

DRUGS, DRIVING,  
AND  
TRAFFIC SAFETY

Edited by  
Robert E. Willette and J. Michael Walsh



WORLD HEALTH ORGANIZATION

GENEVA

1983

ISBN 92 4 170078 5

© World Health Organization 1983

Publications of the World Health Organization enjoy copyright protection in accordance with the provisions of Protocol 2 of the Universal Copyright Convention. For rights of reproduction or translation of WHO publications, in part or *in toto*, application should be made to the Office of Publications, World Health Organization, Geneva, Switzerland. The World Health Organization welcomes such applications.

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the Secretariat of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

The editors alone are responsible for the views expressed in this publication.

PRINTED IN SWITZERLAND

83/5851 - DPS - 7000

CONTENTS

	Page
Acknowledgements .....	4
Preface .....	5
1. Introduction .....	7
2. Epidemiology .....	9
2.1 Introduction .....	9
2.2 Analytical toxicology .....	9
2.3 Epidemiological research .....	12
2.4 Problems in conducting epidemiological research .....	14
3. Effects of drugs on driving performance .....	17
3.1 Introduction .....	17
3.2 Assessment of skills-performance and complex behaviour .....	17
3.3 Recommendations for systematic test procedures .....	20
3.4 Behavioural pharmacokinetics .....	21
4. The role of public health authorities .....	26
5. International collaboration and future approaches to the problem .....	29
References .....	32
Annex 1. List of participants, WHO/NIDA Joint Meeting on Drugs and Driving, Elkridge, MD, USA, 6-10 April 1981 .....	35
Annex 2. Analytical toxicology: an outline .....	38
Annex 3. Analysis of drug concentration-drug effect correlations: a theoretical model .....	46
Annex 4. Recommendations from the Nordic Council concerning drugs dangerous to road users .....	52

ACKNOWLEDGEMENTS

The editors wish to express their thanks to the following for their contributions to the text:

Gene Barnett, Everett H. Ellinwood, Bryan S. Finkle, Alex Irving, Inayat Khan, Vojtech Licko, Markku Linoilla, Arthur J. McBay, Herbert Moskowitz, Graham Starmer, Travis Thompson, and Edward C. Tocus.

## PREFACE

Many countries are now beginning to recognize the major public health problems associated with the impact of drugs and alcohol on traffic accidents, and a global programme was established by the World Health Organization in 1976 at the request of its Executive Board and after subsequent discussion by the World Health Assembly. In developed countries, traffic accidents are often the greatest cause of violent death, and a large proportion of these fatalities are alcohol-related. Interactions between alcohol and other drugs are also a source of concern, since such combinations occur frequently in drivers and operators of machinery.

The knowledge available on the role of alcohol as a primary cause of accidental injury is largely sufficient to permit the formulation of information programmes and of scientifically based control measures. On the other hand, the risk of accidents associated with the taking of drugs, whether obtained on prescription, over-the-counter or illicitly, while widely recognized, is difficult to assess in terms of its magnitude and impact on societies and public health. Continued and intensified research is therefore indispensable. However, the lack of both financial and manpower resources in many countries requires this research to be internationally coordinated. The World Health Organization will contribute to such research coordination as an essential constituent of the Global Strategy for Health for All by the Year 2000.

As part of a continuing effort to develop information and stimulate greater research efforts on the impact of drugs on traffic safety, the World Health Organization and the National Institute on Drug Abuse (USA) convened a meeting of experts in April 1981,<sup>a</sup> and the present publication is one of the outcomes of the meeting. While its content deals mainly with methodological issues and

---

<sup>a</sup> The participants are listed in Annex 1.

techniques, it is hoped that it will have a broad impact in many countries and will help to bring about improved public health measures to reduce drug-related road accidents and fatalities in the future.

## 1. INTRODUCTION

Widespread concern in developed and developing countries regarding the relationship between road traffic accidents and the use of psychoactive drugs<sup>1</sup> led a WHO Expert Committee on the Implementation of the Convention on Psychotropic Substances, 1971 (1) to recommend that WHO strengthen its programmes for investigating the relationship between use of alcohol and psychotropic substances and injury, disability, and death from road traffic accidents. In addition, the Expert Committee recommended that the knowledge and methodology developed for this purpose be extended to the investigation of industrial and other accidents.

Morbidity and mortality resulting from road traffic accidents have been decreasing in developed countries since 1973; however, they continue to rise in developing countries at an alarming rate. The limited availability of forensic laboratory facilities in developing countries led the WHO Expert Committee (1) to support strongly the creation of more laboratory facilities for assessing public health and social problems. The Committee also recommended that governments be urged to require studies of the effects of drugs and drug interactions on driving ability as a precondition for licensing new psychotropic drugs for use in their countries.

Legislation on drugs and driving has been in force in a number of countries for several years and it is important to evaluate the effectiveness of such legislation on drugs and driving and to improve appropriate control measures that can be implemented by the authorities. The areas for further research, including

---

<sup>1</sup> In the context of this report the term "drug" is used in a broad sense to include medicaments (or therapeutic substances taken under the supervision of a physician or by self-medication) and those "psychotropic" substances used non-medically and often illegally.

the estimated cost, and the duration of the investigations required must also be specified. In all of these areas, WHO is trying to set up appropriate channels of communication and cooperation among different countries, institutions, and research centres.

The purpose of this publication is to assess the problems associated with evaluating the effects of drugs on driving and traffic safety and to recommend standardized approaches toward expanding our knowledge in this field.

## 2. EPIDEMIOLOGY

### 2.1 Introduction

The drinking driver has been long recognized as one of the most serious traffic safety problems, and considerable attention and corrective efforts are currently directed at reducing the number of drivers whose driving is unsafe because of the effects of alcohol. But what of other drugs?

An examination of the available facts reveals that (a) there are conflicting opinions among researchers regarding various aspects of the legislation concerning "driving under the influence of drugs", e.g., specified blood levels, methods of detection etc.; (b) many of the existing laws relating to driving under the influence of drugs (including alcohol) are rarely enforced; and (c) analytical methods in toxicology and pharmacology are generally inadequate to support enforcement of these laws. This dilemma results from the tendency to legislate or regulate without thorough and objective study of the needs and priorities and of the means for effective law enforcement.

### 2.2 Analytical toxicology

Analytical methods that are suitable for the detection and identification of drugs and their primary metabolites in small specimens of blood, urine, and saliva are fundamental to any determination of the role of drugs in driving impairment and highway safety. These methods are also necessary for epidemiological and survey studies of drugs in drivers.

The technical capability required to analyse small blood samples to determine the presence of common drugs and their metabolites is available in only a few research centres; and, except in rare instances, knowledge of toxicology to support interpretation of the analyses is extremely limited. This toxicological knowledge cannot

be acquired until the analytical capability is sound; and, in public health laboratories in most countries, the cost, time, and effort needed to become analytically proficient cannot be justified until a significant problem has been defined.

Genuine social concern has caused an increase in government-sponsored research in the USA and elsewhere in recent years. Sensitive, specific, and quantitatively accurate analytical techniques have now become available (i.e., gas chromatography with selective detectors, mass spectrometry, and immunological methods for screening purposes). These laboratory techniques are the only ones that can provide a legally acceptable analysis of a blood, urine, or saliva sample for a broad range of drugs, rapidly and specifically. However, it should be realized that there is still no ideal, routine method for the detection in blood samples of cannabinoids (following ingestion of marijuana) or of many hallucinogenic drugs of abuse, because these drugs, and others, are chemically unstable, extensively degraded in the body, and, at best, occur in very low concentrations (nanograms per millilitre).

