DOT HS-805-299

DRUG RESEARCH METHODOLOGY
VOLUME II
THE IDENTIFICATION OF DRUGS OF INTEREST IN HIGHWAY SAFETY

Kent B. Joscelyn
Alan C. Donelson

The University of Michigan
Highway Safety Research Institute
Ann Arbor, Michigan 48109

Contract No. DOT HS-7-01530
Contract Amt. $234,000

MARCH 1980
FINAL REPORT

Prepared For
U.S. DEPARTMENT OF TRANSPORTATION
National Highway Traffic Safety Administration
Washington, D.C. 20590

NOTICE

This document is disseminated under the sponsorship of the Department of Transportation in the interest of information exchange. The United States Government assumes no liability for the contents or use thereof.

Technical Report Documentation Page

1. Report No.	2. Government Accession No.	3. Recipient's Catalog No.
DOT-HS-805 299		

4. Title and Subtitle	5. Report Date
DRUG RESEARCH METHODOLOGY. VOLUME TWO. THE IDENTIFICATION OF DRUGS OF INTEREST IN HIGHWAY SAFETY	March 1980
	6. Performing Organization Code
7. Author(s)	8. Performing Organization Report No.
Kent B. Joscelyn and Alan C. Donelson	UM-HSRI-80-13
9. Performing Organization Name and Address	10. Work Unit No. (TRAIS)
Highway Safety Research Institute The University of Michigan Huron Parkway and Baxter Road Ann Arbor, Michigan 48109	11. Contract or Grant No. DOT-HS-7-01530
	13. Type of Report and Period Covered Final report. 1977-1980
12. Sponsoring Agency Name and Address U.S. Department of Transportation National Highway Traffic Safety Administration 400 Seventh Street, S.W. Washington, D.C. 20590	14. Sponsoring Agency Code

15. Supplementary Notes

Other reports produced under this contract: Drugs and Highway Safety 1980; Drugs and driving: A selected bibliography. Supplement One. (DOT-HS-803-879); Drug research methodology. Volumes One, Three, Four, Five.

16. Abstract

This report presents findings of a workshop on the identification of drugs that should be the focus of near-term highway safety research. Drugs of interest are those that have a potential to increase the likelihood of traffic crashes and their attendant losses. This report summarizes efforts by a cross-disciplinary panel of experts (1) to develop a procedure by which to estimate the risk potential of drugs; and (2) to produce an initial rank ordering of identified drugs of interest, based on subjective estimates of their risk potential. Criteria of risk that describe a drug's user population, its pattern of use, and its effects related to driving are outlined. A list of drugs of interest ranked by the procedure developed in this workshop is included.

17. Key Words	18. Distribution Statement
Drugs, Highway Safety, Risk, Risk Factors, Drug Use, Drug Effects	This document is available to the public through the National Technical Information Service, Springfield, VA 22161.

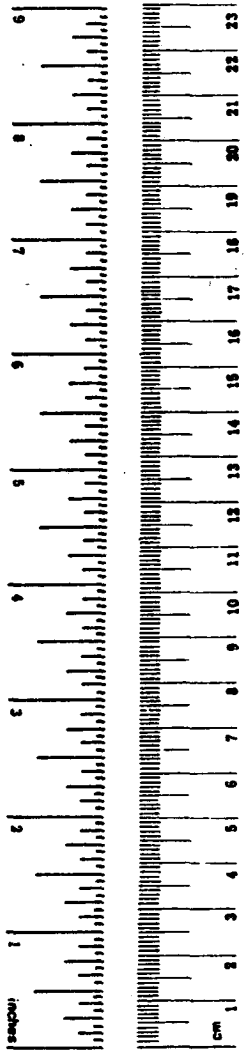
19. Security Classif. (of this report)	20. Security Classif. (of this page)	21. No. of Pages	22. Price
Unclassified	Unclassified	48	

METRIC CONVERSION FACTORS

Approximate Conversions to Metric Measures

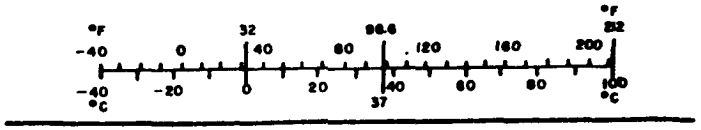
Symbol	When You Know	Multiply by	To Find	Symbol
		LENGTH		
in	inches	*2.5	centimeters	cm
ft	feet	30	centimeters	cm
yd	yards	0.9	meters	m
mi	miles	1.6	kilometers	km
		AREA		
in^2	square inches	6.5	square centimeters	cm^2
ft^2	square feet	0.09	square meters	m^2
yd^2	square yards	0.8	square meters	m^2
mi^2	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



ACKNOWLEDGMENT

This report results from a multidisciplinary effort involving many persons and reflects their able and welcome contributions. We thank all who assisted in its development, preparation, and production.

Special recognition is due to those who participated in the workshop and whose expert contributions form the basis for the report:

- Fred B. Benjamin
- Stephen D. Benson
- John A. Carpenter
- Pamela K. Ennis
- Michael A. Evans
- James C. Garriott
- Marvin M. Levy
- Markku Linnoila
- Roger P. Maickel
- James L. Nichols
- Oakley S. Ray
- Harvey A. Siegal

Each of the participants gave freely of their time, energy, and knowledge, often continuing to work after long, formal sessions. Their willing support has made this report possible.

We gratefully acknowledge the staff of the Belmont Conference Center, who provided a warm and gracious setting and who maintained an atmosphere most conducive to productivity. We especially thank Mrs. Mary Force, director of the center, and Ann Higgins, our conference coordinator, both of whom assisted us through the vagaries of planning and arranging this workshop.

The technical approach of the project was designed by Kent B. Joscelyn and Roger P. Maickel. This report was drafted by Alan C. Donelson from notes and records of the workshop session. Early drafts of the report were reviewed by colleagues at The University of Michigan, in particular, Ralph K. Jones and James E. Haney. Stephen D. Benson, Ph.D., the NHTSA Contract Technical Manager, also reviewed early drafts. Their assistance was invaluable in developing a working draft for circulation to participants, who reviewed it for accuracy and comprehensiveness. The final text was then prepared, based on their

comments.

Other HSRI personnel also made important contributions. This report was edited by James E. Haney. Debbie Dunne served as production editor and produced the report. Draft versions of the report were produced by clerical staff of the Policy Analysis Division under the supervision of Jacqueline B. Royal and Olga S. Burn.

We thank all who contributed.

Kent B. Joscelyn
Principal Investigator

Alan C. Donelson
Principal Investigator

PREFACE

This report presents the results of one of a series of workshops on methodological issues in research on drugs and highway safety. The workshops addressed discrete--but interrelated--topics. The workshops were conducted by the University of Michigan Highway Safety Research Institute (HSRI) for the National Highway Traffic Safety Administration as part of a larger research program on drugs and driving.

A reader interested in the subject area will find the other workshop reports and technical reports produced under the research program of value. The workshop reports are:

- Drug research methodology. Volume one. The alcohol and highway safety experience and its applicability to other drugs.
- Drug research methodology. Volume two. The identification of drugs of interest in highway safety.
- Drug research methodology. Volume three. The detection and quantitation of drugs of interest in body fluids from drivers.
- Drug research methodology. Volume four. Epidemiology in drugs and highway safety: The study of drug use among drivers and its role in traffic crashes.
- Drug research methodology. Volume five. Experimentation in drugs and highway safety: The study of drug effects on skills related to driving.

Other reports prepared under the HSRI project include an annotated bibliography of literature on drugs and driving and related topics:

- Joscelyn, K.B., and Donelson, A.C. 1979. Drugs and driving: A selected bibliography. Supplement one. National Highway Traffic Safety Administration technical report DOT-HS-803-879;

as well as a comprehensive review of past, ongoing, and planned efforts

related to study of and response to the drug and driving problem:

- Joscelyn, K.B.; Donelson, A.C.; Jones, R.K.; McNair, J.W.; and Ruschmann, P.A. 1980. Drugs and highway safety 1980. National Highway Traffic Safety Administration contract no. DOT-HS-7-01530.

