epidemiological studies of drug involvement in traffic accidents.

C.6 Summary

Several factors influence the overall assessment of analytical techniques and drug analysis methods. These factors, which include the specific application intended and the type and range of drug(s) to be analyzed, are critical to decisions concerning the selection of analytical methodology in drugs and highway safety. The development of well-designed drug screening systems is a significant research requirement in epidemiological research. All research areas in drugs and highway safety need well-characterized drug analysis methods.

Drug screening methodology involves all aspects of drug analysis, from the initial separation of drugs from the biological liquid to the qualitative identification of individual compounds. Screening methodology ranges from general, systematic approaches to specific methods developed for

single compounds. In a general drug screen, "trade-off" analysis based on user's requirements includes the range of drugs detected and the analytical characteristics of the analytical techniques. Drug screening methodology required for epidemiologic research in drugs and highway safety must adhere to exacting specifications relative to other applications. Analytical methods used in implementation of legal countermeasures must conform to forensic standards. As yet, little evaluation research has been performed that will allow specification of superior methods for these applications.

The development and evaluation of methodology for the **separation** of drugs from body fluids remains a significant research issue. The specification of a restricted list of drugs and their respective detection limits in blood would simplify the fulfillment of this research requirement. How drugs are isolated from biological specimens and then detected depends greatly on the requirements of research and the type of methodology applied to a given problem. The design of drug screening systems comprised of several techniques appears best in highway safety research. Gas chromatography-mass spectrometry-computer methods in combination with more specific techniques, such as immunochemical and spectrophotofluorometric procedures, may provide one of the best approaches to general drug screening.

Drug screening systems described in the analytical and toxicological literature were also reviewed. The main factors that appeared to influence selection of primary identification techniques were the **number of samples** to be analyzed and the **cost** of drug analysis. The intended application area of each drug screening system determines the analytical characteristics of the method to a great extent. Two general drug screening systems used in drug-and-driving research were described. One that combined several techniques, including gas-liquid chromatography, appeared greatly superior to the other, which was based on thin-layer chromatography.

The state of the art in quantitative drug analysis appears quite adequate for the determination of most drugs in body fluids. The constituents of marijuana and some hallucinogens still require the

development of adequate methods for their routine analysis. The selection and application of reliable methods depends largely on the judgment and experience of the analyst.

The selection and evaluation of **laboratories**, rather than analytical methods per se, may be of greater concern in the field of drugs and highway safety. Research issues involved in choosing drug analysis laboratories were reviewed. Published evaluations of laboratory performance indicate that substantial differences between laboratories exist. The inclusion of performance evaluation measures in any study of drug incidence in drivers appears to be a necessity if comparability between individual analyses and between research studies is to be attained.

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