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Background

Recent research[1-5] demonstrates that driving under the influence of drugs (DUID) other than alcohol is common. However, a major problem in assessing the true impact of drugs on driving and overall traffic safety is the fact that the variables being measured across studies vary significantly. In studies being reported in a growing global literature, the basic parameters being assessed, the analytical techniques being used, and the drugs being tested for are simply not comparable due to a lack of standardization in the field.

The International Council on Alcohol, Drugs & Traffic Safety's (ICADTS) Working Group on Illegal Drugs and Driving identified this problem in 2005 and recommended that a set of standards or guidelines for drugged driving research was sorely needed. Furthermore, the ICADTS working group recommended that a consensus meeting of international researchers, representing the various aspects of the drugged driving research community (e.g., toxicologists, epidemiologists, behavioral scientists, trauma specialists, police) should be held to develop these standards to serve as a basis for future international DUID research. Such a set of guidelines or standards would enable researchers to design future experiments and to begin to collect data on core standardized variables that could facilitate cross-study comparisons.

As a result of the ICADTS working group's recommendations, in September 2006, a 4-day experts' meeting, **"Developing Standards for Research in Drugged Driving,"** was held at the Tufts University European Center in Talloires, France. The meeting brought together international experts in drugged driving to discuss the harmonization of protocols for future research on Drugged Driving. The meeting was co-sponsored by the U.S. National Institute on Drug Abuse (NIDA), the European Commission, the **European Monitoring Centre for Drugs and Drug Addiction (EMCDDA),** French Society of Analytical Toxicology (SFTA), ICADTS, and the International Association of Forensic Toxicology (TIAFT).

The principal objective of the meeting was to develop a consensus report and set forth guidelines, standards, core data variables, and other controls that would form the basis for future international DUID research.

The organizing committee agreed to use the Delphi technique as the method for achieving consensus. The Delphi technique is an excellent tool for gaining input from recognized sources of expertise without relying totally on face-to-face meetings. This technique uses a highly structured, focused approach to establish a consensus opinion from experts. The focus was specific to three areas of research: behavior, epidemiology, and toxicology. The Delphi technique is an iterative process and initially aims to obtain a broad range of opinions. The results of an initial survey are summarized and form the basis for a second round of consideration. In the second round of deliberation, the document is refined and forms the basis for a third-round document for consensus consideration. The aim of the iterative process is to progressively clarify and expand on issues, identify areas of agreement or disagreement, and establish priorities.

We ultimately settled on a modified Delphi technique using the 4-day meeting in Talloires to conduct the first two iterative rounds of deliberation and to develop a draft set of guidelines. Subsequently, the draft guidelines were posted on the websites of ICADTS and TIAFT for a 45-day review and comment period with the expectation of reaching virtually all the world's experts in drugged driving research, providing them the opportunity to be involved in the process by commenting and making recommendations. In the last stage, comments received from the global research community were considered and integrated into the final document that follows.

This guideline document is divided into three major sections focusing on the different aspects of drugged driving research (e.g., roadside surveys, prevalence studies, hospital studies, fatality and crash investigations) within the subject areas of behavior, epidemiology, and toxicology: (1) The **Behavioral** section contains 32 recommendations; (2) the **Epidemiology** section contains 40 recommendations; and (3) the **Toxicology** section contains 64 recommendations.

We would like to express our sincere gratitude to NIDA, the European Commission, EMCDDA, SFTA, ICADTS, and TIAFT who provided funding and various other support for the planning and implementation of this important project. We also would like to thank the Tufts University European Center and its director, Gabriella Goldstein. The Prieuré in Talloires provided a setting that was instrumental in facilitating the group's discussions and deliberations on this important international issue.

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Drugged Driving Research: Call for Renewed Emphasis on Guidelines and Standards

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Drug-impaired driving continues to be an underrecognized problem in many countries throughout the world. While recent evidence suggests that driving while under the influence of illegal drugs frequently occurs, and approaches levels of driving under the influence of alcohol among younger drivers in the United States (NSDUH, 2004), the research database remains incomplete and often does not provide adequate scientific bases for legislation and policies directed toward the problem. Several efforts have been made over the last 25 years to identify significant research gaps in this area, and progress is being made to address them. However, there appears to be need and opportunity for the field to significantly address these gaps by a concerted effort to develop and adhere to a number of standards for research that would improve the overall state of knowledge in this important area and form a stronger basis for sound policy to address its impact.

To that end, this paper will provide a brief review of prior reports from a number of different workgroups and symposiums of experts in research fields contributing to the knowledge base on drugs and driving. These reports emphasize gaps in the existing knowledge base and ways to address them. They also suggest and recommend research guidelines and standards. These reports have provided the starting point for the discussions leading to the recommendations contained within this report.

What has been done?
As early as 1991, a workshop held in Padova, Italy, addressed methodological issues related to drugged driving. Three major areas of study related to research on drugged driving were addressed. These included studies on man-machine interaction, epidemiology and special population surveys, and toxicological assay of psychoactive substances in biological fluids (Ferrara and Giorgetti, 1992). The need for standards and guidelines in research in each of these areas was stressed, and an ultimate goal was to develop a comprehensive set of methodological guidelines for future research. These guidelines are intended to improve the quality of experimental research and "…to provide regulatory authorities with criteria for judging whether evidence provided by particular studies can be used for identifying a drug's hazard potential as part of the registration process" (Ferrara and Giorgetti, 1992).

The Padova report also concluded that systematic experimentation is required to make conclusions regarding particular drugs or doses and that such conclusions cannot be made on the basis of single studies. A review of a rather lengthy literature on drugs and driving shows that many of the empirical studies that contribute data for categorizing drug effects on driving performance are flawed, and thus the extant database as a whole is not entirely suitable for that purpose (Ferrara and Giorgetti, 1992). Some weaknesses in the literature include a great variety of methods used so that valid comparisons across studies are often difficult and failure to document validity and reliability of test methods or the rationale behind the choice of methods.

A report by a working group on guidelines on experimental studies undertaken to determine the effects of medicinal drugs on driving or skills related to driving sponsored by ICADTS suggested that "empirical studies, as a whole, are suitable as a database for categorizing the potential hazard of medicinal drugs only when they are based on a sound methodology and when the results of different studies are comparable. A review of the literature leaves the impression that these prerequisites are not met due to, among other things, the considerable variety of elements of the study design, of the sample choices, of the treatment, of the methods of testing driver fitness, and of the statistical evaluation" (ICADTS, 1999).

Another report dealing with drugs and driving (ICADTS, 2000) focusing on legislative initiatives concluded that "developing strategic initiatives to deal with this problem is hampered by the fact that there are significant technical and methodological gaps in our knowledge about the way in which illegal drug use affects driving skills, and further complicated by the complexities of DUI laws." Some of the methodological issues pointed out by the report included inability to get biological specimens in all cases in surveys to make prevalence estimates and interpretation of drug concentrations in biological fluids with regard to behavioral effects requires some knowledge about the dose, route of administration, pattern or frequency of use, and dispositional kinetics (e.g., distribution, metabolism, and excretion) of the drug.

A symposium on Drugs in Traffic at Woods Hole in 2005 sponsored by the Transportation Research Board (TRB) stated that "many states and other countries have implemented laws designed to deter drugged driving. Attempts to control drugs in traffic, however, are subject to gaps in knowledge about drugs and an array of practical difficulties" (TRB, 2005).

Although much progress has been made since the Padova report (Ferrara and Giorgetti, 1992), many of the methodological concerns are still at the forefront. It is time for the field to become re-energized and develop a model of consensus for research methods and guidelines that are likely to lead to solving many of the extant problems preventing development of a complete and coherent knowledge base.

What needs to be done?

Although progress is continuing to be made, recent workgroups and conferences have consistently noted a need for more targeted research in a number of important areas. For example, an experts panel on drugged driving research needs and opportunities in Glasgow in 2004 sponsored by NIDA (NIDA, 2004) made specific recommendations for research under several major categories, including (1) the need for more epidemiological research on prevalence and crash risk of drugged driving; (2) new technology for drug detection; (3) better identification techniques for recognizing impaired driving; and (4) policy studies.

Epidemiological research. Perhaps one of the most important areas of research involves a better understanding of the epidemiology of drugged driving in the general driving population, among injured and fatally injured drivers, and the crash risks associated with drugged driving. The Glasgow group (NIDA, 2004) expressed a sense of urgency that further research is needed on the prevalence of drugged driving in the general population, especially considering evidence that the problem appears to be growing. These studies are needed to demonstrate to the public and policymakers that drugged driving requires attention and effective public policy is needed.