The latter report supported the preparation of a report to Congress by the Secretary of Transportation as requested in Section 212 of the Highway Safety Act of 1978. Both reports cited above developed from and extended similar work done under earlier contracts from NHTSA:

- Joscelyn, K.B., and Maickel, R.P. 1977a. Drugs and driving: A research review. National Highway Traffic Safety Administration technical report DOT-HS-802-189.

- Joscelyn, K.B., and Maickel, R.P. 1977b. Drugs and driving: A selected bibliography. National Highway Traffic Safety Administration technical report DOT-HS-802-188.

- Joscelyn, K.B., and Maickel, R.P., eds. 1977c. Report on an international symposium on drugs and driving. National Highway Traffic Safety Administration technical report DOT-HS-802-187.

- Joscelyn, K.B.; Jones, R.K.; Maickel, R.P.; and Donelson, A.C. 1979. Drugs and driving: Information needs and research requirements. National Highway Traffic Safety Administration technical report DOT-HS-804-774.

- Jones, R.K., and Joscelyn, K.B. 1979a. Alcohol and highway safety 1978: A review of the state of knowledge. National Highway Traffic Safety Administration technical report DOT-HS-803-714.

- Jones, R.K., and Joscelyn, K.B. 1979b. Alcohol and highway safety 1978: A review of the state of knowledge. Summary volume. National Highway Traffic Safety Administration technical report DOT-HS-803-764.

- Jones, R.K.; Joscelyn, K.B.; and McNair, J.W. 1979. Designing a health/legal system: A manual. The University of Michigan Highway Safety Research Institute report no. UM-HSRI-79-55.

These reports provide entry points to the literature on alcohol, other

drugs, and highway safety for readers desiring general reviews as well as information on specific topic areas. In addition, the reports can serve as sources for identifying both U.S. and foreign literature pertinent to each reader's needs.

CONTENTS

1.0 INTRODUCTION

This report presents the findings of a workshop on the identification of drugs of interest in highway safety. The workshop was held 5-7 March 1978, at the Smithsonian Institution's Belmont Conference Center, Elkridge, Maryland. The workshop was one of a series conducted by the Policy Analysis Division of The University of Michigan Highway Safety Research Institute, under the sponsorship of the U.S Department of Transportation, National Highway Traffic Safety Administration contract DOT-HS-7-01530.

1.1 Background

The extent to which the use of drugs by drivers contributes to highway safety problems is unknown (Joscelyn and Maickel 1977a; Willette 1977; Joscelyn, Jones, Maickel, and Donelson 1979). Research has not established that any drug besides alcohol increases the probability of a traffic crash and associated losses. Although present knowledge about drugs and driving is limited, available evidence indicates that drugs alone or in combination with alcohol or other drugs **can** impair driving skills and **may** increase the likelihood of traffic crashes. Further inquiry in this area is warranted. Among the factors that limit the state of knowledge are problems and issues in major areas of drug and driving research.

In November 1976, The University of Michigan Highway Safety Research Institute (HSRI) received a contract entitled "Drug Research Methodology" from the National Highway Traffic Safety Administration (NHTSA). Its general objectives are:

- to develop a greater understanding of the nature of the drug and driving problem on the basis of existing literature; and
- to define directions for future research with greater precision than has been done in the past NHTSA-sponsored efforts.

The project emphasizes the generation of possible solutions to research issues in drugs and highway safety. The overall task is to identify methodologies applicable to research on drugs and driving. Specific objectives of this study are:

- to identify problems and issues that should be addressed in the area of research methodology;
- to identify alternative approaches to research that could be implemented with current technology; and
- to provide a listing of priority items of research that NHTSA could address in the foreseeable future.

To accomplish these objectives, an approach based on workshops was used to examine issues in four distinct but interrelated areas:

- The Identification of Drugs of Interest in Highway Safety;
- The Detection and Quantitation of Drugs of Interest in Body Fluids from Drivers;
- Epidemiology in Drugs and Highway Safety: The Study of Drug Use Among Drivers and Its Role in Traffic Crashes; and
- Experimentation in Drugs and Highway Safety: The Study of Drug Effects on Skills Related to Driving.

The division of topics had advantages as well as a possible disadvantage. On one hand, a tighter focus on specific issues could be achieved. On the other hand, for some topics the wisdom and expertise of participants in other workshops might be lost. To offset this disadvantage, summaries of earlier workshops were mailed to invitees, and participants were later asked to comment on findings as well as issues in those areas.

These workshops, conducted in the spring and summer of 1978, were highly productive and brought to focus other issues in related areas of drugs and driving. In 1978, a contract modification called for additional workshops within the scope of the statement of work. In January 1979 a fifth workshop dealt with the alcohol and highway safety experience and

its relevance to the study and control of the drug and driving problem. The remaining workshops will address other topics of priority interest to NHTSA.

These workshops constitute a series in which each is an integral part. Although the workshops were self-contained and are reported in separate volumes, in general the progression of topics has been systematic. An apparent exception is Workshop V, The Alcohol-Highway Safety Experience and Its Applicability to Other Drugs, which is reported in Volume One. This deserves some explanation.

The alcohol-crash problem was the first recognized drug and driving problem. Knowledge of the relationship between alcohol use and traffic crashes has led to an awareness that other drugs also have the potential to increase traffic crash risk. In discussing research issues, participants in the first four workshops often made references and comparisons to the study of and the response to the drinking-driving problem. Workshop V, therefore, was planned to examine in its entirety the alcohol issue in highway safety, including its history, research methodology, and efforts to reduce the magnitude of the drinking-driving problem. It was hoped that Workshop V would describe more precisely the alcohol and highway safety experience and express more clearly the differences between alcohol and other drugs and their importance to continued study of drugs and driving.

As Volume One, the report on Workshop V serves as an introduction to the others, provides a historical perspective, and describes the relation of the alcohol-highway safety experience to other drugs. The workshop reports are designed to be read sequentially. A reader desiring information on a specific topic area, however, can refer to the particular volume of interest.

Another task under this contract was to update the literature review performed for NHTSA under contract DOT-HS-4-00994 (Joscelyn and Maickel 1977b). A report produced under this contract (Joscelyn and Donelson 1979) presents an annotated bibliography of recent literature on drugs and driving to supplement the parent volume. Another in this series of bibliographic reports is planned for publication in Summer of 1980.

1.2 The Purpose of Workshop I, The Identification of Drugs of Interest in Highway Safety

The aim of drug and driving research is twofold:

- to define the drug and driving problem, its nature and magnitude; and
- to identify drugs and groups of driver-users that should be targeted for control measures.

Substances that can impair driving performance number in the thousands. They vary greatly in their use, in their effects, and in their social, legal, and medical status. The number and diversity of drugs complicate research on drugs and driving as well as the resolution of methodological and other issues. Practical constraints limit the number and type of drugs that can be investigated. For example, a specific question concerns which drugs should be included in the chemical testing of driver body fluids. Because funding available for their study is limited, the number and types of drugs under consideration must also be limited, preferably to those of greatest interest in highway safety. Workshop I addressed this issue. Its purpose was to identify drugs (1) that should be the focus of near-term, NHTSA-sponsored research on drugs and driving, and (2) that should be the focus for discussing research issues in the other workshops.

In highway safety, the term **risk** has been defined as the likelihood, or probability, of a traffic crash and its consequences, such as loss of life or property, injury, medical costs, etc. Thus, for the purpose of this workshop, a "drug of interest" was defined as one whose use by drivers has a **potential** to increase traffic crash risk, or more simply, a **risk potential.** Although it can be argued that all drugs have a finite risk potential, the contribution of many drugs to highway safety problems is probably negligible, if measurable at all. For instance, a drug used by one in ten thousand (or even one in a thousand) drivers involved in a fatal crash would not justify large expenditures of funds for action programs directed at the drug or its user population. Drugs of greatest interest, therefore, would be those whose use had the greatest potential

to increase the probability of a traffic crash.