Since about 1978 an analytical system for the detection and specific identification of 75 common drugs and metabolites in 5-10 ml blood specimens has been under development at the Center for Human Toxicology, University of Utah, USA. This approach has been applied to pharmacokinetic studies of prototype drugs in subjects undergoing driving-behavioural tests, and also to limited surveys to determine the occurrence of these drugs in drivers involved in accidents.

The approach involves three processes: (a) a broad, general analysis to detect the presence or absence of drugs in the specimen; (b) specific identification of any drugs detected; and (c) accurate and precise quantitative analysis of the drug concentrations. A prototype quality control system is outlined in detail in Annex 2. It is presented as a guide to other

laboratories which are considering initiating such studies. Although it represents the state-of-the-art technology, suitable alternatives can be found in many instances to fit local conditions. The first screening-detection system involves gas-liquid chromatography (GLC), high-pressure liquid chromatography (HPLC), and immunological methods. To achieve adequate sensitivity, GLC requires flame ionization, electron capture, and nitrogen-selective detectors. For many drug classes, such as narcotic analgesics, tranquillizers, and anti-histamines, the test must be able to detect less than 50 ng of the substance per millilitre of plasma when single oral doses of these drugs have been ingested.

The total system is a relatively inexpensive way of gathering reliable data on the incidence of drug use and the quantities and kinds of drugs used by drivers. The equipment and expertise necessary are readily available throughout those parts of the world with heavy traffic density, including Asia (certain parts), Australia, Europe, and North America. Countries lacking these facilities should seriously consider shipping samples to existing laboratories until the number of accidents or local laws justify the establishment of an adequate laboratory.

There is still much to be learned about the interpretation of drug and metabolite concentrations in biological fluids taken from arrested drivers or those involved in accidents. The technical methods to acquire such knowledge, however, are now available and could be more widely applied. In areas or countries where the laboratory instrumentation is not readily available, other less specific techniques could be used, such as high performance thin-layer chromatography and "receptor-assays", although they would have to be supported by reference laboratories and by quality control and proficiency testing programmes. This is a matter of organization and support rather than new technical development, and if feasible would be preferable to using laboratories in other countries.

There is also a critical need, beyond the simple publication of methods in the scientific literature, to transfer analytical expertise to other toxicologists so that they can carry out their own studies and provide services locally. This technology transfer and education could be best accomplished by the governmental bodies concerned providing support so that a few experienced laboratories can accept toxicologists for training. A complementary need exists for experienced scientists to help establish analytical systems and train technicians in laboratories where there is a need for programmes on drugs and driving. This is particularly important because local conditions, e.g., availability of organic solvents, other chemicals, and instruments may preclude the direct transfer of methods without modification. The need to capitalize on current analytical knowledge and expertise is urgent, and it is strongly recommended that WHO take the lead in supporting these activities.

### 2.3 Epidemiological research

The full impact of drug use on driving behaviour is unknown. Thus far few attempts have been made to determine the frequency with which drugs are present in drivers arrested for driving infractions or killed in crashes. As yet, few empirical data are available which could be used to relate drug concentrations in biological specimens to behaviour, except for those relating to alcohol and gross concentrations of a few other depressant drugs.

Researchers in North America (2-8) and in Ireland (9) reported on the analyses of specimens obtained from drivers arrested for impaired driving or killed in crashes. Alcohol concentrations over 0.09% were present in the majority of specimens. Barbiturates were the most commonly found drug in earlier studies and diazepam was prominent in the later studies. No tests for marijuana constituents were reported.

In further reports from the United Kingdom (10), USA (11,12), and Canada (13) in which marijuana was tested for, alcohol was again the most prevalent drug. When testing for drugs other than alcohol, marijuana occurred most frequently, with diazepam and barbiturates following closely. In these studies of fatally injured drivers and pedestrians, it appears that about 50-60% were impaired by alcohol and that roughly 10-30% had used other drugs.

A number of studies have used survey, questionnaire, or interview techniques in an effort to arrive at estimates of the impact of drugs on driving and traffic accidents. Sterling-Smith (14) reported that drivers involved in fatal accidents were more likely to use marijuana (45%) than control drivers (34%); Johnston (15) surveyed 16 000 high-school seniors and reported that those who smoked marijuana received more traffic citations and were involved in more accidents than students who did not smoke marijuana. More recently Hingson (16), using telephone interviews of 6000 North American teenagers (in the 16-19 year age group), found that those who drove after smoking marijuana on at least 6 occasions per month were 2.4 times more likely to be involved in traffic accidents than those who did not smoke marijuana.

However, we are still far from knowing the true impact of drugs on traffic safety, and millions of automobile accidents occur each year without fatalities and the number in which drugs are involved is unknown. The various methods of assessing the role of psychotropic substances, many of which are particularly appropriate for use in developing countries, were discussed at a recent seminar in Helsinki (22).

One major reason for the lack of knowledge in this field is the fact that though there are efficient and widely available methods for determining alcohol levels, methods for determining other drugs are only beginning to become available for widespread use. The promise of the availability of new assay techniques within the next

two years may well facilitate the epidemiological studies that are needed to establish the relationship between drug use and automobile accidents.

#### 2.4 Problems in conducting epidemiological research

Research on drugs and highway safety seeks to determine whether the use of drugs increases the likelihood of a traffic accident. The principal goal of this research is to identify which drugs and which drivers should be targets for countermeasures.

Epidemiological studies of drug use among drivers include:

(1) The chemical analysis of drivers' body fluids (blood, urine, and saliva) for the presence and amount of drugs.

(2) Questionnaires that ask drivers to report on their use of drugs.

(3) Examination of driving records of those who use drugs.

Research studies that do not include the analysis of drugs in body fluids are generally considered to be unreliable indicators of a drug and driving problem, because it is not possible to state positively that drugs are present. Such studies provide a limited basis for defining the relationship between drugs and road safety.

In addition to research studies, some police agencies, medical examiners, or coroners compile data on traffic cases involving drugs, sometimes including analyses of body fluid specimens for drugs. However, this information is often not compiled for publication, and since these are usually not planned studies, the quality of the data is often insufficient. Throughout the world there is considerable variation in the way in which cases are reported. Often only a single local

area is represented, and such findings generally do not support broad statements about drugs and driving or about legislative initiatives.

Work on alcohol and road safety has helped to establish that drugs other than alcohol are likely to give rise to safety problems. Case reports clearly indicate that alcohol and a variety of drugs are often used in combination. Preliminary efforts to identify the presence of drugs in accident victims and in the driving population as a whole have been undertaken; however, the results of early studies have been inconclusive.

In the past few years there have been significant advances in the analytical techniques to determine the amount of drugs present in the body. Technical issues remain, however, which must be addressed in order to determine the nature and scope of the road safety problem that can be attributed to drugs. A major issue is the collection of baseline data to compare with the levels that are found in various types of driver (fatally injured drivers, drivers involved in non-fatal injury accidents, and drivers involved in property damage accidents). In an ideal world, data from a comparison group are required if one is to determine whether the use of a drug or drugs increases the likelihood of a traffic crash. However, the ethical and practical considerations involved in obtaining body fluid samples from a random population of drivers makes this somewhat impracticable. One need not, however, take the position that such methodological difficulties mean that no conclusions can be reached. Significant conclusions may be possible without a perfect study design.

Because of the problems associated with conducting large or nationwide studies, the following considerations are recommended:

- (1) Studies to determine the nature and scope of the road safety problem associated with drug impairment should be encouraged.

(2) Model protocols should be developed that would facilitate individual studies and comparisons between them.

(3) Analytical protocols should be designed to meet specific needs and could be provided to those requiring analytical assistance.

(4) Studies should be designed to include all accident victims, not just fatalities.

(5) Studies in this area should avail themselves of new developments in epidemiology and analytical toxicology.