Recommendations for epidemiological studies included roadside surveys to establish prevalence; emergency room studies to establish prevalence among injured drivers and prevalence among fatal accident victims; DUI suspect studies to establish prevalence among uninjured but presumably impaired drivers; crash risk and culpability studies; high-risk population studies; and fitness for driving in drug-dependent individuals (NIDA, 2004). The ICADTS report on illegal drugs and driving (2000) recommended research critical for the development of sound public policy as including epidemiological studies on prevalence of illegal drug use in drivers, emergency room studies linking drug use with motor vehicle accidents, studies on the causative role of drugs in driving accidents, and a stronger knowledge base of the hazards connected to drug use and the magnitude of the problem.

Better case-control studies on risks for crash for different drugs, especially studies using better measures for presence of drugs in crash research to disentangle effects of medicinal drugs used as prescribed as compared to used in overdose or illegally were noted as research needs by the TRB report (TRB, 2005).

Performance effects of commonly used drugs. One of the significant gaps in the research base is in terms of the performance effects of many drugs that affect the central nervous system. Although there is considerable evidence that many drugs can impair some aspects of performance, the knowledge of the impact on driving skills or actual driving is much more limited. More thorough studies of performance effects of the range of commonly used drugs is needed using valid and consistent methodologies and consistent protocols for performance testing that will allow for making valid comparisons and summaries across studies (TRB, 2005).

New technology for drug detection. One of the limitations of conducting epidemiological studies and of enforcing laws against drug-impaired driving is the difficulty in obtaining and testing appropriate biological specimens. Blood draws require trained personnel and are invasive, and urine collections involve privacy issues. Research is needed to develop and evaluate quicker, more reliable and accurate roadside testing devices (Walsh et al., 2004). In order to broaden the scope of drug detection, alternative matrices such as sweat and saliva need to be evaluated. Research on windows of detection of drugs in different body fluids and practical screening tests also are needed (NIDA, 2004; Walsh et al., 2004).

Better identification techniques for recognizing impaired driving. In many situations, police officers require some evidence of impaired driving to make an arrest or order a drug test. Better techniques are needed to recognize impaired driving. More research is needed on understanding sensitivity and specificity of different methods for identifying DUID, such as driving performance, performance testing, cognition, motor skills, or eye signs such as dilation and nystagmus. Each aspect of identification should be analyzed to determine the relevant factors in DUID detection (Walsh et al., 2004). Studies on behavioral tests, including establishing sensitivity and specificity of the tests for impairment, are important (NIDA, 2004; Walsh et al., 2004). Developing standardized training on drug detection for police and evaluating different identification techniques (e.g., drug recognition experts vs. physicians) has been cited as an important research need (NIDA, 2004)

Policy studies. Policy and law enforcement efforts regarding drugs and driving have been moving forward, often with inadequate research data to support such efforts and often without appropriate evaluations to test the effectiveness and efficiency of legislative or enforcement efforts. A constant danger of developing policies in the absence of adequate research studies involves unintended consequences of the new efforts. In terms of policy and enforcement efforts combating drugged driving, several research recommendations have been offered. The Glasgow report (NIDA, 2004) recommends identification of best practices for identification, conviction, and referral for treatment of drugged drivers and evaluation of the effects of per se laws on the prevalence of drugged driving and traffic safety. The Walsh et al. (2004) symposium report made research recommendations for the evaluation of the preventive effect of random roadside tests including their cost-effectiveness; research on what it takes to pass effective DUID laws; what penalties provide the most effective deterrents; and research on methods for garnering public support. Evaluation of the effects of various legal approaches to drugged driving and of the effects of increased enforcement on traffic safety was recommended by the 2005 symposium on drugs and traffic (TRB, 2005).

How we can get there: Benefits of research standards

Although progress is being made, there is a large list of important research priorities that require attention for the knowledge base to continue to move forward. However, progress will continue to be slow or even stalled in important areas without close attention to appropriate research methodologies. There have been calls for standardized protocols and research guidelines for many years. This would certainly improve the knowledge base and allow for consolidation and comparisons of often diverse research studies and conflicting or ambiguous research results. The 1991 workshop held in Padova, Italy (Ferrara and Giorgetti, 1992), developed a set of recommended guidelines for experimental research in the areas of man/machine interactions, epidemiological research (surveys of the general and driving population,

fatally injured drivers, and injured drivers), and toxicological assays that has relevance today. Unfortunately, most of those recommendations have not been implemented to date.

An ICADTS working group (ICADTS, 1999) provided guidelines on experimental studies to determine a medicinal drug's effects on driving or skills related to driving, many of which replicated the earlier recommendations from 1991, indicating continued need for such guidelines. A more recent report (de Gier, 2004) concluded that "the application of epidemiological research to drugs (other than alcohol) and driving can only permit meaningful cross-cultural comparison if standardized data-gathering methods are used," and that "a review of investigations of prevalence of illicit drugs in road traffic in selected countries will therefore include studies in which numerous methodological problems are to be encountered." Because of the continued methodological problems which hamper progress in the field, the time is ripe for renewed calls for standard research guidelines agreed on by the top experts in the field.

Conclusions

A review of a number of workshop and symposium reports produced by the top experts in the field of drugged driving over the past 15 years has shown that progress is being made in understanding the role of drugs (both medicinal and illicit) in traffic safety. However, the problem of driving under the influence of drugs is far more complex than the problem of driving under the influence of alcohol and the knowledge base is much more fragmented and inconsistent. Some of the recent progress in identifying knowledge gaps in the field has been outlined here as well as the long list of research priorities for work still needed. This work is critical in a number of areas as legislation is being passed and enforcement priorities changed often based upon an incomplete knowledge base. Furthermore, enforcement of many existing impairment laws on driving under the influence of drugs requires reliable assessments of impairment and established associations between drug levels and driving performance behaviors. Registration of new medications now often requires an assessment of impairment potential that needs to be based on standard methodologies.

In spite of the progress that has been made and the recognized need for research in a number of defined and agreed-upon domains, forward progress will continue to be slow until much needed standardization is brought to research so that studies can build toward a coherent and complimentary knowledge base rather than be fragmented and often contradictory. Such standards have been pushed for at least the past 15 years, yet recent reports continue to repeat the same concerns. Hopefully, the time is opportune for change, and this report is an attempt to garner the support and consensus of the scientific community that in turn can be used to encourage government and other funding agencies to focus support on research studies that will truly advance the state of knowledge in this important area and form a solid scientific base for policy and program decision-making.

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Road Safety and Driver's Impairment

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Road safety is a central issue of transport policy. Europe has the ambitious target of reducing by 50% the number of road fatalities by the year 2010. In its mid-term review of the Road Safety Action Programme, adopted on 22 February 2006, the Commission pointed out that the European Union (EU) has reached a 17% reduction in the number of fatalities in the last 4 years, when 27% would have been needed to be on track to meet the 2010 target. The situation has improved during the last 12 months: less than 8% of persons killed on the EU roads. This figure would allow achieving the target. However, improvements still are needed and progress must be made especially in the field of drivers' behavior, where speeding and drink-driving still constitute the main causes of road accidents. Moreover, the number of accidents attributed to the consumption of psychoactive substances is increasing and the reduction of this number is therefore imperative.

In this respect, the issue of fitness to drive is a very important one. Annex III of the driving license directive 91/439/EEC, which deals with minimum standards of physical and mental fitness for driving a power-driven vehicle, needed to be updated. In fact, the contents of this Annex are based on decisions made more than 20 years ago. Therefore, three specialized working groups with experts of different Member States have been set up, in three different matters, that is, eyesight, epilepsy, and diabetes. Results and final reports of these groups are now published on the driving license website and will be discussed with the Member States in view to update the Annex III within the next few months.

In Annex III of the directive mentioned above, there are also two specific paragraphs on "alcohol" and "drugs and medicinal products" (§ 14 and 15). The contents of these paragraphs also need to be updated since it is only said that "driving licenses shall not be issued or renewed to persons who are dependent on psychotropic substances or regularly abuse or use them." But we know that drink-driving is still an issue to be addressed, as well as drugged-driving, because the prevalence of drug consumption in road accidents can reach 15%. The expert group on alcohol, drugs, medicines, and driving will soon make some proposals to update these paragraphs of Annex III.

This expert group was set up several years ago upon request of the Road Safety High Level Group. The role of the members of this group is mainly to make recommendations and to invite the Commission and the Council to implement these recommendations. For instance, a Council Resolution on combating the impact of psychoactive substances use on road accidents was adopted 27 November 2003. This Resolution underlines the importance of promoting research on the influence of psychoactive substances on driving ability, developing research to improve road tests, ensuring the exchange of information among Member States, launching prevention campaigns, taking any appropriate measures (sanctions), and gathering and evaluating information regarding measures for rehabilitation of drivers.

However, more knowledge in this field is still needed and that is the reason why the Directorate-General for Energy and Transport decided to put the emphasis on fighting this phenomenon; therefore, the European Commission (EC) decided to fund a research project in the framework of the 6th Work Product [WP] which is called DRUID (driving under the influence of drugs, alcohol, and medicines). The project started on 15 October 2006, and the kick-off meeting took place in Köln, Germany, on November 13 and 14, 2006; its duration is 4 years, and the EC contribution is about 19 millions Euros. The main objective of DRUID is to analyze the influence of consumption of psychoactive substances on fitness to drive.