At present, a lack of data precludes an objective answer to the question of which drugs warrant further study in drug and driving research. Nevertheless, a set of drugs that appear to pose the greatest risk to highway safety must be selected on the basis of present knowledge. Prior efforts to identify high-risk drugs have not applied methods that permit a structured, comprehensive approach (Smart 1974; Waller 1975; Clayton 1976; Smart 1977; Willette 1977). Past reports have singled out a few drugs that are widely available and used. For example, many mention marijuana and tranquilizers in this context. The risk potential of other substances with lower profiles of social interest has been largely ignored. Therefore, this workshop had two main objectives:

- to develop a way to estimate the risk potential of drugs, based on an approach that formulates subjective judgments of experts and that synthesizes present knowledge in distinct fields related to drugs and driving; and
- to produce an initial rank ordering of identified drugs of interest, based on subjective estimates of their risk potential.

The area of drugs and highway safety contains elements of both drug and transportation research. Drug and driving research itself is multidisciplinary. In order to estimate the risk potential of drugs, research findings in many fields must be gathered for synthesis. Basic research in pharmacology, and the behavioral and social sciences, as well as applied research, supply data needed for a comprehensive approach. Few persons, however, have command of all the data required. Thus, the workshop featured the following, eclectic approach.

An effort was made to assemble a cross-disciplinary group. The researchers invited to the workshop each represented one or more disciplines directly or indirectly related to drugs and driving. Areas of expertise included physiology; pharmacology (basic, clinical, and behavioral); toxicology; psychology (experimental, clinical, and social); evaluation research; medicine; law; and epidemiology. The experts (see List of Participants, Appendix A) have published in the following areas

relevant to this workshop:

- the pharmacological, behavioral, and psychological effects of drugs, including effects on human performance related to driving;
- the interactive effects of alcohol and other drugs;
- the interactive effects of drugs and conditions of disease;
- the use of drugs in society (drug use patterns);
- the presence and amount of drugs found in drivers; and
- the relationship between concentrations of drugs in human biofluids and their effects on behavior.

The participants, both government and nongovernment, functioned as an interdisciplinary group in an informal workshop setting. A moderator with an extensive background in alcohol, drugs, and highway safety functioned as "lowest common denominator." The moderator served (1) to link panel members from different areas of research, (2) to provide a ground for basic understanding in a many-disciplined group, and (3) to ensure that the workshop's product could be used by a lay audience.

Based on the objectives of the workshops, the task assigned to the group was twofold. First, the group was asked to devise a procedure for estimating the risk potential of drugs that exist in present use; the framework of the procedure was to provide a basis for evaluating drugs introduced later. Second, the group was asked to use the procedure to obtain a list of drugs ordered according to their estimated risk potential. Explanation of the reasoning that produced the list was also an explicit goal.

1.3 Scope of Report

This report has four sections. The three that follow are briefly described below.

Section 2.0, "A Procedure for Estimating the Highway Safety Risk Potential of Drugs," describes the characteristics, approach, and structure of the procedure developed in this workshop.

Section 3.0, "A Rank-ordering of Drugs of Interest in Highway Safety," reports the findings of this workshop.

Section 4.0 presents the conclusions and recommendations of the panel.

Appendix A provides a list of the workshop participants.

References cited in the report are listed in a bibliography following the appendix.

2.0 A PROCEDURE FOR ESTIMATING THE HIGHWAY SAFETY RISK POTENTIAL OF DRUGS

The initial sessions of this workshop dealt with its first main objective: to develop a procedure for estimating the risk potential of drugs. The procedure would constitute an operational definition of "estimating the highway safety risk potential of drugs." This section summarizes discussions among participants in four topic areas:

- desirable characteristics of a procedure to estimate risk potential;
- approaches to developing such a procedure;
- identification of criteria for estimating the risk potential of drugs; and
- rating of criteria in the procedure to estimate risk potential.

Preliminary discussion focused on the meaning of the term "drug." This word has both medical and nonmedical connotations and can refer to licit and illicit substances. A broad definition would include substances not normally regarded as drugs, that have adverse effects on driving and to which the driving population may be exposed (e.g., carbon monoxide and volatile solvents). Thus, to avoid the question of whether a given substance is a "drug," the group first adopted the following general definition: a drug is any substance which, introduced into an organism, produces a functional change or effect. Of interest, of course, were effects that could increase the likelihood of a traffic crash. The following discussions were based on these definitions.

2.1 Desirable Characteristics of a Procedure to Estimate Risk Potential

Participants first discussed major characteristics or attributes desirable in a procedure to estimate the risk potential of drugs.

First, the procedure should be **comprehensive,** incorporating specific features of drug use and current drug problems. These include:

- use of two or more drugs at the same time ("polydrug" or "multidrug" use);
- effects of combined drugs (drug interactions);
- regular (chronic) use of a drug versus a single (acute) use;
- human characteristics that influence the nature and degree of drug effects, for example, the age and sex of the user;
- active versus passive intake of drugs; and
- other patterns in the use of drugs that imply needed features of programs to counter their adverse effects in driving populations (countermeasures), for example, the frequency of driving after drug use.

In addition, because a single estimate of risk potential was required for each drug or class of drugs, the procedure had to integrate or combine these and other aspects of drug use and effects, such as variations in geographic patterns of usage and in individual responses.

Second, the procedure should be **flexible.** It should provide a starting point for dealing with the broad range of substances and diverse patterns of drug use that could present highway safety problems now and in coming years. The procedure should be **specific** enough to provide a preliminary estimate of the risk potential of known drugs and their current patterns of use. The procedure should also be **general** enough to apply both to new substances as they are introduced and to new or changing patterns of drug use. Furthermore, the procedure should apply present (albeit limited) knowledge relevant to drugs and highway safety and should still allow the inclusion of more and new kinds of information as it becomes available.

Third, the procedure should be useful in the planning and design of research to define the drug and driving problem. The estimated risk potential of a drug indicates the level of effort needed for its further study. This estimate should reflect a **national** perspective, focusing on

large driving populations rather than predicting for the individual driver.

The group stressed that a procedure or approach with these characteristics demands that persons applying it have a comprehensive knowledge of drugs; of methods and techniques used to produce data for synthesis; and of limitations in methodology, past and present. Otherwise, findings both wrong and misleading could result.

The findings for drugs of interest resulting from use of this kind of procedure can only be validated by epidemiologic research, including surveys

- that indicate increased traffic crash risk associated with the use of drugs by drivers; and
- that determine the magnitude of risk attributable to the effects of drugs on driving performance.

Beyond identifying drugs or classes of drugs as priority concerns for further research, a procedure to estimate the risk potential of drugs may also serve to identify new drug products or changing patterns of drug use that unequivocally appear to pose problems for highway safety. A response to such perceived problems might be initiated without need for extensive research. For the purpose of targeting drugs or user populations for possible control action, however, it would be desirable (1) to replicate findings for the drugs of interest using the procedure developed in this workshop and (2) to refine the procedure through additional efforts by another group of experts. In this way, potential problems stemming from drug use among drivers could be identified with greater precision.

In summary, a procedure to estimate the highway safety risk potential of drugs represents a way to identify drugs of greatest interest and to focus research efforts to define the drug and driving problem. Its characteristics should enable both inclusion of all information relevant to its purpose and its use over time. Pending the validation of findings resulting from the use of this kind of procedure, replication of findings and refinement of the procedure to be developed in this workshop could lead to its application in targeting drugs and user populations for action

programs.

2.2 Approaches to Developing a Risk-Estimation Procedure

The participants suggested a number of ways to develop a procedure to estimate the risk potential of drugs.