### 3. EFFECTS OF DRUGS ON DRIVING PERFORMANCE

#### 3.1 Introduction

One of the main concerns of WHO as regards drugs and driving is to characterize the risks associated with driving under the influence of drugs. These risks are wide-ranging; for example, marijuana is known to impair reaction time, tracking, perception, and a variety of other skills that are required for safe driving. An associated objective is to develop methods for determining the degree to which driving performance is impaired as a consequence of a driver having taken a drug. For the past 20 years, research has focused on the development of behavioural tests believed to be indicative of impaired driving performance.

#### 3.2 Assessment of skills-performance and complex behaviour

Researchers investigating the effects of drugs on driving have employed a wide range of human performance tests. This diversity of tests has sometimes led to difficulties in understanding and reconciling what appear to be differing results. For example, a review by Joscelyn et al. (17) of seven studies evaluating the effects of amobarbital on driving performance noted that each study used different behavioural tests and drug dosage levels. It may well be that some of the apparent contradictions among studies result from the choice of experimental tasks.

In such a research situation, it is not surprising that contradictory and unsubstantiated findings are often reported. A test protocol is required which would allow both freedom of methodological choice for individual researchers and the possibility of making meaningful

between-study comparisons. The requirement, therefore, is for agreement on a minimum selection of tests to measure a common core of performance functions rather than for specific physical details of the tests.

There are three kinds of test that can be used for testing driving-related skills: actual driving, driving simulators, and less complex driving-related tasks performed in the laboratory.

However, there are severe practical difficulties in using real driving as an experimental measure in testing drug effects. In most countries the administration of drugs, with the resulting possible impairment of a driver's ability to control vehicles in traffic situations, would be unacceptable for ethical and safety reasons. Moreover, in the few instances in which open-road situations have been used for the study of drug effects, there have been serious technical problems (18).

A major difficulty has been to define and control the variables of the test situation. No two drivers can experience exactly the same road conditions when driving in real traffic situations. Hence, the possibility of finding differences between drug and placebo treatments is reduced owing to the variability of responses to the ever-changing characteristics of road traffic. In addition, recording of responses in these studies has tended to use subjective observer measures, which are difficult to replicate.

An alternative method is the use of closed-course driving, where the tasks may be more closely specified and controlled and the subjects and other persons are more adequately safeguarded. Another advantage of closed-course car studies is that the mechanical demands on the driver are equivalent to those of open-road driving. Some difficulties are that the subjectively

perceived risk is reduced in comparison to that of open-road traffic, and that the complexity of information-processing demand induced by other traffic and the (usually) urban environment is reduced, thus decreasing the psychological demands on the driver and making his task easier.

In both open-road and closed-course driving studies it is an advantage to include instrumented measures of changes in performance. In addition, if enriched environments can be utilized in place of the non-road environments, such as the airfields or parking areas typically used in closed-course studies, the driving task will be more realistic.

A frequently used approach to studying the effects of drugs on driving performance employs driving simulators, which use normal car equipment and project the driving situation on to a screen. These have major safety advantages, but may reduce the realism of the situation for the subjects. Driving simulators have the additional advantage that the stimulus situations are reproducible, ensuring that all subjects are exposed to the same experimental conditions.

There are several types of research-oriented driving simulators. They differ considerably in the aspects of driving behaviour that are sampled, and therefore it is always important to be fully aware of the characteristics of each simulator, so that proper inter-study comparisons can be made.

The most common way of testing driving skills involves tests of human skills-performance in a laboratory situation. In contrast to driving simulators, each such task samples only a few elements of the overall driving task. On the other hand, the behavioural elements being assessed are more clearly specified. Among the advantages of these tests are the relative simplicity of the required measuring

instruments and the shorter time needed to sample that behaviour adequately. As such, they are very useful in studying drug effects over time, since behaviour can be sampled repetitively, in contrast to driving simulators and car-driving situations which require an extended period to obtain an adequate sample of the behaviour.

Such tests of behavioural and psychophysical functions remain complementary, however, to the more complex testing situations such as driving simulation and actual car performances.

In summary, various approaches exist, and each has a particular advantage that supports its retention as a viable research method. With careful experimental design, each may yield useful information.

### 3.3 Recommendations for systematic test procedures

Many of the drugs in current use that have been implicated as causative factors in traffic accidents have not been investigated for their potential safety hazards. There is an urgent need to implement systematic test procedures. Despite the enormous amount of information that must be generated in most countries prior to the introduction of a new drug, there is no requirement to evaluate the effects of the drug on human performance.

Driving is a multi-function task that includes:

- visual search and recognition;
- vigilance;
- information processing under variable demand;
- decision-making and risk-taking;
- sensorimotor control.

Tests to investigate these functions can reveal behavioural impairments relevant to road safety that are induced by reference drugs such as alcohol, diazepam, and pentobarbital. The precise way in which these functions are tested is unimportant, as long as the tests are capable of revealing impairment relevant to traffic safety induced by reference drugs in a dose-related manner.

Ideally, in order to obtain a complete understanding of the relationship between a drug and its effect on road traffic safety, a complete range of driving-related performance tests, varying from the less complex neurological and behavioural tests to driving itself, would need to be examined. However, to be realistically cost-effective, the strategy of a drugs and traffic safety programme should be first to screen new drugs with a battery of relatively simple but sensitive behavioural tests, and, where impairment is demonstrated, to proceed to progressively more complex tasks that approximate to driving.

The screening procedure should at least involve testing in each of the five areas previously listed. Drugs already on the market that are primary candidates for investigation include those that have a proven activity on the central nervous system and are commonly taken by drivers. Provisions should also be made for the examination of any drug if evidence that it affects driving ability becomes available.

#### 3.4 Behavioural pharmacokinetics

Modern quantitative concepts and experimental methods demand a synthesis of pharmacokinetic and pharmacodynamic analyses of drug action and the results of behavioural tests. There are important reasons for clearly understanding the relationship between drug concentrations in blood and other body fluids and impairment as a function of time after

both acute and chronic dosing. The judicial system has exerted pressure on forensic toxicologists to interpret blood concentrations in terms of implied impairment. It is important to know whether there are threshold concentrations above which impairment can be reliably measured.

Several recent research studies have indicated that for many psychotropic drugs, impairment is not proportional to blood concentration, as it is with alcohol (19, 20). Some drugs act very quickly, in that their effects occur before concentration in the blood has risen, while for other drugs the reverse is true. It is important that future research should develop general principles for categorizing individual drugs into families or classes that have common profiles for both acute and chronic dosing. The development of a data base that documents time-relationships will be important for warning patients and physicians about the times at which peak impairment may occur.

Such an approach involves analysis of the relationships between three variables: time, behavioural effects, and concentration in body fluid. A simple example is the effect of alcohol on behaviour. First, behaviour may be examined as a function of time, which would constitute a pharmacodynamic analysis. Secondly, a pharmacokinetic analysis would describe the blood-alcohol concentration as a function of time. Thirdly, analysis of the relationship between blood-alcohol concentration and the behavioural measure as a function of time could be described as a behavioural-pharmacokinetic analysis.

A prerequisite of such an analysis is an understanding of the mechanisms of drug action and the effects of drugs on behaviour. It is essential that these behavioural mechanisms should be understood

first in the absence of a drug. The degree to which a subject's performance is regulated by his past history, as well as his biological profile, can be a causal determinant of drug action. A single dose of a drug may produce a wide variety of behavioural effects in different individuals, and even in the same individual on different occasions. Many factors, including age, sex, physical health, anxiety, and fatigue, may influence the magnitude of a drug's effect. The role of antecedent factors (e.g., the subject's medical and psychological history), current stimulus factors (e.g., the complexity of the task to be performed), and the consequences of a certain behaviour (e.g., rewards/punishments) must also be taken into consideration in order to understand the behavioural mechanisms.