The expected outcomes of the project are as follows:

- Have available reference studies on the impact of alcohol, illicit drugs, and medicines on fitness to drive
- Fix thresholds for driving a power-driven vehicle
- Evaluate the best tracking devices
- Define a labeling system corresponding to European classification
- Define rehabilitation schemes for drivers
- Define strategies of driving bans
- Define the doctors' legal responsibility
- Inform the general public.

With this important knowledge, after discussions within the expert group on alcohol, drugs, medicines, and driving and after debates with the Member States, community actions, even legislative, in this field might be proposed. At the same time, European researchers are very keen to collaborate with Americans, Canadians, and Australians in this area of work.

Collection and Harmonisation of Drug-Related Data, the EMCDDA's Experience

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1. Introduction

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is the central reference point for drug information in the European Union (EU). Its role is to provide the EU and its Member States with objective, reliable, and comparable information on drugs and drug addiction.

Evidence-based information on drugs is one of the most vital tools at our disposal today to address this global challenge. By offering information of this kind within the EU, the EMCDDA helps policymakers, researchers, and specialists in the field understand the nature of the problem and formulate appropriate responses.

2. Data collection: Areas covered

Providing an accurate and up-to-date picture of this ever-changing landscape forms the cornerstone of the agency's activities under its work program. Although a great deal has already been achieved, much remains to be done to perfect monitoring instruments and develop a truly "common language" with which to describe this European and global phenomenon.

EMCDDA's mission statement sets out the agency's four main tasks:

- Collecting and analyzing existing data
- Improving data comparison methods
- Disseminating data and information
- Cooperating with EU institutions, international partners, and non-EU countries.

The information collected, analyzed, and disseminated by the EMCDDA focuses on:

- The demand and reduction of the demand for drugs
- National and EU strategies and policies.

In addition, the EMCDDA also has the mandate to work on international cooperation and the geopolitics of supply; control of the trade in narcotic drugs, psychotropic substances, and precursors; and implications of the drug phenomenon for producer, consumer, and transit countries.

Collecting reliable, comparable, and up-to-date information on drug use and its consequences is both methodologically and practically challenging. The EMCDDA, therefore, works in partnership with national experts to develop the infrastructure and technical tools necessary for countries to gather data in a uniform way. Such instruments offer countries a "common language" with which to interpret and compare the nature of their shared problem. They also help policymakers across the EU identify key issues, take action, and assess the impact of their work.

At the heart of EMCDDA's information system are five key harmonized epidemiological indicators: standard tools for collecting and reporting comparable drug data. Through these indicators, the agency is gaining an increased understanding of Europe's drug problem and is generating the sound evidence needed for effective decision-making.

Knowing which interventions are effective in dealing with a specific drug situation is crucial for policymakers to design successful response strategies. Monitoring and analyzing responses to availability, accessibility, and quality of responses in the fields of drug prevention, treatment, social

rehabilitation, and harm reduction are therefore additional central tasks of the EMCDDA. The Centre also helps exploit research and promote scientific knowledge on responses as the basis for decision-making in policy and practice.

The agency also disseminates information on best practices and quality assurance which have been achieved via careful planning, systematic implementation, adequate monitoring and evaluation, and sound scientific knowledge.

Through these activities, the agency hopes to contribute to a productive and mutually beneficial European exchange of knowledge, increase information on positive response choices, and provide guidance on the optimal use of resources and skills.

3. Data collection: Organization

The Centre collects information at the European level through the European Drug Information Network (Reitox).

The Reitox national focal points constitute the main information interface between the EMCDDA and its Member States and as such play a dual role. On the one hand, under the responsibility of their governments, they are the national authority providing drug information to the agency. On the other, under EMCDDA guidance, they are "ambassadors" representing and promoting Reitox at home.

The focal points submit to the EMCDDA on a yearly basis—for EU-level analysis—regular statistics, qualitative information, and annual national reports on the main drug trends and developments in their country (respectively, key indicators and other statistics, structured questionnaires for qualitative information, national report). They also disseminate European drug information at the national level.

Quality of information is ensured largely by the use of consensually agreed guidelines and data collection tools, which are under continuous revision and improvement. The EMCDDA assesses the quality of all data received from the network (i.e., data management, control, feedback); discusses results individually with the focal points; and will sometimes triangulate additional information sources (e.g., EuroHIV, Eurostats). Therefore, the role of the national focal point is crucial (EU countries + Norway + candidate countries).

4. The 5 key indicators

The five key epidemiological indicators underpin the EMCDDA's reporting on trends and developments in the EU drug situation. They are also a necessary component of any analysis of the coverage of responses or the assessment of the impact of policies and actions.

The key indicators provide a reporting format supported by methodological guidelines that is common across the EU: protocols for implementation of the indicator at the national level, common templates, and guidelines for reporting. These instruments for data collection are under continuous update and improvement. In addition to the annual data reporting, expert meetings are organized to gather national experts in order to refine the picture of the EU situation as well as to discuss protocols and guidelines. This, together with an understanding of national reporting systems and how they influence the data available, can generate effective monitoring at the European level.

Since 2000, the EU Action Plan on Drugs calls for Member States to provide reliable information on these epidemiological instruments according to the EMCDDA's recommended technical tools and guidelines. The five key indicators are the following:

- Prevalence and patterns of drug use among the general population (population surveys)

- Prevalence and patterns of problem drug use (statistical prevalence/incidence estimates and surveys among drug users)
- Drug-related infectious diseases (prevalence and incidence rates of HIV and hepatitis B and C in injecting drug users)
- Drug-related deaths and mortality of drug users (general population mortality, special registries' statistics, and mortality cohort studies among drug users)
- Demand for drug treatment (statistics from drug treatment centers on clients starting treatment).

EMCDDA key indicator: Example of drug-related deaths

- Number of cases of deaths that are caused directly by the consumption of drugs of abuse (T + M + F), no age limitation, broad age groups (<15, 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, ≥65)
- Standard definition for mortality registries (GMR): based on the selection of ICD9 or ICD10 codes. Substances include opioids, cannabinoids, cocaine, other stimulants, hallucinogens, and multiple drug use.
- Standard definition for special registries: includes deaths due to poisoning by opiates, amphetamines, cocaine or crack, cannabis, hallucinogens, solvents, or synthetic designer drugs.

More information on the 5 keys indicators is available at: http://www.emcdda.europa.eu/?nnodeid=1365.

The base-level work carried out in developing protocols for the original EU Member States is, in general, strong enough to be transported to the new Member States, a process supported by the preparatory work for enlargement. The EMCDDA has supported implementation in a number of ways. There has been an increased commitment to training on protocol implementation; more attention has been directed to quality control on the reported data; and in response to the increased volume of data reported, the EMCDDA is adopting a forward-looking, single automated web-based data collection scheme for all reporting countries.

It is possible to say that considerable progress has been made in implementing the key indicators, although further efforts are required. In particular, most countries now have good quality population survey data but there is a need for more regular data collection exercises; the possibility exists for better coordination at the European level. Complementary estimates of problem drug use are available in many countries but not all, and there is a need for regular updating of estimates. Treatment demand data are available from most countries, but coverage problems do exist. Information on drug-related deaths has improved considerably, but there remains a need for more toxicological verification and to extend the indicator to better record non-opiate-related deaths. Information collected for the infectious disease indicator could be improved in most countries, especially in respect to hepatitis C virus infections and information necessary to monitor incidence.

Monitoring the EU drug situation presents different challenges for the national focal points and the EMCDDA and requires them to achieve as much as possible different challenges.

For the national focal points, the challenge is to achieve the following:

- Implement the Key Indicators
- Improve coverage of methods and quality of estimates
- Provide up-to-date information
- Consolidate the series
- Increase the number of analyses

- Consolidate the national expertise.

For the EMCDDDA, the challenge is to achieve the following:

- Improve guidelines continuously
- Change/adapt the tools to monitor changing patterns
- Allocate time for new developments and analysis
- Ensure compliance to protocols and guidelines (technical support and training, but with budget/political constraints)
- Fit to EU enlargement: 10 new Member States in 2004 + candidate countries
- Reply to new requests in the framework of the evaluation of EU action plan.

5. Legislation regarding drugs and driving across the EU and Norway, relevant to common research issues (Based on the ELDD Topic Overview)

One of the EMCDDA's products is the European Legal Database on Drugs (ELDD), a public website giving information on various aspects of the countries' and the Union's drug laws. This is informed by a network of national legal correspondents, experts well placed to describe their countries' legal framework on drugs.

An earlier study of drug-driving laws was carried out by the ELDD and presented at the last Pompidou Group seminar in 2003. It was a comparative study in the form of a legal textual report. This study has been updated with the new EU Member States and is now presented in a simpler tabular format, which we call a Topic Overview. Today, 22 countries have completed this table.