The alcohol and highway safety experience was proposed as a basis for further discussion. Research to define alcohol's use and effects in driving populations forms a pattern or framework that has guided efforts concerning other drugs. Using this framework, the group could organize knowledge on other drugs for later evaluation. This approach has advantages and disadvantages. On one hand, alcohol is a drug that is familiar to most people. The alcohol-highway safety problem is the most studied drug-and-driving problem. On the other hand, alcohol is unique—chemically, pharmacologically, and socially. Alcohol is a single, simple entity. Widely consumed in beverage form, it is used almost entirely for "recreational" purposes. Other drugs differ greatly, not only from alcohol, but also from each other. For example, most other drugs are complex chemicals; some, such as marijuana, are complex mixtures of chemicals. Most drugs other than alcohol are used therapeutically in the treatment of disease. In addition, two facts not applicable to most drugs have facilitated efforts to define and to deal with the alcohol and driving problem:

- as commonly used, the taking of any alcoholic beverage results in measurable concentrations of a single active drug (ethanol); and
- the higher the dose (or concentration of ethanol in blood), the more predictable its effect and the less user characteristics (e.g., age, sex) influence the magnitude of effect.

In contrast, many drugs have active metabolites that contribute to their effects; and most psychotherapeutic drugs, in doses commonly used, produce a much more marked variability in the magnitude of response. The panel concluded that, alone, research on alcohol does not provide an adequate basis for discussing the risk potential of other drugs.

Several participants suggested approaches that involved a review and evaluation of present knowledge of drugs (other than alcohol) and driving. The approaches were similar in that each proposed to select drugs based on prior findings and to add other drugs believed missed by past research. The approaches differed in the type of data first applied. One approach, for example, was to consider those drugs detected in drivers and to ascertain which drugs were not detected by the analytical techniques employed. Other approaches emphasized demographic variables, patterns of drug use, and research on drug effects, both basic and applied. The group concluded that the approaches were too limited for the stated purpose of the risk-estimation procedure. In some areas, particularly in the study of drugs in drivers, available data did not provide an adequate information base; an inaccurate, biased estimate of risk potential might result. For example, such an approach would select many drugs only because they were studied in the past; it would exclude other drugs a priori.

Another general approach involved the identification of **criteria** for estimating a drug's risk potential prior to discussing particular drugs or classes or drugs. Participants could either (1) list specific criteria by which to estimate risk potential or (2) develop lists of drugs believed to have a substantial risk potential and then, by a process of induction, identify criteria applied intuitively in compiling the drug lists.

The approach finally agreed upon by participants contained some elements of all those described above. Basically, the panel would first define **criteria of risk** and then estimate risk potential based on available information pertaining to these criteria. The prior identification of risk criteria has several advantages. **First,** it promotes a systematic assembling of many types of information about each drug or class of drugs. **Second,** it allows the inclusion of criteria for which few or no data yet exist but which could aid in later attempts to estimate risk potential. This ensures that relevant information now unavailable, but forthcoming in the future, would find a place in the procedure. **Third,** this approach excludes no drug from consideration a priori.

Although risk criteria would not be based solely on the alcohol and

highway safety experience, they would reflect acknowledged parallels between research on alcohol and that for other drugs. For example, findings from relevant epidemiologic and experimental studies of all kinds would be categorized. In this way, the criteria would cover both the patterns of use and the effects of drugs. Participants recognized that, for some drugs, either general category—use or effect—would be sufficient for estimating risk potential. For example, drivers might never use a psychotherapeutic drug administered only to nonambulatory patients in a hospital. Other drugs, though widely used in the general driving population, might have no discernible effects on driving performance. Participants noted, however, that the use and effects of most drugs cannot be evaluated separately in estimating risk potential.

The specification of risk criteria and the categorization of available information would facilitate a complete evaluation of risk potential for each drug or class of drugs of interest.

2.3 Criteria for Estimating the Risk Potential of Drugs

The panel identified two distinct sets of criteria for estimating the risk potential of drugs. One set, termed "Exposure," includes risk factors related to the use and users of drugs. In the other set, "Effects," criteria pertain only to those effects of drugs believed relevant to driving. Of secondary interest were effects that enhanced driving ability or, when drugs were not used, effects from their absence that degrade driving ability. Under the major headings, "Exposure" and "Effects," the panel listed subgroups of factors needed for estimating risk potential. These are briefly described below.

2.3.1 Risk Factors Related to Exposure.

Under Exposure, the panel formed two subgroups of risk factors: **characteristics of the exposed population** and **characteristics of exposure (use).** Within these, simple questions specify risk factors to which operational measures apply. The operational measures define the data of value for the risk-estimation procedure.

The first grouping, chararacteristics of the exposed population, contains

data that answer the questions:

- Who uses the drug?
- Why is the drug used?

"Who" refers to such variables as age, sex, ethnicity, socioeconomic status, health status, and whether users of a drug belong to the driving population. "Who" might also refer to measures of driving ability or driving experience, when this information is available. These characteristics can greatly influence the risk potential of certain drugs. For example, some drugs with effects that impair driving may be used mostly by persons below driving age; their estimated risk potential would thus be low. "Why" pertains to the reasons or motivations for use of a drug. Drugs commonly used for "recreation" (i.e., intoxication) would be likely to have a higher risk potential than similar drugs used only as therapeutics.

The second grouping, characteristics of exposure (use), is more extensive:

- How is the drug used?
- How often is the drug used?
- What amount of the drug is normally taken?
- How prevalent is its use in the general population?
- What is the availability of the drug?
- When is the drug normally used?
- Where is the drug normally used?
- With what other drugs, if any, is the drug commonly combined?

"How" refers both to the route of administration (e.g., oral, intravenous) and to whether exposure is active or passive. **Active** exposure includes, for example, self-administered medication or administration of drugs by authorized medical personnel; the unwitting (or unavoidable) intake of a toxic substance in the environment is an example of **passive** exposure. "How often" includes two aspects of drug use: the

protocol (how many doses per unit time for how long) and the history (how many times a protocol was used). For example, the intensity of a drug's effects may differ among chronic, subacute, and acute use. The "normal" amount of drug taken aids in estimating the degree of expected effect in the exposed population. The prevalence of drug use includes measures of a drug's use by the general population (e.g., prescription units per year). Although the frequency of use of a drug is to some extent a function of its availability, when little or no data exist on its use, its availability may aid in estimating the drug's risk potential. "When" and "where" are factors that relate the use of drugs to driving itself. For example, a drug administered only to inpatients in hospitals should pose little risk to highway safety. The final factor concerns "polydrug" use, the combined use of two or more drugs. Some drugs with mild effects may, when taken with others, especially alcohol, produce much greater effects than otherwise.

Taken together, these risk factors and their operational terms outline a taxonomy of exposure and describe, at least partially, one aspect of the risk potential of drugs.

2.3.2 Risk Factors Related to Effects. Under Effects are risk factors in both pharmacologic and behavioral (or psychological) categories. To estimate the risk potential of drug effects requires that both types of effects be considered together. First, the same action of the drug underlies both pharmacological and behavioral effects; second, these effects overlap to some degree. Moreover, by knowing a drug's basic pharmacology, one can often predict its general effects on behavior. For example, central nervous system depressants will generally impair vigilance. Studies of behavior, however, do show the nature and degree of drug effects in tests more closely related to driving. To accommodate findings in both research areas, the panel defined two subgroups of risk factors for pharmacologic and behavioral data on drug effects.

Unfortunately, for most drugs, comprehensive data on human behavioral effects are not available. Information specifically related to drug effects on driving-related skills is especially sparse. For most drugs,

particularly new drugs, only basic pharmacologic data exist:

- information about pharmacologic effects and pharmacokinetic characteristics of a drug in animals, including chronic and acute toxicity tests in several species;
- data from initial and controlled clinical studies of a new drug in normal volunteers and patients (to demonstrate its efficacy and safety), with some information on its pharmacokinetics and side effects in man; and
- limited data from a drug's general clinical use, after approval for marketing.

Beyond these data, the availability of information on a drug's effects in man, pharmacological or behavioral, depends largely on the interest--and funding--of researchers. For a few drugs, like those receiving some social attention (marijuana, antianxiety agents), much experimental work is done. But for other drugs, very few published data exist. Unfortunately, for any of the drugs of interest, few of the experimental efforts are directly relevant to the study of drug effects on skills related to driving. With this in mind, the panel specified risk factors to which available data on most drugs could be applied.