Historically, studies of drugs in relation to driving began with the correlation of performance decrements with blood-alcohol concentrations. The appeal of applying this model to a wide range of psychotropic drugs has been misguided and fraught with serious problems. It has become clear from recent research that there is rarely a direct time-independent relation between blood concentrations of most psychotropic drugs and most behavioural performances. For example, diazepam appears to produce maximum behavioural impairment shortly after ingestion, when plasma concentrations of the drug are low; when plasma concentrations reach a peak at approximately four hours after ingestion, behavioural impairment is minimal (21). This does not imply that it is fruitless to search for relationships between blood concentrations and behavioural variables; however, it is important to bear in mind that these relationships are embedded in the three-dimensional nature of behavioural pharmacokinetics, i.e., the relations among plasma concentrations, behavioural output, and time.

In considering the relationship between drug concentration and drug effects, the complications arising from two main sources involved should be taken into account. Firstly, a time delay may exist between the drug concentration in the blood and the drug effect, or the relationship may be distorted if the drug-effect curve has a different profile from that of drug concentration. If the drug's effects are immediate, then a time-independent correlation may exist between drug concentration and drug effect. Such a correlation would make it feasible to draw up legislation to detect impaired drivers on the basis of plasma concentrations. If, in addition, there is no distortion, this correlation becomes the familiar linear correlation that is seen with alcohol.

Secondly, the drug effect may be brought about not only by the drug concentration per se, but also by the rate of change in its concentration (22). In this case the behavioural effect of the drug may decline more rapidly than the observed drug concentration, so that, by the time the peak blood concentration is reached, the behavioural effect may have faded to almost nothing. The existence of such a phenomenon would bring into question any legislation based solely on peak plasma concentrations.

In general, these models indicate that the time coordinate is an essential factor in the analysis, and that correlations of drug concentration with behavioural impairment independent of the time variable may not exist. Therefore, in terms of drafting legislation for driving under the influence of drugs, the alcohol model may not be appropriate and alternative approaches must be developed. For the interested research worker, a discussion of these theoretical models appears in Annex 3. These behavioural pharmacokinetic phenomena have important implications for our understanding of the mechanisms underlying the

behavioural actions of drugs and driving-related performances, and more specifically for the development of drug analyses for predicting impairment.

#### 4. THE ROLE OF PUBLIC HEALTH AUTHORITIES

Many countries suffer from the consequences of road traffic accidents, but in a number of them there is no real awareness of the role drugs play in causing such mortality and morbidity. One important step in eradicating this widespread problem would be to evaluate the behavioural toxicity of a psychoactive substance at the time of its registration.

In most countries, when new drugs are first marketed there are no specific requirements for their safe use by drivers. The sponsor of a new drug is generally required only to prove the purity, "safety", and specific therapeutic effectiveness claimed for the product. During the examination of safety and effectiveness, scientific information is obtained relating to the pharmacological and toxicological actions of the product, and if these studies indicate that the substance may produce effects that would put a patient at risk when operating a motor vehicle or machine, then a warning statement is generally added to the information material supplied with the drug. The value of such warnings has not been exhaustively evaluated, and further study of this problem and new initiatives are needed.

One viable alternative would be to place a greater emphasis on behavioural toxicity during the development of a new drug. This could take the form of more specific tests in animals to quantify the motor or neurological deficit produced by the substance relative to a standard drug. If the activity were shown to be significant in animals, specific studies might be required to determine the effects of the new substance on driving or other performances in humans.

In addition to responding to early warning signs indicated by animal studies, human performance testing would also be required for certain classes of drugs known to be potential safety hazards.

It is recognized that a new drug taken alone may not impair performance but that it may constitute a hazard when taken in combination with another substance. However, determination of all drug interactions is impracticable before marketing because of the enormous number of possible drug-dose combinations. However, the effects of a drug in combination with ethanol should be investigated, because it is well known that alcohol causes a deterioration in driving performance and is widely used. The effects of drug combinations on behaviour can be studied, however, by careful post-marketing surveillance. Once a drug interaction has been determined, this information should be widely disseminated to prevent further accidents.

In order to be successful, a programme for the prevention of accidents resulting from drugs and alcohol must be supported by professional groups, governmental agencies, practitioners, the drug industry, and the public. It is not sufficient to determine that a danger exists; it is necessary to notify all the individuals concerned so that action can be taken to prevent that danger from recurring. Since the addition of a warning label on a package has already been found to be inadequate, it is necessary to examine other means of communicating with the professionals, who can then notify their clients. A number of possible procedures, graded according to the severity of the danger, may be developed. If a drug poses significant public health risks because of its effects on driving performance, it may be necessary to place severe restrictions on the substance, such as control of availability or distribution. If the risks are not so severe, widespread education and information programmes may be sufficient.

In the Nordic countries new initiatives have been undertaken along these lines. The Nordic Council on Traffic Safety has recommended a system for labelling the seven main classes of drugs considered to be potential hazards to driving safety (see Annex 4). This new system requires pharmacists to label these drugs with a red triangle and issue a leaflet to the purchaser which describes the potential risk involved. This system has been in operation in Norway, where all pharmacies are state-owned, since 1981 and was implemented in other Nordic countries in January 1983. This effort to educate the public about the behavioural effects of drugs is noteworthy, and other countries should consider this innovative method.

5. INTERNATIONAL COLLABORATION AND FUTURE  
APPROACHES TO THE PROBLEM

International collaboration is vital to the successful achievement of the goals of the World Health Organization. It is recognized that some countries already have well developed programmes for the prevention of accidents and could provide information, assistance, and advice to many other Member States, especially developing countries. The obstacles that exist in some countries may possibly be overcome through such international collaboration.

Various approaches to the study and prevention of traffic accidents have been tested and the methods used in some countries may provide models for others. For example, Brazil has approached the problems via local programme development with federal support, while the United States of America has, until recently, primarily approached these problems from a centralized federal starting point.

Cooperation between developed and developing countries is essential. The growth of the traffic accident problem in recent years, and the expectation that this growth will continue, suggest the need for a more aggressive strategy - one that would make full and well coordinated use of the available (and potential) manpower and financial resources. Naturally, the main responsibility for implementing such a strategy and any actions that might be agreed upon must rest with individual governments. WHO and other interested organizations can only contribute within the limited scope of their designated functions and responsibilities.

Recommendations

The following recommendations for international collaboration and for future approaches to the problem are offered for consideration. Efforts should be made to:

- (1) develop and utilize uniform nomenclature and statistical systems with regard to accidents;
- (2) promote and implement epidemiological studies at the national, regional, and international levels to collect information on the role of drugs in traffic accidents;
- (3) develop preventive policies and programmes;
- (4) promote the exchange of information between scientists and experts in the field;
- (5) improve the existing facilities for training in different disciplines with regard to drug use (including dependence), highway safety, and statistical analysis;
- (6) provide techniques and laboratory apparatus for the detection of drugs in body fluids, especially in the developing countries;
- (7) improve the methods employed to educate the public about the dangers of drugs and their relation to traffic accidents, making use of audiovisual aids, films, tapes, lectures, posters, etc.;

(8) develop better information on new drugs before they are marketed and through post-marketing surveillance. This should include information on behavioural toxicity, and in particular on cognitive, neuromuscular, perceptual, and attention functions. Provision of such data by the manufacturer to the national authorities and WHO at the time of review for international drug scheduling is of great importance and is strongly recommended;

(9) clarify new and existing legislation to emphasize the point that driving under the influence of drugs is concerned mainly with the adverse influences of that drug on driving performance, and not solely with the taking of a drug;

(10) implement more widely the Nordic countries' drug warning system, whereby drug packages are suitably labelled when they contain drugs that interfere with driving skills, and educational material is provided regarding the potential hazards;

(11) provide more resources for studies on the adverse effects of psychoactive drugs and for programmes to educate the public and members of the health professions on the safe use of these drugs.