If you wish to see the Topic Overview, you will find it published on the ELDD at http://eldd.emcdda.europa.eu/ in the Topic Overview section.

The Topic Overview addresses the following aspects of drug-driving laws:

- Status of offence – criminal/non-criminal
- Police may stop to test – random/suspicion
- Substances specified
- Tolerance–zero/impairment
- License suspension period
- Fine range
- Prison sentences available
- Legal basis

Status of offence

Regarding the status of the offence, we have chosen to distinguish simply between "criminal" and "non-criminal." Defining this distinction could warrant a seminar in itself, with different countries' legal systems across Europe containing administrative codes, misdemeanor codes, and administrative sanctions. For the purposes of this Topic Overview, "non-criminal" is crudely defined as having no prison or no criminal record (again, a complex topic) as a result of the offence.

Thirteen countries[1] have established driving after taking drugs as a criminal offence only. Three countries[2] have established it only as a non-criminal offence, although here it should be noted that under §§81, 88, and 89 of the Austrian Penal Code (StGB), endangerment of persons, while under the influence of any substance, is a criminal offence punishable by up to 3 months in prison or 180 day-fines.

[1] Belgium, Denmark, Greece, France, Ireland, Italy, Luxembourg, Hungary, Netherlands, Sweden, Finland, UK, Norway

[2] Lithuania, Austria, Slovenia

Negligence resulting in death, if under the influence of any substance, is a criminal offence punishable by up to 3 years in prison, and if resulting in injury, is punishable by up to 6 months in prison or 360 day-fines. These might be applied to driving under the influence of drugs.

Finally, six countries[3] have the offence established both as criminal and non-criminal; we will see that this may be due to differences in tolerance, in that zero-tolerance detection of substances is a non-criminal offence, whereas impairment is defined as a criminal offence. Of these six, note that Slovakia is the only country to report specific mention of a defined offence/punishment for drivers of public transport.

Can police stop at random?

The issue of when police can stop a driver to test for drugs—at random or only when they suspect that an offence has been caused—is a controversial one, and this study shows that there is certainly no agreement on the issue across Europe. Indeed, the division is equal; 11 countries[4] report the possibility of random stopping, and 11[5] report that suspicion is required. In some countries, police are obliged to test following an accident or (fatal) injury—these have been included as grounds for suspicion.

Which drugs?

The third issue is which drugs drivers can be prosecuted for using. In 16 countries,[6] the laws prohibit the influence of any substance, whether illicit or medicinal, and whether controlled as a narcotic/psychotropic or not. A further three countries prohibit the influence of most substances: in Luxembourg, the law applies to all controlled substances; in France, it applies to substances or plants classed as narcotics; and in Austria, the law refers to "Suchtgift," which is generally drugs controlled under the UN 1961 Convention and Schedules I and II of the UN 1971 Convention. These systems of control raise the question of what happens when a person is found to be driving under the influence of a new synthetic drug, or (in the case of France and Austria) benzodiazepines.

The remaining three countries have a two-tier system. All three prohibit driving when impaired by any substance. Yet in Belgium and Germany, there is zero tolerance toward seven named substances (although in Germany, this is now subject to a decision of the Federal Constitutional Court in February 2004, which stated that a certain minimum level of substance was to be detected before the offender could be convicted), and in Finland there is zero tolerance toward a narcotic substance other than a medicinal product which a person has a right to use.

Impairment or zero tolerance

The next matter regards the amount of drug used. Some countries may tolerate a certain amount of drug found in the test sample, provided the driver's skill to operate a vehicle is not affected—thus the tolerance is to "impairment." On the contrary, other countries will not tolerate any amount of substance found, no matter what the effect on the driver—the "zero-tolerance" level. The zero-tolerance principle can be seen in the laws of seven countries,[7] whereas the impairment principle is used by 10.[8] What is perhaps interesting is that four countries in Europe have both systems active in their laws. We have seen that three of them are Belgium, Germany, and Finland, with an impairment offence for any substance but zero tolerance for a certain number, and the fourth is the Czech Republic.

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[3] Czech Republic, Germany, Estonia (if recidivist even for alcohol), Spain, Portugal, Slovakia (if recidivist or public transport)

[4] Belgium, Czech Republic, Denmark, Germany, Spain, Estonia, (Luxembourg if ordered by Public Prosecutor), Hungary for alcohol, Portugal (but test on suspicion), Slovenia, Slovakia, Finland

[5] Greece, France, Ireland, Italy, Lithuania, Luxembourg, Netherlands, Austria (on assumption), Sweden, UK, Norway

[6] Czech Republic, Denmark, Estonia, Greece, Spain, Ireland, Italy, Luxembourg, Hungary, Netherlands, Portugal, Slovenia, Slovakia, Sweden (but no liability if in accordance with prescription), UK, Norway

[7] Estonia, France, Lithuania, Portugal, Slovenia, Slovakia, Sweden (but no liability if in accordance with prescription)

[8] Denmark, Greece, Ireland, Italy, Luxembourg, Hungary, Netherlands, Austria, UK, Norway

Suspension of license, level of fines, prison sentences
The ELDD Topic Overview considers these in detail, but we have omitted them here, as they have less relevance to the research standards we are discussing here.

Legal basis
Finally, we looked at the legal basis for the drug-driving law offences. This was not always clear but still gives an interesting picture. Eight countries[9] set out criminal offences in the Penal Code, whereas 14 countries[10] established the criminal offences in the road traffic laws. Three countries[11] established their non-criminal offences in the (administrative or misdemeanor) code, but 6 countries[12] described their non-criminal offences in the road traffic laws. Thus, none appeared to be set out in the countries' drug control laws (though drug possession offences are often established in Penal Codes), but the majority, whether criminal or non-criminal, seemed to be established in the road traffic laws. This may merit further or deeper analysis, but at first sight this would indicate a road safety objective rather than a drug control objective.

Pompidou Group survey
A consultant for the Pompidou Group surveyed the Pompidou Group Permanent Correspondents regarding various aspects of their laws on drugged driving. Twenty-two countries replied (a different 22 than the above), and presented them in July 2006. We have briefly included a few of these as relevant to this seminar:

Is there simultaneous or consecutive testing for illegal drugs and alcohol? Fourteen countries answered yes, 7 answered no (1 did not answer). Thus, a number of countries may test for alcohol and gain a simple prosecution for that, rather than bothering to determine whether the offender has drugs in the blood as well.

Does your country follow a Driving Impairment Observation Protocol? Seven answered yes, but 12 answered no. This means that police stops for suspicion of drugged driving will vary greatly around the country. Is there any legal regulation on prescriptions for drivers? Seven said yes, but 15 answered no. Are prescribing guidelines known (e.g., have physicians adopted ICADTS guidelines)? Similarly, 6 answered yes, but 14 said no. This suggests a great variation in drivers possibly driving after taking impairing medications.

Are ICADTS guidelines applied in studies on drugged drivers in your country? Three said yes, but 14 answered no. Is there any institution collecting data that allows the association of alcohol and drug statistics (e.g., unifying body)? Twelve answered yes, but 7 said no. These two results suggest that study designs in each country may have serious compatibility issues, and even collecting the results at the national level may not be simple.

Is a post-mortem examination obligatory? In 14 countries the answer was yes, but no in as many as 6. When asked which is obligatory, autopsy and/or toxicology reports, 13 answered autopsy, 9 answered toxicology reports, but only 5 countries answered both. Once again then, studies made on fatal accident victim results could not expect to receive as standard all the information necessary to detect the presence of drugs at the time of the accident.

[9] Czech Republic, Germany, Estonia, Spain, Hungary, Portugal, Slovakia, Finland
[10] Belgium, Denmark, Estonia, Greece (?), France, Ireland, Italy, Luxembourg, Netherlands, Portugal, Slovakia (?), Sweden, UK, Norway
[11] Czech Republic, Lithuania, Slovakia
[12] Germany, Estonia, Spain (?), Austria, Portugal, Slovenia

Toxicological Considerations in Impaired Driving Research and Enforcement: Sample Selection

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Introduction

Any centrally acting drug if taken in sufficient quantity has the ability to impair a person's normal driving ability. Both prescription and illicit drugs are frequently encountered in populations being studied in impaired driving populations including arrested drivers (Jones et al., 2007), fatally injured drivers (Schwilke et al., 2006), road trauma patients (Walsh et al., 2005), and roadside survey or checkpoint subjects (Steinmeyer et al., 2001). There are consistent patterns to the drugs that show up most frequently, with marijuana, cocaine, amphetamines, benzodiazepines, and opiates invariably appearing in the top five, irrespective of jurisdiction. Studying these various driving populations and the drugs they use allows assessment of accident risk, targeting of prevention messages, development of specific remedial sanctions, development of deterrence and legislation, planning of treatment, and identifying priorities for future research. Monitoring changes in patterns of drug use over time allows assessment of the effectiveness of new deterrent measures and the emergence of new threats to traffic safety. Toxicology plays an essential role in this process by providing analytical services to identify and quantify the drugs found for the purposes of prosecution, demographic trend analysis, development of appropriate warnings for prescription medications, and assessment of progress in the application of preventive measures.