The column of pharmacologic risk factors divided drug effects into two kinds: pharmacodynamic (the effect of a drug on the body) and pharmacokinetic (the effect of the body on the drug). Pharmacodynamic effects include those most likely known for any drug, for example, effects reported to the Food and Drug Administration (FDA) for an investigational new drug (IND), as well as early clinical data from studies for a new drug application (NDA) to the FDA. Effects that pertain to highway safety risk potential include, but are not limited to, the following:

- central nervous system effects (stimulation, depression);
- skeletal muscle responses;
- pupil, eyelid responses;
- self-administration (a test for the abuse potential of drugs);

- interactions with other drugs, including alcohol; and
- clinical data in man:
  - duration of the action and presence of drug;
  - some behavioral effects, side effects;
  - tolerance.

Pharmacokinetic data describe the absorption, distribution, metabolism (both rate and route), and excretion of drugs. These factors may modify the intensity of a drug's effects. How quickly a drug is absorbed, whether it reaches the brain, whether a metabolite with effects of its own is produced by the body, how quickly a drug is removed from its active site—each factor can increase (or decrease) the risk potential of a drug. Pharmacokinetic data also describe such effects as tolerance (e.g., increased metabolism of a drug) and interaction with other drugs (e.g., the ability of a drug to displace other drugs bound [and therefore inactive] to blood proteins). Pharmacokinetic data of themselves are not adequate to evaluate a new drug but are needed in conjunction with pharmacodynamic data for a complete evaluation.

Taken together, the risk factors described above are not a complete listing of all the pharmacologic characteristics of a drug, but rather the minimum that the FDA requires. The structured process of developing and testing a new drug then feeds into a nonsystematic process of investigation within the scientific community. From this come separate reports of drug effects on skills related to driving.

For behavioral effects of drugs, a general scheme was designed to include most findings in this research area and to relate them to driving. Main headings are:

- sensory reception,
- information sampling,
- information processing,
- decision-making,
- response, and
- judgment.

These headings parallel psychological classes of drug effects: sensory

functions, perceptual skills, cognitive skills, motor skills, and motivation (cf. Clayton 1976). The advantage of these headings is their apparent relation to the driving task. This outline allows evaluation of the full range of data available on drug effects. The panel noted that "judgment" was an inclusive heading, and effects of drugs on judgment could affect any stage of behavior listed above this heading.

In summary, the panel identified criteria by which to estimate the highway safety risk potential of drugs. Two categories of criteria--Exposure and Effects--were specified. The set of risk factors under Exposure deals with the characteristics of the use and users of drugs. The risk factors under Effects pertain to effects specific to driving and to other effects for which data exist for most drugs. They present a limited but realistic picture of the data available to evaluate a new drug and to decide whether the drug should be tested for its effects on skills related to driving. Taken together, these criteria incorporate the major factors of the risk potential of drugs.

2.4 Rating of Criteria for Estimating the Risk Potential of Drugs

One purpose of the desired risk-estimation procedure was to structure the subjective judgments of experts with a framework that arranges objective knowledge of drugs and highway safety. As described above, the panel produced an outline of risk factors to aid the systematic review of data for each drug or class of drugs. An estimate of actual risk could not be expected. What was expected was a ranking of drugs according to their estimated **potential** to increase the likelihood of a traffic crash and associated losses. **Subjective estimates** of risk potential would be developed for drugs of interest from ratings of the two sets of risk criteria. To complete the required procedure for estimating risk potential, a rating scheme was needed to facilitate the process.

The panel faced three questions in devising a rating scheme for estimating the risk potential of drugs based on the specified criteria:

- How should each set of risk factors--Exposure and Effects—be rated?

- How should the separate ratings be combined to yield an integral estimate of risk potential?
- What standard or reference should be used as a basis for estimating the risk potential of drugs?

In answering these questions, the panel completed the task of developing a risk-estimation procedure.

The participants had defined two distinct sets of risk criteria that could be evaluated separately in terms of various risk factors. Two ways to rate each set were suggested. One approach would assign a high (H), medium (M), or low (L) rating to each risk factor for which data existed. Participants raised two objections. First, while this rating system might be desirable in a category lacking hard data, an H for one risk factor might not be as important as an M for another. In other words, risk factors themselves varied in importance. Second, an **ordered** ranking of drugs was needed; this approach would not produce a detailed ranking based on single estimates of risk potential.

The other approach proposed for rating risk criteria would establish an ordinal scale of one to ten for each set of criteria. This approach, which was adopted, permits greater differentiation among drugs. At the same time, risk factors within each set of criteria could receive relative ratings of high, medium, and low as necessary. Once data pertaining to each risk factor were assessed, a single numerical rating for the whole set of risk factors would be assigned.

Because the scheme described above produced separate ratings for Exposure and Effects, some method for developing a single estimate of risk potential was still required for the purpose of rank ordering the drugs of interest. It was recognized that the numerical ratings for Exposure and Effects were numbers assigned by ordinal measurement (that is, 10 is greater than 9, 9 is greater than 8, etc.) and as such could not be combined logically by arithmetic operations (e.g., addition, multiplication). It was also recognized, however, that greatly disparate ratings of Exposure and Effects tended to cancel each other out. For example, a widely used drug with no effect on driving ability and a powerful drug

never used by drivers both had negligible risk potential. A drug occasionally used by drivers with moderate effects on driving performance would have a higher estimated risk potential. Thus, to simplify the process of risk-estimation and to facilitate subjective judgments required to rank order the drugs of interest, the panel decided to combine the numerical ratings of Exposure and Effects by simple multiplication. The ratings so combined could be supplemented by comparing drugs or groups of drugs with others previously rated to develop as consistent a rank ordering as possible.

The panel stressed that the mathematical operation was not essential to the risk-estimation procedure. It was simply a convenient technique for producing an initial rank ordering of drugs of interest. **In other words, the numbers obtained by combining the ratings cannot be considered a numerical indication of a drug's potential to increase traffic crash risk.**

Finally, in order to establish a reference for estimating the risk potential of drugs, the panel assigned to alcohol an arbitrary rating of ten for both exposure and effects. In doing so, participants acknowledged alcohol as the primary drug-and-driving problem. (The rating of ten for the effects of alcohol indicates its ability to impair driving greatly at doses often consumed. Although all drugs may be presumed to have this ability at some dose level, not all drugs are normally used in such amounts. The rating of effects for a drug other than alcohol, therefore, would reflect the normal dose or its average pattern of use.) The ratings for alcohol served as a standard for rating the risk criteria for other drugs. The ratings for other drugs would be subjective estimates of their risk potential, relative to alcohol. The numbers thus obtained are not in themselves indicative of actual relative risk.

Participants then tested the risk-estimation procedure by examining data on several drugs. In reviewing the rank order determined by its initial use, the panel judged the procedure satisfactory. Nevertheless, it was recognized that combining Exposure and Effects ratings by multiplication was artificial and should be supplemented with careful, iterative, subjective judgments throughout the rank-ordering process. In

fact, the ratings themselves would be based partly on previous ratings for drugs already considered. Thus, the final rank ordering of drugs of interest would reflect not only the combined ratings of risk criteria but also the subjective judgments of participants.

Table 2-1 presents an outline and summmary of the risk-estimation procedure developed for use in this workshop.

2.5 Summary

In order to produce a rank ordering of drugs of interest, the panel of this workshop developed a procedure to estimate their highway safety risk potential. Desirable characteristics of such a procedure are:

- the comprehensive inclusion of all relevant information about any substance (drug) of interest;
- the flexibility to incorporate new information on a drug presently in use and to handle data on new drug products introduced at a future time; and
- the ability to produce estimates of relative risk potentials for drugs of interest so that the procedure could be useful in the planning and design of research to define the drug and driving problem.

The approach to developing a risk-estimation procedure involved several steps:

- identification of risk factors related to highway safety based on criteria pertaining to Exposure (use, user) and Effects (pharmacological, behavioral);
- development of a rating scheme to produce a single estimate of risk potential for each drug or class of drugs, relative to alcohol; and
- testing the procedure to evaluate its usefulness in developing a rank-ordering of drugs of interest.