REFERENCES

1. WHO Technical Report Series, No. 656, 1981  
(Assessment of public health and social problems associated with the use of psychotropic drugs: Report of the WHO Expert Committee on the Implementation of the Convention on Psychotropic Substances, 1971).
2. FINKLE, B. S. Drugs in drinking drivers: A study of 2500 cases. Journal of safety research, 1: 179-183 (1969).
3. STERLING-SMITH, R. S. Marihuana and other drug patterns among operators involved in fatal motor vehicle accidents. In: Israelstam, S. & Lambert, S., ed., Alcohol, drugs and traffic safety, Toronto, Addiction Research Foundation of Ontario, 1975, pp. 93-105.
4. TURK, R. F. et al. Involvement of alcohol, carbon monoxide, and other drugs in traffic fatalities. In: Israelstam, S. & Lambert, S., ed., Alcohol, drugs and traffic safety, Toronto, Addiction Research Foundation of Ontario, 1975, pp. 597-606.
5. LUNDBERG, G. D. et al. Drugs (other than or in addition to ethyl alcohol) and driving behaviour: A collaborative study of the California Association of Toxicologists. Journal of forensic sciences, 24: 207-215 (1979).
6. GARRIOTT, J. C. et al. Incidence of drugs and alcohol in fatally injured motor vehicle drivers. Journal of forensic sciences, 22: 383-389 (1977).
7. BLACKBURN, R. R. & WOODHOUSE, E. J. A comparison of drug use in driver fatalities and similarly exposed drivers. Washington, DC, National Highway Traffic Safety Administration, 1977 (DOT Report No. 802-488).

8. WHITE, J. M. et al. Testing for sedative-hypnotic drugs in the impaired driver: A survey of 75 000 arrests. Paper presented at the Meeting of the American Academy of Forensic Sciences, Atlanta, GA, 1979.
9. ROBINSON, T. A. The incidence of drugs in impaired driving specimens in Northern Ireland. Journal of the forensic science society, 19: 237-244 (1979).
10. TEALE, J. D. et al. The incidence of cannabinoids in fatally injured drivers: An investigation by radioimmunoassay and high pressure liquid chromatography. Journal of the forensic science society, 17: 177-183 (1977).
11. REEVE, V. Incidence of marijuana in a California impaired driver population. State of California Dept. of Justice, 1979.
12. MCBAY, A. J. & OWENS, S. M. Marijuana and driving. In: Harris, L. S., ed. Problems of drug dependence, 1980. Washington, DC, US Government Printing Office, 1981, pp. 257-263 (National Institute on Drug Abuse Research Monograph 34. DHHS Pub. No. (ADM)81-1058).
13. CIMBURA, G. et al. Drugs detected in fatally injured drivers and pedestrians in the province of Ontario. T.I.R.F. Reports. Ottawa, Canada, 1980
14. STERLING-SMITH, R. S. & GRAHAM, D. Marijuana and driver behaviors; historic and social observations among fatal accident operators and a control sample. Washington, DC, National Highway Traffic Safety Administration, 1976 (DOT HS 310-3-595).

15. JOHNSTON, L. D. et al. Highlights from student drug use in America 1975-1980. Washington, DC, US Government Printing Office, 1981 (DHHS Pub. No. (ADM)81-1066).
16. HINGSON, R. et al. Teenage driving after using marijuana or drinking and traffic accident involvement. Journal of safety research, 13: 33-37 (1982).
17. JOSCELYN, K. B. et al. Drugs and driving: Information needs and research requirements. Final report. Washington, DC, National Highway Traffic Safety Administration, 1979 (Report No. DOT-HS-804-774).
18. KLONOFF, H. Marijuana and driving in real-life situations. Science, 186: 317-324 (1974).
19. MCLEOD, S. M. et al. Diazepam actions and plasma concentration following ethanol ingestion. European journal of clinical pharmacology, 11: 345-349 (1977).
20. ELLINWOOD, E. H. et al. Use of simple tasks to test for impairment of complex skills by a sedative. Psychopharmacology, 75: 350-354 (1980).
21. SELLERS, E. M. Addictive drugs: Disposition, tolerance and dependence interrelationships. Drug metabolism review, 8: 5-11 (1978).
22. IDANPAAN-HEIKKILA, J. & KHAN, I., ed. Psychotropic substances and public health problems. Report of a seminar convened by the World Health Organization with the collaboration of the Government of Finland and the United Nations Fund for Drug Abuse Control. Helsinki, Government of Finland, 1982.

Annex 1

LIST OF PARTICIPANTS,  
WHO/NIDA JOINT MEETING ON DRUGS AND DRIVING,  
ELKRIDGE, MD, USA, 6-10 APRIL 1981

Professor J. Abreuvalle, Brasilia, Brazil

Dr G. Barnett, Division of Research, National Institute  
on Drug Abuse, Rockville, MD, USA

Dr S. D. Benson, National Highway Traffic Safety  
Administration, Department of Transportation,  
Washington, DC, USA

Dr R. Compton, National Highway Traffic Safety  
Administration, Department of Transportation,  
Washington, DC, USA

Dr C. Diaz-Coller, Ministry of Health, Mexico

Professor E. H. Ellinwood, Jr., Duke University  
Medical Center, Durham, NC, USA

Dr B. S. Finkle, Director, Center for Human Toxicology,  
University of Utah, Salt Lake City, UT, USA

Professor B. Friedel, WHO Regional Office for Europe,  
Copenhagen, Denmark (Co-Secretary)

Dr R. Hawks, Research Technology Branch, Division  
of Research, National Institute on Drug Abuse,  
Rockville, MD, USA

Mr A. Irving, Transport and Road Research  
Laboratory, Crowthorne, Berkshire, England

Dr C. Kaelber, Chief, Epidemiology, National  
Institute of Alcohol Abuse and Alcoholism,  
Rockville, MD, USA

Dr M. Katatsky, Regional Advisor in Alcohol and  
Drug Abuse, Pan American Health Organization,  
Washington, DC, USA

Dr I. Khan, Senior Medical Officer, Division of  
Mental Health, World Health Organization,  
Geneva, Switzerland (Co-Secretary)

Dr A. Kotry, Director General, Abassia Mental  
Hospital, Abassia, Cairo, Egypt

Dr V. Licko, Biodyn, San Francisco, CA, USA

Dr M. Linnoila, National Institute of Mental Health,  
National Institutes of Health, Bethesda, MD, USA

Dr A. J. McBay, Office of the Chief Medical  
Examiner, Chapel Hill, NC, USA

Professor H. Moskowitz, Encino, CA, USA

Dr Sheu Yng-shiuh, National Institute on Drug Abuse,  
Rockville, MD, USA

Dr J. P. Smith, Assistant Director for International  
Activities, National Institute on Drug Abuse,  
Rockville, MD, USA

Dr M. Snyder, Chief, Problem-Behavior Research  
Division, National Highway Traffic Safety  
Administration, Department of Transportation,  
Washington, DC, USA

Dr G. Starmer, Department of Pharmacology,  
University of Sydney, Sydney, NSW, Australia

Professor T. Thompson, Department of Psychology,  
University of Minnesota, Minneapolis, MN, USA

Dr E. C. Tocus, Chief, Drug Abuse Staff, Food and  
Drug Administration, Gaithersburg, MD, USA

Dr J. M. Walsh, Research Psychologist, Division of  
Research, National Institute on Drug Abuse,  
Rockville, MD, USA (Rapporteur)

Dr R. Willette, Chief, Research Technology Branch,  
Division of Research, National Institute on Drug  
Abuse, Rockville, MD, USA (Chairman)

Annex 2

ANALYTICAL TOXICOLOGY: AN OUTLINE

Analytical methods that are capable of detecting and identifying drugs and their primary metabolites in small-volume blood, urine, and saliva specimens are fundamental to any determination of the role of drugs in driving impairment and highway safety. Such methods are also necessary for epidemiological studies of drugs in drivers.