To be most useful, results of toxicological tests should be comparable across and between studies, between jurisdictions, and over time. This is only possible when there are standards of practice for laboratories performing this testing to ensure that the same specimens are being collected, the same drugs are being tested for, and with the same sensitivity.

This overview considers the options for sample choice in postmortem, enforcement, and research, and considerations to reduce the variability in analytical methods between studies.

Sample options

Once swallowed, snorted, smoked, injected, or otherwise introduced into the body, drugs are distributed to variable degrees into all body compartments (e.g., blood, urine, oral fluid, tissues, organs, fatty tissue), based on their acidic or alkaline nature, their lipid solubility, and the ability of the body to actively compartmentalize them in organs such as the brain or bile. The drugs then persist for variable intervals based on the dose, frequency of administration, and the body's ability to metabolize or eliminate them. Their effects also will vary based on interactions between drugs with similar effects, tolerance, and demands of the specific driving task at hand.

Drug test results can have different uses: they can be used roadside to remove offending drivers from the road immediately; they can be used to determine risk for impairment based on crash risk analysis and pharmacokinetics; they can be used for purposes of criminal prosecution; and they can be used to assess demographic trends. For any one of these applications, each sample type has its advantages and disadvantages. In impaired driving research (and impaired driving enforcement), sample choice is also dictated by the invasiveness of the sampling procedure and ease of collection. In roadside surveys, subjects are being voluntarily detained and are less likely to be inclined to submit to a time-consuming and invasive blood or urine sample collection. This can lead to increased refusal rates and correspondingly decreased value of the data obtained from the study. Analytically, some biological samples may be better suited to the detection of certain drugs or drug use within certain time windows, and yet others are easier to interpret. Sample choice typically extends to whole blood, serum, plasma, urine, or oral fluid, and some relative advantages and disadvantages of each are considered here.

Whole Blood

Following administration, drugs are distributed throughout the body via transport in the blood. They bind to plasma protein, adhere to the lipid membranes of circulating cells, and dissolve in the aqueous portion of the blood. Whole blood can be reliably collected from both living and deceased individuals, and other than collection in a tube containing appropriate preservatives (usually an anticoagulant such as heparin or potassium oxalate, and an enzyme inhibitor like sodium fluoride to prevent enzymatic degradation and bacterial growth) requires no special equipment. Considerations in postmortem specimen collection include choice of blood from a true peripheral site such as the femoral or iliac vein, where there is the least chance of redistribution or contamination from other reservoirs (Pelissier-Alicot et al., 2003). With these precautions, blood drug concentrations between living and deceased subjects can be reasonably compared and interpreted. With good technique and a cooperative subject, up to 20mL of whole blood can be easily collected into two tubes, which is an adequate amount for a wide range of tests, screens and confirmations, and reanalysis if needed for legal purposes. Specimens collected in this manner do not need to be immediately refrigerated and are stable for a period of days or weeks without loss or degradation of any drug present. Principally to avoid risks to the living subject from hematoma, infection, or other injury, whole blood sample collection does require a qualified collector or phlebotomist, and this can be a rate limiting step in the field. Further, collection of blood is an invasive process, and subjects in voluntary studies are less likely to agree to provide a blood sample, reducing participation rates and impacting validity.

Both postmortem and antemortem whole blood specimens can be reliably tested with standard immunoassay and extraction/chromatography procedures used with all other sample types discussed below. When dealing with whole blood, the screening procedures may require a protein precipitation step, followed by a homogeneous immunoassay or direct analysis of the specimen in a heterogeneous environment such as enzyme linked immunosorbent assay (ELIZA). The analytical instrumentation, gas chromatography (GC), GC mass spectrometry (GCMS), and liquid chromatography mass spectrometry (LCMS) all allow the detection of drugs at concentrations relevant to effect, and are commonplace and accessible to almost all toxicology laboratories. For purposes of consistency in testing, it is not essential that different laboratories use the same method or even the same technology, but laboratories should strive for a similar list of priority drugs that should be tested for, and a similar analytical threshold for reporting positive results. Laboratories should also observe good laboratory practice such as regular calibration; independent calibrators and controls; use of controls with each assay; established, documented, and validated methods; and broader quality assurance safeguards such as participation in interlaboratory proficiency and accreditation programs.

Interpretation of whole blood drug concentrations is not straightforward, but they are the most interpretable of all specimens. This is due to the large body of literature reporting blood drug concentrations from postmortem reports, and published driving under the influence (DUI) arrest data (Augsberger et al., 2005; Jones et al., 2004). Due to the phenomenon of postmortem change and redistribution, either true peripheral samples should be used or allowances for potential artifactual change must be made in interpretation. Blood drug concentrations can be assessed for consistency with therapeutic use, overdose, and abuse. Parent drug to metabolite ratios may give some indications of recency of use. Care must be taken when comparing whole blood drug concentrations to serum or plasma concentrations, as discussed below, since these are often not comparable matrices. For centrally acting drugs, there is generally some relationship between blood and brain drug concentrations, so the degree of effect is partially reflected in the blood drug concentration. Being able to obtain blood from both living and deceased drivers permits the establishment of relative risk factors (odds ratios) for crash causation (Drummer et al., 2004).

Serum and Plasma

Plasma is the yellowish liquid part of the blood which remains once the red cells have been removed, usually by centrifugation. It contains many vital proteins and clotting factors. Centrifugation of blood

collected in tubes with an anticoagulant will produce plasma. If the blood is allowed to clot before being centrifuged, the resultant liquid fraction is serum, which is plasma with the clotting factors removed. Due to the different water, lipid, and protein content of whole blood, plasma, and serum, the ratio of drug concentrations between these different fractions can differ. For many drugs, the plasma/whole blood ratio has not been studied or reported, making comparisons difficult.

By definition, collection of serum or plasma requires the removal of the blood cells, a process that must be done by centrifugation, and is not readily available in the field. Collection of a specimen from a living person into a tube with an anticoagulant will generally allow the spinning out of cells to be performed later, although there may be some hemolysis depending on storage conditions and length of delay.

In addition, as part of the process of postmortem change, blood begins clotting and hemolysis occurs during the immediate postmortem interval, making it impossible to obtain postmortem plasma specimens. The best that can be obtained is a serum sample, often with hemoglobin, or red cell proteins present, which can affect the distribution or binding of a drug and complicate interpretation.

Serum and plasma can be analyzed using the same immunoassay and chromatography techniques described above without the need for further centrifugation or protein precipitation, often simplifying further analysis.

Plasma or serum drug concentrations are often reported in the literature from premarketing and pharmacokinetics studies of pharmaceutical drugs, but reference concentrations can be lacking for drugs of abuse. In addition, drug pharmacokinetics can become nonlinear and unpredictable at high concentrations, reducing the value of clinical comparators when dealing with real-world concentrations and abuse scenarios. Brain drug concentrations result from equilibrium with or partitioning or active transport from whole blood, making plasma or serum concentrations less directly interpretable.

In summary, serum or plasma is a useful specimen for antemortem drug investigation in living drivers where there is good local support from the laboratory, but comparative concentrations for purposes of interpretation may be lacking.

Urine

Urine can be readily collected either in a clinic or in the field, although privacy for the collection process may be an issue. Observation of collection is typically only important when a subject has the time or opportunity to plan for substitution, which usually does not apply in a survey or enforcement environment. This may be relevant in a post-accident collection setting, in which case urine collection should be observed. Urine is often, although not always, available in a postmortem setting, making it an inconsistent basis on which to compare postmortem and living populations.

Most drugs and/or their metabolites are excreted into urine to some extent, making it an excellent specimen for documenting drug exposure. Urine drug concentrations, however, are subject to dilution, depending on the volume of liquid consumed, and therefore cannot be reliably used to assess impairment. Even creatinine-corrected blood drug concentrations do not accurately reflect blood drug concentrations (Jones and Karlsson, 2005). As a result, urine drug concentrations are of very limited value in assessing impairment. Excreted drug can be detected in urine for longer than in blood, typically for 1 to 3 days following use of the drug, although this varies significantly from drug to drug, and is also a function of dose and duration of use. Urinary excretion half-life is a determining factor, with drug generally being undetectable after about five excretion half-lives. Typically in impaired driving enforcement or research, we are interested in the drug's effect on the driver at the time of the driving, making urine toxicology a less preferred specimen. At best, it can be used to corroborate observations of impairment.