The procedure developed in this workshop appeared useful for its stated purpose. Due to the arbitrary (though convenient) method for combining ratings of risk criteria, participants reserved the opportunity for subjective judgments in conjunction with the rating scheme. In this way, a consistent rank ordering of drugs could be ensured.

TABLE 2-1

A GENERAL OUTLINE OF A PROCEDURE TO ESTIMATE THE HIGHWAY SAFETY RISK POTENTIAL OF DRUGS, RELATIVE TO ALCOHOL

A. CRITERIA OF RISK: FACTORS RELATED TO POTENTIAL HIGHWAY SAFETY RISK

EXPOSURE

- Characteristics of the Exposed Population
  - Who (age, sex driver...)
  - Why (medical, recreation...)
- Characteristics of Exposure (Use)
  - How (route or mode of drug exposure)
  - How often (chronic, acute...)
  - How much (dose, amount...)
  - How prevalent (frequency of use in society)
  - Availability
  - When used (relative to driving)
  - Where used

EFFECTS

Pharmacology

- Pharmacodynamics
  - CNS effects
  - Skeletal muscle response
  - Pupil, eyelid response
  - Self-administration
  - Clinical data (duration of effect and of presence of drug; human behavioral effects, side effects; tolerance; drug interactions)
- Pharmacokinetics
  - Absorption
  - Distribution
  - Metabolism (rate, route)
  - Excretion
  - Tolerance
  - Drug interactions

Behavior

- Sensory Perception
- Information sampling
- Information processing
- Decisionmaking
- Response
- Judgment (includes each of the above factors)

B. APPROACH TO DEVELOPING SUBJECTIVE ESTIMATES FOR RANKING DRUGS OF INTEREST

RATING OF RISK CRITERIA

- Exposure rating (1-10)*
- Effects rating (1-10)*

COMPARISON OF DRUG (OR DRUG GROUP) WITH OTHERS PREVIOUSLY RATED

*Alcohol was assigned an arbitrary rating of 10 for both Exposure and Effects.

3.0 A RANK-ORDERING OF DRUGS OF INTEREST IN HIGHWAY SAFETY

One purpose of the procedure outlined in the previous section was to rank drugs of interest on the basis of subjective estimates of their potential to increase the likelihood of traffic crashes and concomitant losses, relative to alcohol. This section describes how the panel applied the procedure and presents its findings.

3.1 Application of the Procedure to Estimate the Highway Safety Risk Potential of Drugs

To estimate the risk potential of drugs, the panel proceeded as follows. Panel members independently listed the drugs or classes of drugs they believed should be considered for further research in highway safety. Choices were restricted to drugs whose use has a possible effect on driving. The lists were then pooled to obtain a preliminary identification of drugs of interest.

The lists generated by participants identified drugs individually by generic and trade names; by chemical and pharmacologic groupings or classes; and by types of treatment for which drugs are used (therapeutic classes). Common terms for drugs and classes of drugs of interest were needed to indicate which drug or drugs were included. For single drugs or substances, the panel used generic or common names; for drug groupings, a term indicating the use or therapeutic purpose of member drugs was adopted.

The panel initially formed two subgroupings of the following drug classes:

- antianxiety agents (Group I-High Use; Group II-Low Use);
- narcotic analgesics (Group I-High Use; Group II-Low Use);
- antihistamines (Group I-Prescription; Group

II-Over-the-counter); and

- sedative-hypnotics (Group I-Nonbarbiturates; Group II-Barbiturates).

Group II sedative-hypnotics were further subdivided into Group IIa and Group IIb, the former including pentobarbital, amobarbital, and secobarbital, these drugs being more often cited as "drugs of abuse." Finally, individual members of some drug groups were rated separately when their patterns of use or their effects could be distinguished from others in the drug group.

The panel then rated the exposure and effects of each drug or drug grouping to obtain ordinal numbers representing subjective estimates of risk potential. Two methods of rating were used: silent ballot by panel members and group consensus. In the former method, ranges of values were recorded and average values were rounded to whole numbers. As the rank order developed, the relative position of drugs and drug groups helped to place other drugs of interest in the list.

3.2 Results

The panel rated in order the drugs of interest listed in Table 3-1. The drugs of interest are listed as they were rated--as individual agents, subgroupings, or drug classes. The second column of Table 3-1 lists examples of drug groupings identified only by a pharmacologic or therapeutic classification (see note following Table 3-1). Along with the generic name of single substances are listed the class and, where appropriate, the subgrouping of drugs to which it belongs. Note that separate groupings of different drug classes cannot themselves be combined nor can they be considered members of a large grouping. For example, Group I antianxiety agents and Group I narcotic analgesics indicate subgroupings within the respective drug classes **only.**

The third column of Table 3-1 presents the numerical ratings for Exposure and Effects. These numbers represent subjective estimates of risk potential based on a synthesis of drug-specific information pertaining to many risk factors, as outlined in Section 2.0

TABLE 3-1

THE DRUGS OF INTEREST AND RATINGS FOR EXPOSURE AND EFFECTS

DRUG OR DRUG GROUPING IN ORDER OF EVALUATION (GENERIC OR OTHER NAMES)	EXAMPLES *	RATING	
		EXPOSURE	EFFECTS
ethanol	alcoholic beverages	10	10
phencyclidine (PCP)		1	10
cannabis sativa	marijuana, hashish	8	6
diazepam (Antianxiety Agent, Group I)		8	8
chlordiazepoxide (Antianxiety Agent, Group I)		4	5
Antianxiety Agents, Group II	meprobamate, oxazepam, hydroxyzine, prazepam, lorazepam	1	5** (2-8)
codeine (Narcotic Analgesic, Group I)		6	6
pentazocine (Narcotic Analgesic, Group I)		3	5
d-propoxyphene (Narcotic Analgesic, Group I)		5	5
Narcotic Analgesics, Group II	morphine, pethidine, methadone, hydromorphone	2	7
oxycodone (Narcotic Analgesic, Group II)		3	7
flurazepam (Sedative-hypnotic, Group I)		4	7
glutethimide (Sedative-hypnotic, Group I)		2	5
ethchlorvynol (Sedative-hypnotic, Group I)		1	5
methaqualone (Sedative-hypnotic, Group I)		2	5
chloral hydrate (Sedative-hypnotic, Group I)		1	5
Sedative-hypnotics, Group IIa	amobarbital, secobarbital, pentobarbital (inclusive)	3	7

TABLE 3-1

THE DRUGS OF INTEREST AND RATINGS FOR EXPOSURE AND EFFECTS (Continued)

DRUG OR DRUG GROUPING IN ORDER OF EVALUATION (GENERIC OR OTHER NAMES)	EXAMPLES *	RATING	
		EXPOSURE	EFFECTS
Sedative-hypnotics, Group IIb	butabarbital, butalbital, mephobarbital, metharbital	1	7
Anticonvulsants	phenobarbital, phenytoin, primidone, carbamazepine, ethosuximide, trimethadione	1	4
Volatile Solvents	xylene, gasoline, trichloroethylene, toluene, butylnitrite	6	5
carbon monoxide		10	1
Antihistamines, Group I (over-the-counter)	diphenhydramine (OTC doses), chlorpheniramine, methapyrilene, doxylamine	9	2
Antihistamines, Group II (prescription)	diphenhydramine, pyrilamine, chlorpheniramine, pheniramine	1	5
Stimulants	d-amphetamine, methamphetamine, phenmetrazine, methylphenidate	2	2-3
caffeine	caffeinated beverages, OTC stimulants	10	1
cocaine		1	3
nicotine		9	1
Antidepressants	amitriptyline, nortriptyline, imipramine, desipramine, doxepine, lithium	4	3
Hallucinogens	LSD, DMT, mescaline, psilocybin	1	10

TABLE 3-1

THE DRUGS OF INTEREST AND RATINGS FOR EXPOSURE AND EFFECTS (Continued)

DRUG OR DRUG GROUPING IN ORDER OF EVALUATION (GENERIC OR OTHER NAMES)	EXAMPLES *	RATING	
		EXPOSURE	EFFECTS
Antipsychotics	chlorpromazine, prochlorperazine, chlorprothixene, haloperidol, thioridazine	3	4
Anesthetics (outpatient therapy, dental surgery)	lidocaine, procaine, thiopental, methohexital, halothane, nitrous oxide	1	8
Antidiabetics	insulin, tolbutamide, phenformin	1	10
Antihypertensives	reserpine, propranolol, methyldopa, hydralazine	6	4
heroin		1	6

* The examples listed in column two of this table arose from one or two sources. The agents either were mentioned in the course of discussion or were selected by HSRI staff following the workshop. Before completion of this report, workshop participants had the opportunity to review this table. Additions and deletions of drugs under Examples were made based on their comments. The purpose of including examples is to represent members or subclasses of drugs within each grouping ranked. Some drugs given as examples, therefore, may themselves be rarely used by drivers. The examples are intended to illustrate the groups of drugs evaluated by the panel, not necessarily to identify specific drugs of interest within each group.