For the analytical approach to proceed efficiently, the number of false positives and negatives must be reduced to a minimum. This can be achieved most easily by using a well designed quality-control programme. The programme should consist of three major components:

- (1) internal quality control;
- (2) external quality control, including storage and shipment of samples;
- (3) external proficiency testing.

Internal quality control

Each of the analytical procedures must use reference standards as controls; for example, a blood sample containing diazepam, nordazepam, and desalkylflurazepam should be extracted in parallel with each batch of samples being screened for the benzodiazepines.

For quantitative analyses, a standard curve of at least three points must be prepared. The standards used must cover a suitable concentration range, e.g., such a range for diazepam and nordazepam would be 0.05-1.0  $\mu\text{g}/\text{ml}$ . The quantitative assays used must meet accepted limits of accuracy and precision.

### External quality control

It is essential that some form of analysis on a "blind basis" be carried out. There are two alternative ways of doing this:

(1) Requesting a limited number of laboratories to "spike" blood samples and then forward these for analysis together with the routine samples. This, however, has the disadvantage of adding to the workload of the contributing laboratories.

(2) "Spiked" blood samples could be prepared by the analytical laboratory and sent to a number of collaborating centres. These would then be incorporated into the system and returned to the laboratory as "blind" samples, together with the routine samples. If the samples are analysed before shipment to the collaborating laboratories, this procedure has the advantage of monitoring the storage and shipment of samples.

Of these two alternatives, the second is the easier to operate and for this reason is recommended.

### External proficiency testing

This would be accomplished through participation in any existing toxicology or proficiency monitoring programme external to the programme being evaluated. In some countries these programmes are offered by government agencies or by professional societies.

### Techniques for quantification

The analytical methods that are suitable for drug quantification are listed in Table 1. All the procedures involve the addition of internal standards before extraction. Each method will meet the necessary sensitivity, accuracy, and precision required.

Table 2 shows important drug classifications that can be detected and quantified and the sensitivity limits possible for each classification. Drugs listed in Table 3 have been omitted from the basic screening programme because the cost in both sample and development time greatly outweighs possible benefits.

The following abbreviations are used in Tables 1-3: AA, atomic absorption; CIMS, chemical-ionization mass spectrometry; ECD, electron-capture detector; FID, flame-ionization detector; GC, gas chromatography; GLC, gas-liquid chromatography; HPLC, high-pressure liquid chromatography; NPD, nitrogen phosphorus detector; RIA, radioimmunoassay; TC, thin-layer chromatography.

Table 1. Quantification procedures

Classification	Procedure	Internal standard	Reference
A. 1. Ethanol and related volatiles	GLC-FID	<u>n</u> -propanol	<u>1</u>
2. Other volatiles	GLC-FID		<u>1</u>
B. 1. Benzodiazepines	GLC-ECD	flunitrazepam	<u>2</u> <sup>a</sup>
2. Trichloroethanol and ethchlorvynol	GLC-ECD		<u>2</u> <sup>a</sup>
C. 1. Barbiturates	HPLC GLC-NPD (for amo- and pentobarbital)		<u>8</u> <u>9</u>
2. Morphine and codeine	GC-CIMS	deuterated analogues	<u>7</u>
3. Phencyclidine	GC-CIMS	deuterated analogues	<u>7</u>
4. Cocaine and benzoylecgonine	GC-CIMS	deuterated analogues	<u>7</u>
D. Basic drugs (tricyclic antidepressants)	GLC-NPD GC-CIMS	SKF-525A (for example) deuterated analogues	<u>3,5</u> <u>6</u>
E. Anticonvulsants Glutethimide	HPLC HPLC		<u>4</u> <u>4</u> <sup>a</sup>
Carbamates	GLC-FID	diphenhydramine	<u>4</u> <sup>a</sup>
F. CNS stimulants	GLC-NPD	propylamphetamine	<u>7,10</u>

<sup>a</sup> B. S. Finkle, unpublished methods.

Table 2. Drug classifications and sensitivity limits<sup>a</sup>

Classification	Examples	Sensitivity limit
Volatile compounds	ethanol, methanol, ethylene glycol	10 mg/100 ml
Benzodiazepines	diazepam, nordazepam, desalkylflurazepam	0.05 µg/ml
Barbiturates	amobarbital, pentobarbital, phenobarbital	1.0 µg/ml
Non-barbiturate sedative hypnotics	trichloroethanol and ethchlorvynol glutethimide meprobamate methaqualone	1.0 µg/ml 1.0 µg/ml 5.0 µg/ml 0.1 µg/ml
Narcotic analgesics	morphine, codeine methadone, LAAM, pethidine, dextropropoxyphene, pentazocine	0.025 µg/ml 0.1 µg/ml
Antidepressants	amitriptyline, nortriptyline, doxepin, imipramine, desipramine	0.1 µg/ml
Antipsychotics	chlorpromazine, trifluoperazine	0.1 µg/ml
Antihistamines	diphenhydramine, chlorphenamine	0.1 µg/ml
CNS stimulants	cocaine amphetamine, methamphetamine	0.025 µg/ml 0.05 µg/ml
Anaesthetic agents	lidocaine	0.1 µg/ml
Anticonvulsants	phenytoin, phenobarbital primidone, carbamazepine	1.0 µg/ml
"Drugs of abuse"	phencyclidine delta-9-tetrahydrocannabinol (THC)	0.025 µg/ml 0.01 µg/ml

<sup>a</sup> The sensitivity limit will depend upon the technique used; for example, RIA is more sensitive than GLC-NPD as a screening technique, etc.

Table 3. Drugs that have been omitted from a basic drug screening programme

Drug	Available analytical techniques	Reasons for omission
LSD	RIA, HPLC-RIA	1. Not widely abused at present 2. Cost of developing assay 3. Requires extra sample 4. Extensive metabolism
Methylphenidate	GC-CIMS (for metabolites)	1. Extensive metabolism 2. Cost of developing assay 3. Requires extra sample
Antidiabetic agents	HPLC	1. A non-routine procedure 2. Requires extra sample 3. Cost of developing assay
Nicotine	GC-CIMS	Irrelevant
Carbon monoxide	GLC-TC	Not required
Haloperidol	GLC-ECD	An "in-hospital" drug
Digoxin and digitoxin	RIA	Difficult assay
Lithium	AA	Difficult assay
Propranolol	HPLC, GLC-ECD	1. A non-routine procedure 2. Requires extra sample

REFERENCES (ANNEX 2)

1. FINKLE, B. S. et al. Toxicological analyses in cases of sudden infant death: a national feasibility study. Journal of forensic sciences, 24(4):775(1979).
2. PEAT, M. A. & KOPJAK, L. The screening and quantitation of diazepam, flurazepam, chlordiazepoxide and their metabolites in blood and plasma by electron capture gas chromatography and high pressure liquid chromatography. Journal of forensic sciences, 24:46-57(1979).
3. PIERCE, W. O. et al. A new, rapid gas chromatography method for the detection of basic drugs in postmortem blood using a nitrogen phosphorus detector. Part I. Qualitative analysis. Journal of analytical toxicology, 2:26-31(1978).
4. ADAMS, R. F. et al. A micro liquid chromatography procedure for twelve anticonvulsants and some of their metabolites. Journal of chromatography, 145:275-284(1978).
5. KOPJAK, L. et al. A new, rapid gas chromatography method for the detection of basic drugs in postmortem blood using a nitrogen phosphorus detector. Part II. Quantitative analysis. Journal of analytical toxicology, 3:155(1979).
6. CHINN, D. et al. Quantitative analysis for tricyclic antidepressant drugs in plasma or serum by gas chromatography - chemical-ionization mass spectrometry. Clinical chemistry, 26:1201-1204(1980).