Analytically, urine can be readily tested by the methods discussed above for blood. Because it is mostly water, it often requires less pretreatment than does blood. This opens up the possibility of using qualitative onsite presumptive tests for drugs using immunoassay-based technology (Raes and Verstraete, 2005). Various devices have been evaluated, and many are in common use. They give an instant indication of drug use by the subject, although not of intoxication. The limitations of the devices vary with the operator and manufacturer. Some devices are easier to use and more forgiving of an inexperienced operator. Devices typically test from 5 to 10 different drug classes, but with different sensitivities to drugs within a class. For example, a device may offer a benzodiazepine test which would respond positively with an oxazepam concentration of 300ng/mL, but negatively with a diazepam concentration of 500ng/mL, and not respond to lorazepam or flunitrazepam at any concentration. Since the devices do not provide comprehensive screening at roadside, samples still need to be sent to the laboratory for confirmation testing and broader spectrum testing.

The value of point-of-contact drug testing in an enforcement setting is still a topic of debate. The officer has typically made an arrest decision by the time a point of contact drug test is administered. While a positive result would validate the officer's decision, a negative result with evidence of impairment would not be a basis to release the subject. Clearly, officers used to having a roadside breath alcohol test appreciate the real-time validation of their opinion and would enthusiastically welcome a reliable point-of-contact test.

For research purposes, urine drug testing tells us something about the drug use habits of a driver population but not the degree of intoxication or impairment, and it will therefore remain a less preferable sample.

Oral Fluid

For some drugs, oral fluid (saliva) may hold the promise of interpretive advantages comparable to blood, ease of sample collection surpassing either blood or urine, and suitability for onsite testing. This technology is less mature, however, and not without major interpretive problems for some of the drugs of greatest concern.

Many drugs are excreted into oral fluid from blood, and there is some degree of equilibrium between drugs in the blood and oral fluid. This is not true for all drugs, however, notably the most lipid-soluble ones such as delta-9-tetrahydrocannabinol (THC), the major active component of marijuana. Lipid-soluble drugs tend to remain at higher concentrations in the blood and are poorly distributed into oral fluid. THC may persist in oral fluid following smoking as a result of oral contamination from the marijuana smoke or plant debris from the cigarette. This makes the detection timeframe in oral fluid for marijuana highly variable and may not completely include the interval during which the user may be affected by the drug. Once the contamination phase is past, concentrations of THC in oral fluid may be challenging for the majority of laboratories to achieve with current technology. This is a significant limitation since marijuana use is among the most frequently used drugs in the impaired driving population.

The ability to collect oral fluid, a relatively clean and mobile sample, at roadside led to the development of point-of-care/-contact (POC) drug immunoassay drug test devices. These devices apply the same immunochemical principles successfully used in POC urine testing devices; however, recent evaluations of several POC oral fluid drug test devices have been disappointing, showing high rates of false negatives and many device failures. Several devices are not suited to field use, requiring either multiple steps which introduce opportunities for operator error or reader devices which are better used in an office or laboratory setting than at roadside. The devices themselves are able to test for a limited panel of two to five drug classes and tend to focus on the most frequently detected drugs of abuse (opiates, cocaine, amphetamines, marijuana) but may not detect many of the other abused drugs (MDMA, PCP), over-the-

counter drugs (antihistamines, dextromethorphan), or prescription medications (methadone, tramadol, topiramate, benzodiazepines, muscle relaxants), all of which can impair driving and show up with some frequency when more comprehensive testing is performed. Another problematic class of drugs for oral fluid technology is the benzodiazepines and sedating antiseizure medications like the barbiturates and chlordiazepoxide, which are poorly partitioned into the acidic saliva.

Finally, some individuals particularly under stressful situations (such as when under arrest or being interviewed by a police officer) or after use of drugs that can cause dry mouth (marijuana, amphetamines, cocaine, anticholinergics) will be unable to provide sufficient sample for the volume of oral fluid which can be readily collected (less than 2mL). This limits how comprehensive a screening panel can be applied and the ability to confirm and quantitate multiple drugs which might be present, since drug concentrations are typically less than those in a corresponding blood sample from the same individual.

These significant limitations aside, oral fluid offers a convenient method for roadside surveys of rates of drug use, and a number of collection devices exist. Those containing a salivary stimulant such as ascorbic acid can influence the blood/oral fluid partition and should be avoided. It appears that 0.5–1mL of oral fluid can be readily collected from about 80% of subjects and preserved with these absorbent devices for later analysis, and their low invasiveness will encourage greater participation. The window of detection for drug use through oral fluid analysis varies from drug to drug but is generally reliable within hours to a day, and therefore valuable in confirming drug use within some period relevant to the driving in question. The most appropriate setting for their use in enforcement appears to be targeted analysis for a limited proscribed drug menu, in a setting where samples can be compelled with an administrative penalty for the presence of the drug, such as has been successfully demonstrated in Victoria, Australia.

Conclusions

Although oral fluid and urine offer some advantages in ease of collection and onsite testing, they have significant limitations interpretively. Serum and plasma are useful secondary specimens, but without the data to reliably relate them to the circulating blood in equilibrium with the brain. Whole blood, in spite of limitations regarding its collection and lack of onsite testing, remains the preferred specimen due to having an adequate volume for comprehensive testing, retesting and confirmation, interpretability with respect to other relevant populations, and comparison of postmortem and living populations. Serum or plasma samples have some of the advantages of blood over urine, but even with reliable and comprehensive blood-to-plasma ratio data (which are currently lacking), the conversion process will introduce an additional variable.

As a research tool, oral fluid presents some intriguing opportunities for application in roadside surveys, encouraging greater compliance rates than might be expected for more invasive blood sampling. It also has been demonstrated to have great applicability in enforcement of per standards for certain drugs. The inherent limitations regarding excretion of THC and weakly acidic drugs into oral fluid will likely limit its ability to replace blood as the preferred sample.

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Drugs, Driving, and the Measurement of Human Performance

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Introduction

A wide range of experimental studies have assessed drug effects on laboratory test performance over the last 3 decades. Although various investigators have claimed that their task or task battery taps driving-related skills, most studies show no proof for such a claim or even a reasonable theoretical rationale. In general, investigators have employed a wide range of laboratory tests measuring aspects of perception, attention, motor control, cognitive function, or central nervous system (CNS) arousal that are assumed to underlie safer driving. However none of these tests has ever been shown to closely predict driving performance or traffic accidents. Experimental laboratory tests may predict driving impairment, but until now it simply has not been demonstrated.

Two causes can be identified that have hampered attempts to demonstrate the predictive validity of performance test for real-life crash risk: (1) a lack of theoretical performance models integrating all aspects of the driving task and (2) a lack of epidemiological data demonstrating a conclusive relation between drug use and traffic accidents. The former refers to the fact that investigators have never been able to truly define the basic components of the driving task and their underlying psychological and neuropharmacological principles. Instead, investigators have turned to the multifaceted approach for measuring isolated skills in laboratory task driving simulators or on-the-road driving. The latter refers to the fact that availability of reliable epidemiological surveys on drug-induced crash risk accelerates attempts to validate any kind of driving performance tests against a real-life occurrence such as crash risk. To date however, epidemiological data on the association between drug and crash risk are still very limited. Consequently, the construction of a well-founded task battery for evaluating drug effects on performance always has been, and still is, a major research priority.

Nevertheless, there are a number of performance tests with demonstrated sensitivity to both beneficial and detrimental drug effects on driving performance. Most notable is a standardized, road tracking task (O'Hanlon, 1984) that is conducted on the road in normal traffic for measuring lateral position control and which has been used in over 90 experimental studies to date. Some laboratory tests measuring tracking ability, impulse control, and cognitive function have shown exceptional drug sensitivity as well. It is postulated here that it is also possible to establish the reliability and validity of these tests for predicting crash risk by applying some basic psychometric principles.

Reliability

Test reliability covers several aspects of consistency. It indicates the extent to which differences in test scores are attributable to true differences in the characteristic under consideration or to change errors. The measurement of test-retest reliability is essentially simple. The scores from a set of subjects tested on two occasions are correlated. Test-retest correlations have been repeatedly calculated for the standardized, on-the-road driving test by comparing driving performance of subjects who completed the driving test on two occasions during placebo treatment. These analyses show that mean values of the dependent variable obtained during these driving tests (i.e., the standard deviation of lateral position [SDLP]) were highly comparable within individual subjects. Consequently, test-retest correlations or reliability of the driving test has been shown to be very high (i.e., $r > .85$).

Test reliability is a valuable construct that should be relatively easy to calculate for any measure claimed to assess driving or skills related to driving.

Validity

A test is valid if it measures what it claims to measure (Kline, 1999). The validity of a test, however, can be described from several angles.