** This is the average rating for this group of drugs; the range of ratings for individual compounds is given in parentheses

Table 3-2 presents the rank order of drugs of interest as developed in this workshop. The order of drugs and drug groups (or classes) reflects the subjective estimates described above. Rankings of the drugs of interest by individuals on the panel differed slightly in the relative placement of one or more entries in Table 3-2; however, the listing represents the consensus of the panel as a whole.

TABLE 3-2

A RANK ORDERING OF THE DRUGS OF INTEREST

RANK ORDER	DRUG OR DRUG GROUPING	EXAMPLES *
1	ethanol	alcoholic beverages
2	diazepam (Antianxiety Agent, Group I)	
3	cannabis sativa	marijuana, hashish
4	codeine (Narcotic Analgesic, Group I)	
5	Volatile Solvents	xylene, gasoline, toluene, butylnitrite, trichloroethylene
6	flurazepam (Sedative-hypnotic, Group I)	
7	d-propoxyphene (Narcotic Analgesic, Group I)	
8	Antihypertensives	reserpine, propranolol, hydralazine, methyldopa, digoxin
9	oxycodone (Narcotic Analgesic, Group II)	
9	Sedative-hypnotics, Group IIa	secobarbital, pentobarbital, amobarbital (inclusive)
10	chlordiazepoxide (Antianxiety Agent, Group I)	
11	Antihistamines, Group I (over-the-counter)	diphenhydramine, chlorpheniramine, methapyrilene, doxylamine

TABLE 3-2

A RANK ORDERING OF THE DRUGS OF INTEREST (Continued)

RANK ORDER	DRUG OR DRUG GROUPING	EXAMPLES *
12	pentazocine (Narcotic Analgesic, Group I)	
13	Narcotic Analgesics, Group II	methadone, pethidine, morphine, hydromorphone
14	Antipsychotics	chlorpromazine, prochlorperazine, chlorprothixene, haloperidol
15	Hallucinogens	LSD, DMT, mescaline, psilocybin
15	caffeine	caffeinated beverages, OTC stimulants
15	carbon monoxide	automobile emissions, cigarettes
15	glutethimide (Sedative-hypnotic, Group I)	
15	methaqualone (Sedative-hypnotic, Group I)	
16	nicotine	tobacco products
17	Anesthetics (outpatient therapy, dental surgery)	lidocaine, procaine, thiopental, methohexital, halothane, nitrous oxide
18	Sedative-hypnotics, Group IIb	other barbiturates, e.g., butabarbital, butalbital, mephobarbital, metharbital
19	heroin	

TABLE 3-2

A RANK ORDERING OF THE DRUGS OF INTEREST (Continued)

RANK ORDER	DRUG OR DRUG GROUPING	EXAMPLES *
20	Antihistamines, Group II (prescription)	diphenhydramine, pyrilamine, chlorpheniramine, pheniramine
20	Stimulants	d-amphetamine, methamphetamine, phenmetrazine, methylphenidate
20	ethchlorvynol (Sedative-hypnotic, Group I)	
20	chloral hydrate (Sedative-hypnotic, Group I)	
20	Antianxiety Agents, Group II	oxazepam, prazepam, lorazepam, hydroxyzine, meprobamate
21	Anticonvulsants	phenobarbital, phenytoin, primidone, carbamazepine, ethosuximide, trimethadione
22	cocaine	
23	Antidiabetics	insulin, phenformin, tolbutamide

* The examples listed in column two of this table arose from one or two sources. The agents either were mentioned in the course of discussion or were selected by HSRI staff following the workshop. Before completion of this report, workshop participants had the opportunity to review this table. Additions and deletions of drugs under Examples were made based on their comments. The purpose of including examples is to represent members or subclasses of drugs within each grouping ranked. Some drugs given as examples, therefore, may themselves be rarely used by drivers. The examples are intended to illustrate the groups of drugs evaluated by the panel, not necessarily to identify specific drugs of interest within each group.

4.0 CONCLUSIONS AND RECOMMENDATIONS

The purpose of this workshop was to identify drugs that may significantly increase risk to highway safety. Lacking, however, were established methods and criteria for estimating the risk potential of drugs. This required the design of a risk-estimation procedure within the workshop. A procedure to estimate present as well as future potential risks was desired. Taking into account specific aspects of current drug problems, the procedures had to achieve an overall national estimate of their potential risk to highway safety. The workshop accomplished both objectives.

The success of the workshop is due in part to the approach chosen by the panel. Experts discussed and reached agreement on the risk potential of drugs by first making explicit the criteria for subjective judgments that otherwise would have remained implicit and immune from critical review. This approach offered several advantages. Initial discussion focused on specific factors, not values, of risk potential. In later sessions of this workshop, judgments were made. These judgments proceeded more from rational discourse on data, their limitations and their contribution to the risk potential of each drug or drug class than from nonverbalized, intuitive processes. The results are subjective estimates. But this approach helped formulate expert opinions, making the difference between, in the words of one panel member, "a guess and an educated guess."

The procedure as employed produced an ordered ranking of the drugs of interest, but it had additional value. The method helped structure the consideration of myriad facts about drugs. It provided a condensed framework of criteria to bring to mind the factors required for estimating risk potential. The procedure presented risk criteria in terms of operational measures of variables related to driving. Its design facilitated the comprehensive use of available data pertaining directly and indirectly to highway safety. Above all, the procedure organized and made

systematic the process of estimating risk potential; it helped to maintain consistency over an extended list of drugs so that ratings might be comparable among drugs and drug groups rated serially.

An important consideration was that the procedure provide a model or algorithm for estimating the risk potential of new drugs and of changing patterns of drug use. The panel deemed the present method a fair though unrefined beginning. The procedure in its present form is not a "model." First, the component factors are related only by a classification scheme; second, the relative importance, or weighting, of factors has not been determined. Thus, the procedure is more a taxonomy than a model. The procedure is not represented as the best or most rigorous possible; it does provide a starting point for the evaluation of a more careful means to estimate the risk potential of drugs. In time, additional measures may apply to each element of this taxonomy; factors may be weighted to make subjective judgments more objective. Thus, in theory, a method could be developed to render much less subjective the rating of risk criteria.

As described in this report, the panel rated the drugs of interest for exposure and effects. The results are not a "risk identification"; that is, the ranking of drugs does not state their actual risk to highway safety. Instead, the subjective estimates based on present knowledge produced a kind of probability ordering of their **risk potential**, relative to alcohol. Only in the context of this procedure do the numerical ratings have meaning.

The present approach required much judgment to obtain an overall rating for each set of criteria. As stressed above, the ratings for Exposure and Effects result from the subjective weighing of factors by experts. Factors in both sets interact (e.g., use and user characteristics, user characteristics and drug effects). Ratings reflective of a national estimate of risk potential were requested of the panel. Variables showing nonhomogeneity in patterns of use (e.g., geographical variations in a drug's prevalence, coexistence of medical and nonmedical uses for a drug) were averaged subjectively. This subjective averaging was necessary to produce a single-valued estimate of the drug's risk potential. For these reasons,

to use the present approach requires experts knowledgeable in drugs and highway safety and related fields.