7. FOLTZ, R. L. et al. GC/MS assays for abused drugs in body fluids. Washington, DC, US Government Printing Office, 1980 (NIDA Research Monograph 32. DHHS Pub. No. (ADM) 80-1014).
8. KADRA, P. et al. Simultaneous liquid-chromatographic determination of 12 common sedatives and hypnotics in serum. Clinical chemistry, 24:657-662(1978).
9. THOMA, J. SUPELCO Bulletin, p. 768 (1977) (Southwest Medical Foundation).
10. LEBISH, P. et al. Determination of amphetamine, methamphetamine, and related amines in blood and urine by gas chromatography with hydrogen-flame ionization detector. Clinical chemistry, 16:195-200(1970).

Annex 3

ANALYSIS OF DRUG CONCENTRATION-DRUG EFFECT  
CORRELATIONS: A THEORETICAL MODEL

The analysis of correlations between drug concentration and drug effect is based on temporal sequences of both variables. From a mathematical viewpoint, these data represent two separate dependent variables which are functions of time, the independent variable. Thus, a complete representation of the data is possible only in a three-dimensional space. In classical physics, such relationships were successfully compressed (with a loss of a certain amount of information) into phase plots, which are two-dimensional projections, leaving time out of the picture and retaining it only as a parameter (1).

Applications of this old technique in biomathematics (2) are now as common as in the natural and technical sciences in general (3). When the correlation between drug concentration and its behavioural effect is time-independent (i.e., there is no time-lag), the phase plot of the behavioural data against concentration would yield a single-valued function. In the simplest case, this function is a straight line and the use of the correlation coefficient is both legitimate and straightforward. However, when this single-valued function is not a straight line, one should not analyse the relationship with the correlation coefficient, as it is inadequate. As these relationships become time-dependent, and thus more complex, the phase plot analysis becomes more advantageous. Such functions arise in a variety of biochemical situations, notably when saturation, potentiation, or a threshold occurs.

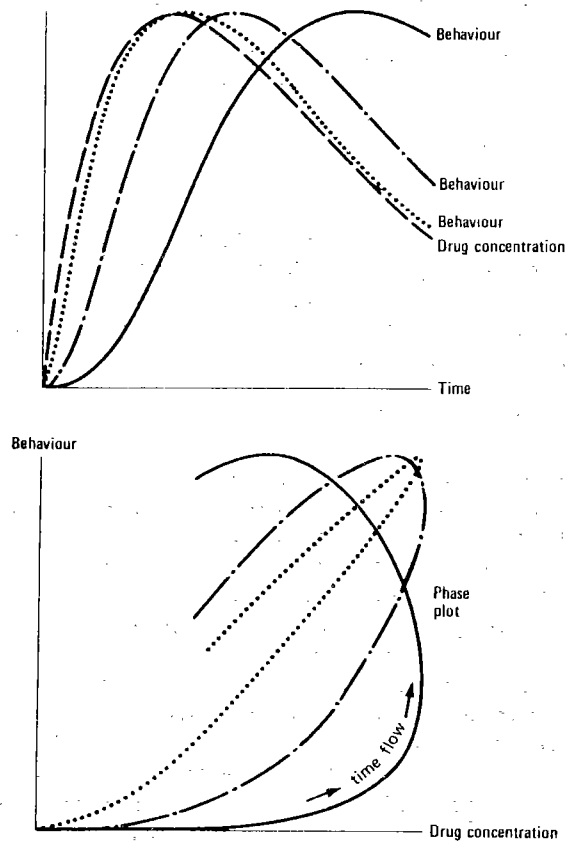
Most of the difficulties of correlation analysis are due to the nature of the drug concentration and/or drug-effect transducer systems, which manifest themselves through double-valued relationships and are graphically represented in the phase plots as loops. Therefore the correlation analysis must be based on an analysis of the systems mediating the behavioural response. These double-valued relationships will require significantly more sophisticated analytical techniques. In biochemical terms, there are two types of mechanism that may lead to double-valued functions in the phase plot.

The first is a simple time-delay mechanism: the drug concentration in plasma triggers a chain of events through various intermediates  $X_i$ , and ultimately a change in behaviour may be observed. Diagrammatically, this is represented as follows:

Drug concentration  $\rightarrow X_1 \rightarrow X_2 \rightarrow X_n \rightarrow$  Behaviour

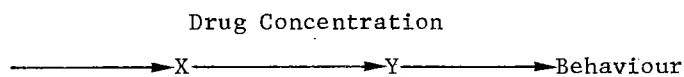
The intermediates are biochemical, physiochemical entities such as metabolites, membrane states, receptor mediated messengers, etc. The curves of behaviour and drug concentration are, generally, shifted and/or distorted as a function of time. The upper panel of Fig. 1 shows three distinct behaviour curves which are shifted in various degrees from the drug concentration curve. The shift is progressively greater from the dotted to the dashed to the solid curves. The resulting phase plots (the lower panel of Fig. 1) illustrate that as the time delay increases, the looping characteristic of the phase plot is magnified. In contrast, when the time delay is minimal the phase loop narrows and in the limiting case collapses into a single-value function (not illustrated). Once again, however, only if this function is a straight line can a time-independent linear correlation test be applied.

Fig. 1. Hypothetical relationships between drug concentration in plasma and the effect on behaviour: simple time-delay mechanism



WHO #3635

The second type of mechanism is that whereby drug effects are brought about not only by the drug concentration per se, but also by the rate of change of the drug concentration. Thus, the duration of the behavioural effect may be shorter than the duration of drug concentration, i.e. the observed behavioural effect may disappear well before the drug is eliminated. This is shown graphically in Fig. 2. These relationships are characteristic of those biochemical pathways in which the drug concentration is affecting the rate of production of some mediator (Y) of the drug effect (i.e. behaviour):

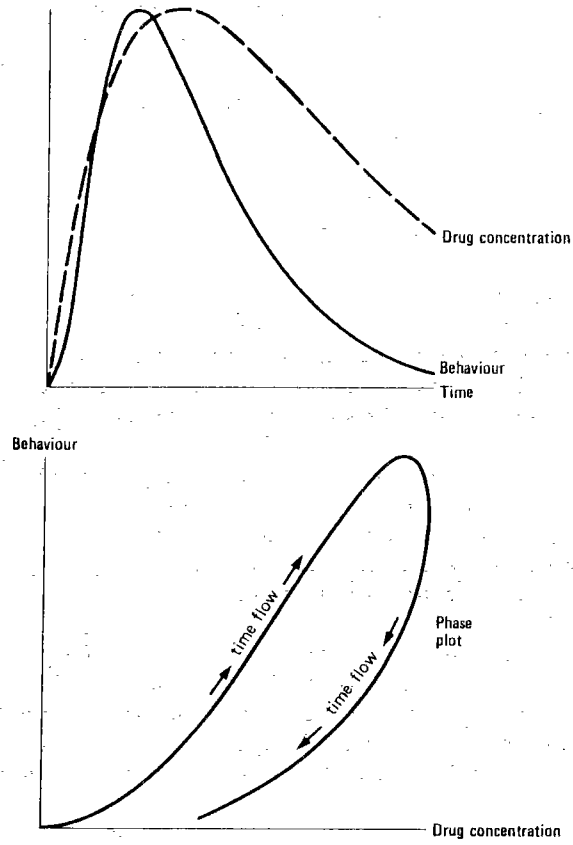


In these systems, the response is proportional to the fractional change of the drug concentration, such that repeated drug administration yields gradually smaller drug effects, a phenomenon often referred to as the development of tolerance (4).