Content validity
Content validity is concerned with a test's ability to include or represent all of the content or a representative sample of the behavior domain (Anastasi and Urbina, 2006). Content validity is usually a bottleneck problem when measuring driving or skills related to driving because a broadly accepted reference framework or model integrating all basic skills underlying the driving task is missing. To date, no single performance test exists that comprises all relevant aspects of the driving task. Even one of the most accepted tests for measuring drug-induced driving impairment, that is, the standardized road tracking test as described above, validly measures only a part of the driving task and a part of total drug action. Likewise, laboratory tests usually assess single aspects of the driving task and none of them is capable of encompassing all the potential danger areas for the effects of drugs. Consequently, investigators have usually decided to include a wide range of laboratory tests comprising performance areas such as motor control, decision-making risk taking, vigilance and attention, and perception. The final evidence that the drug in question would be safe or hazardous should subsequently be based on the combined results of laboratory tests, simulator tests, and actual driving tests (ICADTS Working Group, 1999).

Predictive validity
Predictive validity is the ability of a measure to predict something it should theoretically be able to predict. A high correlation between changes in the measure and changes in the construct that it is designed to predict would provide good evidence for its predictive validity. Thus in the field of experimental drugs and driving research, the question that needs to be answered can be formulated as: Do actual driving tests or laboratory tests of skills related to driving predict crash risk in real life?

The predictive validity of performance tests in drugs and driving research is usually unknown, primarily due to a lack of real-life epidemiological (crash risk) data in general. The absence of such data has made attempts to correlate laboratory data to real-life driving accidents extremely difficult. However, it should also be noted that in the past, investigators have often neglected to calculate the predictive validity of their performance tests for alcohol-induced crash risk, even though a wealth of epidemiological data is available. This can be considered a major negligence in experimental drugs and driving research, for any performance task with demonstrated predictive validity for alcohol-induced crash risk is also likely to be sensitive to drug-induced crash risk.

In the case of the standardized on-the-road driving test, sufficient alcohol calibration data are available to calculate the relation between alcohol-induced changes in SDLP and alcohol-related crash risk as a function of blood alcohol concentration (BAC). It is noteworthy that both SDLP and crash risk rise exponentially with increasing BAC, and it thus comes as no surprise that alcohol-induced changes in SDLP are highly correlated with alcohol-induced changes in crash risk ($r = .99$). The conclusion is thus warranted that the validity of the road tracking test for predicting alcohol-induced crash risk is very high.

Recent epidemiological data on THC- and BZD-induced crash risk also offer the opportunity to calculate the predictive validity of the driving test with respect to these drugs' potential for crash risk. The present presentation demonstrates that diazepam-induced changes in SDLP do correlate highly with diazepam-induced crash risk as a function of time after dosing ($r = .97$). Moreover, equally high correlations can be found between THC-induced changes in SDLP and THC-induced crash risk as a function of THC concentration in serum ($r = .91$). Together, these data demonstrate that the standard road tracking test is a very reliable predictor of alcohol- and drug-induced crash risk.

Yet, despite these impressive data on the predictive validity of the actual driving test, it should be recognized that it measures only partial aspects of the driving task, that is, tracking ability and vigilance. Obviously these are keys aspects of the driving task that should never be neglected, but other aspects of the driving task may be important as well. For example, laboratory tests measuring impulse control (risk taking) and decision-making/judgment of drivers also assess aspects of the driving task that are critical to safe driving. This notion is supported by recent data showing that THC-induced changes in laboratory tracking performance (r = .86), impulse control (r = .95), and decision-making (.96) are about equally predictive of THC-induced crash risk.

External validity

External validity is related to generalizing. External validity is the degree to which the conclusions from a study or measure would hold for other persons in other places and at other times. The issue is particularly relevant in studies assessing medicinal drug effects on driving, because these are usually conducted in healthy volunteers. It has been argued that patients do not experience side effects to the same degree as healthy volunteers. For example, most driving studies on the effect of antidepressants on actual driving performance have been conducted in healthy volunteers. It could be argued that healthy volunteers respond differently to antidepressant treatment than depressed patients and that one response does not predict the other. The obvious example is that depressed patients may respond favorably to antidepressant treatment, whereas healthy volunteers cannot. However, the rationale for studying antidepressant effects in healthy volunteers is that they experience side effects just like patients. This is certainly so at the beginning of therapy and in the minority of patients who do not respond to antidepressant treatment. It is assumed that somnolence or sedation is by far the most important cause of driver impairment in patients treated with antidepressant drugs. Regression analyses of elevations in SDLP observed in experimental driving studies and the number of patients in clinical trials complaining of somnolence with the same antidepressants strongly supports this notion. Elevations in SDLP caused by antidepressants in healthy volunteer trials sharply increase as a linear function of the percentage of depressed patients complaining of somnolence in clinical trials (r = .95). These data thus indicate that the external validity of the actual driving test applied in a healthy volunteer model is very high.

Propositions

1) Investigators should be able to justify the use of a performance test on the basis that it provides valid indices of (a) a specified pharmacological effect and (b) a specified mental/behavioral reaction relevant to driving.
2) A test battery should measure (a) as many as possible of the relevant pharmacological aspects of a drug, and (b) as many as possible of the mental/behavioral reactions of relevance to driving.
3) In general, performance measures used to define the effect of drugs on driving should possess a high test-retest reliability coefficient for raw scores measured in the absence of a drug effect (e.g., r > .70).
4) Investigators should always fit experimental performance data with epidemiological crash risk data in order to define the reliability of a specific performance test for predicting drug-induced crash risk.
5) Studies for showing a drug effect on driving or skills related to driving should be designed to establish a dose-effect as well as a concentration-effect relation (i.e., multiple doses and quantification of drug concentration in blood).
6) It is possible to attain results of practical relevance from studies employing healthy volunteers as subjects. This is not the case only when it is known or strongly suspected that healthy volunteers and ambulant patients experience different drug reactions capable of influencing their driving ability.

7) Studies for establishing the driving hazard potential of a particular drug should proceed from conventional laboratory testing to driving simulators and actual driving tests. The final evidence that the drug in question would be safe or hazardous should be based on the combined results of these tests (ICADTS Working Group, 1999).

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Drugs and Driving: Available Sources of Data on Injured Drivers

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Although quite a few studies have now documented the prevalence of alcohol use among injured drivers admitted to trauma centers, few have addressed the prevalence of other drug use in this population. Alcohol is known to be a major factor in crash causation, and if patients are tested for substances of abuse upon admission to a trauma center, the tests are usually limited to alcohol (Soderstrom et al., 1994). Not many studies have addressed specific drugs among trauma patients; those that have vary considerably with respect to the methods used and the populations studied (Kirby et al., 1992; Soderstrom et al., 1988, 1995; Sloan et al., 1989; Rivara et al., 1989). In addition, many of these studies were conducted 10 to 20 years ago.

As reported in a more recent publication by Walsh et al. (2005) based on patients admitted to the R Adams Cowley Shock Trauma Center in Baltimore, more than half (50.9%) of injured motor vehicle drivers tested positive for drugs other than alcohol. Moreover, among those testing positive for drug use, 30.9% had also been drinking. The most frequently detected illegal drug was marijuana, which was found in more than one-quarter of drivers. The authors concluded that focusing only on alcohol in traffic safety initiatives will exclude the detection of other drug use, which is obviously evident in a significant proportion of crash victims.

Trauma center patient populations represent a rich resource for the study of drugs and driving, since there are large numbers of individuals (drivers) involved in crashes, and many patients have toxicology testing for a variety of licit and illicit substances. Since they have already been injured in a crash, it is not possible to use this population to determine the risk of injury due to drug use. However, it is possible to monitor trends in drug use over time, as well as to conduct studies of crash culpability, that is, among a population of injured drivers, were those using a certain drug more likely to be responsible for their collision, as compared with those who were not?

The purpose of this paper is to describe the sorts of data available in the trauma/emergency medical services and medical examiner settings that can be brought to bear on studies of the epidemiology of drugged driving. Although much of this experience is based on research conducted in Maryland, some of the data described are more generally available throughout the United States.

Sources of Data

Data Available from Trauma Centers

Most trauma centers now maintain trauma registries, which are data repositories dedicated to the documentation of records of trauma patients cared for by a given trauma center. Trauma registrars, who are responsible for the quality control and maintenance of the registry, usually work outside of the jurisdiction of the medical records department. In many centers, trauma registry data are recorded during the patient's hospital stay, as opposed to after discharge from the hospital, which also improves the accuracy of the data collected (Scheib et al., 1989; Wynn et al., 2001). Results of alcohol/drug testing, if available, are often available in the registry.

However, testing for alcohol and/or drugs has not been consistently carried out at trauma centers in the United States. In a 1994 survey, routine drug testing was only conducted at 40% of trauma centers; approximately 64% conducted routine blood alcohol testing (Soderstrom et al., 1995). In 1999, the American College of Surgeons' Resources for the Optimal Care of the Trauma Patient document

rescinded alcohol and drug testing as an essential characteristic of a Level I or Level II trauma center, apparently following a lengthy debate over the clinical relevance of the testing (ACS, 1998). Despite the temporary rescinding of this criterion for trauma centers, it has since been reinstated following successful reports of brief intervention for alcohol use among trauma center patients. The forthcoming updated Resources for the Optimal Care of the Trauma Patient document states that Level I and Level II trauma centers are required to screen for alcohol and drug use and Level I trauma centers have to offer intervention for alcohol use problems (Soderstrom, unpublished communication).