In the view of this panel of experts, the present procedure for estimating the risk potential of drugs produced a ranking that seems to reflect accurately the present state of knowledge in drugs and driving. This list of drugs of interest should be of value in making decisions about research in this area. In light of this experience, we recommend the following:

- Surveys to establish the actual increase in traffic crash risk associated with drug use among drivers should be funded.

  The rank-order of drugs of interest can only be validated by epidemiologic research. Surveys of drug use among drivers--comparing drug prevalence in both crash-involved drivers and drivers from the population at risk--are needed to define the drug and driving problem and to provide a basis for action programs to deal with any identified problem.

- The ranking of drugs and classes of drugs from this workshop should be replicated.

  Using the same procedure, or the same procedure refined, a different and larger group of experts should confirm estimates of the risk potential for these drugs relative to alcohol.

- Development of more objective methods of risk estimation should continue.

  This effort suggests several ways to refine the present method. Two are to increase the number of main headings and to create hierarchies of risk factors. The interaction and weighting of risk factors should also be studied.

- Data required by this procedure for evaluating risk criteria should be gathered for a more objective approach to estimating the risk potential of drugs.

  The nature of this workshop's effort, the constraints of time, and limited access to existing data precluded a more objective rating of exposure and effects for the drugs of interest. Future efforts would be enhanced by ready access to all relevant data. To accomplish this, desired

information must be identified, selected, collected, and stored for later use. Existing data should be filed conveniently in categories that parallel those of a risk-estimation procedure developed in this workshop.

In conclusion, this workshop produced a ground-breaking effort in providing a general procedure for estimating the highway safety risk potential of drugs. The present approach outlines risk criteria for identifying drugs that warrant closer monitoring for highway safety. It includes factors of risk that describe a drug's user population, its pattern of use, and its effects. The list of drugs of interest as ranked by this procedure should be the focus of near-term research in the area of drugs and driving. If research (studies of drug effects on driving skills, field studies of drugs in driving populations) establishes that a drug is a highway safety problem, this approach will also aid in the design and development of countermeasures.

APPENDIX A

LIST OF WORKSHOP PARTICIPANTS

DRUG RESEARCH METHODOLOGY

IDENTIFICATION OF DRUGS OF INTEREST IN HIGHWAY SAFETY RESEARCH

LIST OF WORKSHOP PARTICIPANTS

This workshop was held on 5-7 March 1978. The following persons participated, their titles, positions, addresses, and telephone numbers being those at the time of the workshop.

Fred B. Benjamin, Ph.D., D.M.D.
Senior Research Physiologist
U.S. Department of Transportation
National Highway Traffic Safety Administration
Trans Point Building
2100 Second Street, S.W.
Washington, D.C. 20590
Tel.: (202) 426-2977

Stephen D. Benson, Ph.D. NRD-42
Contract Technical Manager
U.S. Department of Transportation
National Highway Traffic Safety Administration
Trans Point Building
2100 Second Street, S.W.
Washington, D.C. 20590
Tel: (202) 426-2977

John A. Carpenter, Ph.D.
Director
Center of Alcohol Studies
Smithers Hall
Rutgers University
New Brunswick, NJ 08903
Tel: (201) 932-2190

Alan C. Donelson, Ph.D.
Assistant Research Scientist
Highway Safety Research Institute
The University of Michigan
Huron Parkway at Baxter Road
Ann Arbor, MI 48109
Tel.: (313) 763-1276

Pamela K. Ennis, Ph.D.
Scientist
Evaluation Studies Department
Addiction Research Foundation
33 Russell Street
Toronto, Ontario M5S 2S1
Tel.: (416) 595-6150

Michael A. Evans, Ph.D.
Assistant Professor of Pharmacology
Department of Pharmacology
University of Illinois
Chicago Medical Center
P.O. Box 6998
Chicago, IL 60680
Tel.: (312) 996-2379

James C. Garriott, Ph.D.
Chief Toxicologist
Southwestern Institute of Forensic Sciences
and
Assistant Professor
Department of Pathology and Pharmacology
University of Texas Southwestern Medical School at Dallas
P.O. Box 35728
Dallas, TX 75235
Tel.: (214) 638-1131

Kent B. Joscelyn, J.D.
Head, Policy Analysis Division
Highway Safety Research Institute
The University of Michigan
Huron Parkway at Baxter Road
Ann Arbor, MI 48109
Tel.: (313) 763-1276

Marvin M. Levy, Ph.D.
Research Psychologist
U.S. Department of Transportation
National Highway Traffic Safety Administration
3112 Trans Point building
2100 Second Street, S.W.
Washington, D.C. 20590
Tel.: (202) 426-2977

Markku Linnoila, M.D., Ph.D.
Head, Clinical Psychopharmacology Laboratory
Box 2921
Duke University Medical Center
Durham, NC 27710

Tel.: (919) 684-2044

Roger P. Maickel, Ph.D.
Professor of Pharmacology and Toxicology
Head, Department of Pharmacology and Toxicology
School of Pharmacy & Pharmacal Sciences
Purdue University
West Lafayette, IN 47907
Tel.: (317) 494-8430

James L. Nichols, Ph.D.
Highway Safety Management Specialsit
U.S. Department of Transportation
National Highway Traffic Safety Adminstration
Nassif Building
400 Seventh Street, S.W.
Washington, D.C. 20590
Tel.: (202) 426-9744

Oakley Ray, Ph.D.
Professor, Department of Psychology
Vanderbilt University
Associate Professor, Department of Pharmacology
Vanderbilt University School of Medicine
Chief, Mental Health and Behavioral Sciences Unit
Veterans Administration Hospital
Nashville, TN 37203
Tel.: (615) 327-4751 ext. 752

Harvey A. Siegal, Ph.D.
Assistant Professor
Department of Medicine in Society
School of Medicine
Wright State University
Dayton, OH 45435
Tel.: (513) 873-3050

BIBLIOGRAPHY

Clayton, A.B. 1976. The effects of psychotropic drugs upon driving related skills. Human Factors 18:241-52.

Joscelyn, K.B., and Donelson, A.C. 1979. Drugs and driving: A selected bibliography. Supplement one. National Highway Traffic Safety Administration technical report DOT-HS-803-879.

Joscelyn, K.B.; Jones, R.K.; Maickel, R.P.; and Donelson, A.C. 1979. Drugs and driving: Information needs and research requirements. National Highway Traffic Safety Administration technical report DOT-HS-804-774.

Joscelyn, K.B., and Maickel, R.P. 1977a. Drugs and driving: A research review. National Highway Traffic Safety Administration technical report DOT-HS-802-189.

Joscelyn, K.B., and Maickel, R.P. 1977b. Drugs and driving: A selected bibliography. National Highway Safety Administration technical report DOT-HS-802-188.

Smart, R.G. 1974. Use of psychoactive and hallucinogenic drugs in relation to driving risk. In Alcohol, drugs, and driving, ed. M. W. Perrine, pp. 334-37. National Highway Traffic Safety Administration technical report DOT-HS-801-096.

Smart, R.G. 1977. The problem of drugs and driving: An overview of current research and future needs. In Report on an international symposium on drugs and driving, eds. K. B. Joscelyn and R. P. Maickel, pp. 217-32. National Highway Traffic Safety Administration technical report DOT-HS-802-187.

Waller, J.A. 1975. Epidemiologic issues about alcohol, other drugs and highway safety. In Alcohol, drugs, and traffic safety. Proceedings of the Sixth International Conference of Alcohol, Drugs, and Traffic Safety, Toronto, 8-13 September 1974, eds. S. Israelstam and S. Lambert, pp. 3-11. Toronto, Canada: Addiction Research Foundation of Ontario.

Willette, R.E., ed. 1977. Drugs and driving. National Institute on Drug Abuse Research Monograph 11. U.S. Department of Health, Education, and Welfare publication no. (ADM) 77-432.