These models indicate that the "time" coordinate is an essential factor in the correlation analysis between drug concentration and behaviour, and thus direct time-independent correlations, as commonly understood, may not actually exist.

Laboratory studies examining the behavioural effects of marijuana indicate that THC appears to be mediated via the "time-delay" mechanism. Similar studies indicate that diphenhydramine (a prototype antihistamine) follows the "rate of change" mechanism.

Fig. 2. Hypothetical relationships between drug concentration in plasma and the effect on behaviour; behaviour affected by rate of change of drug concentration



REFERENCES (ANNEX 3)

1. TOLMAN, R. C. The principles of statistical physics, London, Oxford University Press, 1938.
2. DANZIGER, L. & ELMERGREEN, G. L. Mathematical theory of periodic relapsing catatonia. Bulletin of mathematical biophysics, 16:15(1954).
3. MINORSKI, A. Nonlinear oscillations, New York, Van Nostrand, 1962.
4. LICKO, V. Transient response in metabolic and endocrine systems. Federation proceedings, 39:604 (1980).

Annex 4

RECOMMENDATIONS FROM THE NORDIC COUNCIL CONCERNING  
DRUGS DANGEROUS TO ROAD USERS<sup>a</sup>

1. Introduction

Some drugs may, like alcohol, affect the user's driving ability or his ability to work in situations where risk is involved. Not all drug users are aware of this and the health authorities have discussed how information about drugs could be conveyed to the drug users in the best possible manner.

A committee was therefore established by the Nordic Council to produce a booklet on drugs and traffic safety and make proposals for the labelling of drugs considered dangerous for road users. On the basis of this committee's proposals, lists of drugs which must be labelled with a red warning triangle have been produced. A similar label must also be applied by the pharmacist when a prescription is dispensed. Moreover, if a physician or dentist considers that a drug not included in the list may pose a problem, he is entitled to direct the dispensing chemist to affix a warning label. In addition to this label, the patient also receives an explanatory leaflet, and is urged to consult a physician about the possible risks involved in driving or the operation of complex machinery. Such information is expected to reduce the risk of accidents caused by the therapeutic use of those drugs to a minimum.

The Nordic Council recommended that the committee's system of drug labelling be implemented in all Nordic countries by 1 January 1983 and in Norway by 1 April 1981.

---

a

In the Nordic countries, pedestrians are also deemed to have a responsibility in traffic situations.

2. Instructions to Norwegian physicians, dentists, and pharmacists

Drugs that may impair the ability to drive a motor vehicle, to operate machinery, or to carry out work in a high-risk environment shall be labelled with a red triangle. The Director of Health decides which drugs shall be labelled and how the warning sign (a red equilateral triangle on a white background) shall be printed on the label. When such a drug is dispensed, the patient should also receive an informatory leaflet, Drugs dangerous to road users, the text of which has been drawn up by the Ministry of Health. These leaflets are not required when the drug is dispatched to a physician's surgery, hospital, etc. The prescriber has the authority to direct that a warning label be affixed for drugs not appearing on the list. Even if no such endorsement is given, the chemist must label drugs appearing in the official list with a red warning triangle and provide a leaflet for the patient. (Note: all Norwegian pharmacies are state-owned.)

Any drugs prepared from primary ingredients in the pharmacy must bear a red triangle if they contain any of the listed substances. In particular, all preparations for systemic use containing more than 100 g of ethanol per litre must bear a warning label, but there are no concentration limits for other substances.

Since 1 January 1983, pharmaceutical manufacturers have been required to print warning labels on all their listed products.

3. Text of the leaflet Drugs dangerous to road users issued by the Norwegian state drug control authority

(a) Drugs dangerous to road users

Everyone knows that alcohol impairs your ability to drive a motor vehicle in a reasonable manner and that there are heavy penalties for driving when intoxicated. But are you aware that drugs may also impair your ability and that it is an offence to drive when your ability to do so is reduced by drugs?

(b) Which drugs are dangerous to the road user?

All drugs which act on the nervous system may be dangerous. They may make you tired and unable to concentrate, they reduce your reaction speed, and your movements are less precise. They may also make you feel excited and perhaps reduce your critical faculties.

Drugs used to treat high blood pressure may make you feel tired and lethargic and may also cause vertigo or even fainting. Anti-motion-sickness drugs may make you feel drowsy.

(c) Be aware of these reactions and do not venture on to the road if you have reason to expect such symptoms

Apart from this, many drugs have side-effects which may make you feel unwell and less able to drive.

All drugs which are considered to be dangerous to the road user are labelled with a red warning triangle; this mark means that you should be aware of the fact that the drug may make you less able to drive a car or a motorcycle, operate complex machinery, or carry out work with a high-risk content. You will find below a list of the main groups of medicines that are liable to do this.

In certain situations, medications other than those marked with a red triangle may also impair your driving ability. However, the most important ones are listed. To be on the safe side, though, you should consult with your physician if you have any suspicion that your concentration may be impaired.

(d) Main drug groups which are dangerous for the road user

(i) Drugs used for nervous ailments. The most widely used drugs contain diazepam (Valium, etc.) but there are other types of drugs, e.g., antidepressants, which may cause problems.

(ii) Sleeping tablets. It is obviously dangerous for a driver to take sleeping drugs. Be aware of the fact that some of these drugs have a prolonged presence in the body and that there is thus a possibility that their effect may still be present the following morning.

(iii) Drugs used to treat motion sickness and allergy (antihistamines). Such drugs may make you feel tired and drowsy. Do not take them when you are going to drive soon afterwards. Some of these drugs include caffeine to counteract drowsiness, but it is important to realize that caffeine is short-acting and its effect does not last as long as the other ingredients which make you drowsy. You may therefore suddenly feel drowsy some considerable time after the medication was taken if it contains caffeine. Some motion-sickness drugs may also impair your vision and increase your susceptibility to dazzle.

(iv) Pain-relieving drugs. Many of these act in a tranquillizing manner and make you feel tired and less alert. They may also make you excited and lead to a loss of critical sense. All these factors will reduce your ability to drive.

(v) Stimulants. Powerful stimulants sold and used illegally may be lethal to the driver.

(vi) Drugs for epilepsy. These may make you drowsy and tired the first few times you use them. Epileptics usually know this and realize that they may only drive when the medication ceases to affect them in this way and when they have not had a seizure for a long time. An epileptic who changes from one medication to another should be particularly careful.

(vii) Drugs for high blood pressure. These may, among other things, make you feel tired and drowsy. People who use these drugs must therefore find out how they react before they decide to drive a motor vehicle.

(e) Get to know how you react to drugs

Not everyone reacts to drugs in the same way. It is therefore important that you find out how YOU react to the medication you are using, whether you use drugs occasionally, periodically, or regularly. Your reaction is usually stronger during the first few hours after you have taken a dose and many medications will produce the worst side-effects (e.g., tiredness and impaired concentration) during the first few days or the first week of treatment. During this time you should therefore be particularly careful in driving. When you use medication it is always important to follow the instructions carefully. You must not increase the prescribed dosage or use other medications at the same time without consulting your physician.

Many medications increase the effect of alcohol, and it may be particularly dangerous to use alcohol and drugs at the same time.

(f) Points to remember

- Get to know how YOU react to the medication you are using and take this into account before venturing on to the road.
- Always follow your physician's advice on how to use the medication.
- Never use a medication prescribed for others.
- Remember that alcohol and drugs used at the same time may increase each other's effects.
- It is an offence to drive when your driving ability is impaired due to drugs.
- Physicians and chemists will give further information on drugs which are dangerous to road users.

= = =