Not only are many patients not tested, but in addition many centers test only those persons who are suspected to be alcohol or drug users, thus preventing an accurate estimate of the prevalence of drug use in the trauma center population. For example, Treno and colleagues (1994) found that alcohol testing was performed more often in young patients (ages 21-34), in men, among victims of vehicular crashes, and among those injured as a result of violence. Rivara et al. (1989) reported that alcohol and drug testing at their center was performed more frequently in those who were seriously injured or who appeared to be intoxicated. In addition, Sloan and associates (1989) reported that testing was only conducted among patients with mental status changes. Such biases must obviously be considered in order to adequately interpret the data.

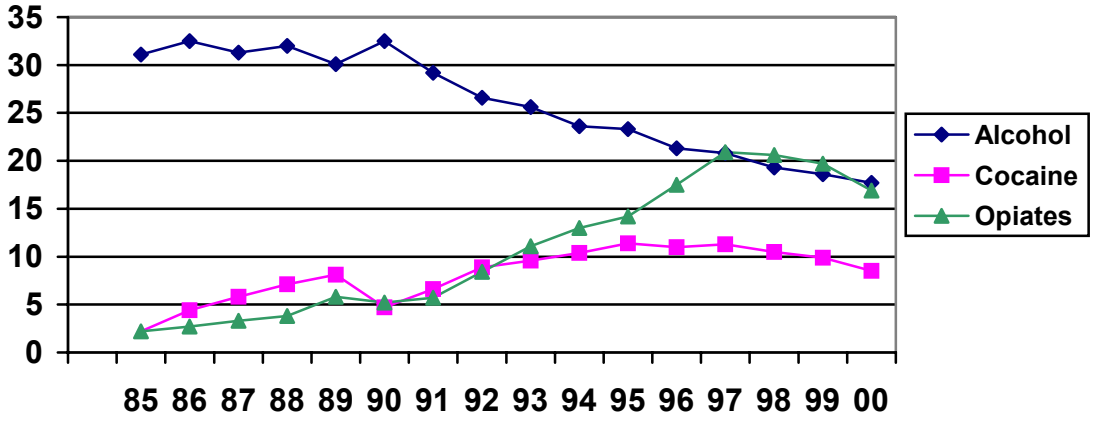
At the R Adams Cowley Shock Trauma Center in Baltimore, Maryland, patients are routinely tested on admission for a battery of licit and illicit drugs. This testing is conducted to assist care providers with clinical decision-making, and not for legal purposes; the primary reasons to obtain this information are for identification of patients at risk of withdrawal and for pain management, as well as to identify patients with substance use diagnoses. Although the trauma center is located in an urban setting (Baltimore), it serves as the primary adult trauma center for the entire state. The majority of patients are transported from the most populous counties of central Maryland, as well as Baltimore City. Thus, the patient profile, with respect to age, sex, and mechanism of injury, is representative of that seen in trauma centers throughout the United States (American College of Surgeons, 2002).

At the Shock Trauma Center, toxicology screens are conducted for alcohol and the following drugs: acetaminophen, amphetamines, barbiturates, benzodiazepines, cocaine, marijuana, methadone, opiates, PCP, phenothiazine, propoxynol, and salicylates. Blood and urine samples for testing are obtained immediately upon arrival at the trauma center, often within 1 hour of the injury event. The blood alcohol concentration (BAC) is determined from whole blood using gas-liquid chromatography. Urine drug screens are based on enzyme immunoassay techniques. Almost all patients are tested for BACs, but all other tests are currently conducted on urine samples; the rate of testing for drugs is lower than that for alcohol, due to lack of sample availability.

Although the toxicology screening is done for clinical reasons, by monitoring the screening findings in the aggregate, over time, it is possible to gain a greater understanding of alcohol and drug use patterns among the population of people seriously injured in motor vehicle crashes. A database that houses this clinical toxicology data is maintained at the National Study Center for Trauma and EMS, also in Baltimore, and it currently includes data on more than 60,000 trauma patients.

Soderstrom et al. (2001) analyzed the toxicology findings for all patients admitted to the Shock Trauma Center between 1985 and 2000. As shown below, it is apparent that over time, the proportion of patients testing positive for alcohol declined significantly, while positive tests for cocaine and opiate use increased dramatically.

Figure 1- Percentage of Trauma Patients with Unintentional Injuries and Positive Tests for Alcohol & Other Drug Use



Excerpted from Soderstrom et al., 2001.

In order to determine any demographic or other biases that might be inherent in the patients tested, it is necessary to determine the testing rates for subgroups by age, race, gender, and mechanism of injury (Soderstrom et al., 2001). The results from the Baltimore Center show that there were no differences in testing rates between men and women, nor by age. However, contrary to some preconceived notions of possible bias, white patients were significantly more likely to have been tested, as were victims of blunt trauma. Over 90% of patients are tested for BAC; however, the rate of testing for other drugs is closer to 50%, due to the lack of an available urine specimen (Soderstrom et al., 2001).

To further maximize the value of the toxicology data obtained from trauma centers, it is possible to link the data to police crash reports and strip all identifiers from the resultant database. This process is described in more detail below. The resulting linked file then includes a wealth of data on the nature of the crash that resulted in the hospitalization, the police perception of the driver, whether safety equipment was used, the time of day, urban/rural location, etc.

Other Sources of Data on Injured Vehicle Drivers

Emergency Department and Hospital Discharge Data. Many states have databases available that capture information on all persons hospitalized or treated in emergency departments. This information is collected primarily for billing purposes, not research, but the data provide a rich source of information on injury types, severity, causes, and outcomes. Injury diagnoses are available from ICD-9 codes, and data on the mechanism of injury may be obtained from E-codes. Data on drug and alcohol use are not provided, however, unless substance abuse is listed as one of the patient's discharge diagnoses. However, by linking police report and hospital discharge data, it is possible to determine police perception of drug use among a population of hospitalized drivers (see Data Linkage section below). In a recent comparison of Maryland hospital discharge and Maryland trauma registry data, the authors concluded that the hospital discharge data are a valid source for documenting the nature and severity of injuries sustained by trauma patients (McCarthy et al., 2005).

Emergency Medical Services. In Maryland, there is a centralized database with information on all persons transported by ambulance or helicopter to a treatment facility. This includes data on the

mechanism of injury (e.g., motor vehicle crash) and provides details concerning transport time, nature of the injury, and treatments rendered en route. While nonspecific data on drug use are collected, the first responders are instructed to only complete part of the form if they have definitive physical evidence that drugs or alcohol were used by the injured party.

There is a group of Federal agencies and other organizations sponsoring the creation of guidelines to standardize Emergency Medical Services (EMS) data collection nationwide. This is the National Emergency Medical Services Information System (NEMSIS). In these guidelines, it is recommended that alcohol and/or drug use be captured according to smell of alcohol on patient's breath, admission of alcohol/drug use by patient, or presence of paraphernalia at the scene. Information on this program can be found at http://www.nemsis.org.

Police Report Data. Police crash reports provide details about the crash event, which are usually not adequately captured by trauma registries. This includes information on the type of crash (single vs. multi-vehicle), number and ages of occupants, safety equipment use, and culpability (as ascertained by the responding police officer). There is also an assessment by the officer of the driver's condition. The categories on the Maryland crash report include the following: apparently normal, had been drinking, using drugs, physical defects, other handicaps, ill, fatigued, and apparently asleep.

Also on the Maryland crash report, under the variable "Substance Use Detected," the options available include: "none detected, alcohol present, illegal drug present, medication present, combined substances present, alcohol contributed, illegal drug contributed, medication contributed, combination contributed, or other/unknown/not applicable."

There is also a group of Federal agencies and other organizations sponsoring standards for crash report data collection nationwide. These are the Model Minimum Uniform Crash Criteria (MMUCC). In these guidelines, it is recommended that alcohol and/or drug use be captured based on physical evidence at the scene or suspicion. However, as is the case with the EMS data, no specific information on drug types is available. Information on these guidelines can be found at http://www.mmucc.us.

Medical Examiner Data. The organization of medicolegal death investigative systems varies by state within the United States (Hanzlick et al., 1998). Systems can be medical examiner-based, coroner-based, or both. Investigation systems may also be either centralized (i.e., emanating from one state-level office) or decentralized (i.e., conducted in more than one regional, county, or city-based office). Finally, medicolegal death investigation offices can also vary in their organizational position in the government; some are components of the public health department, others are independent of other government agencies.

In Maryland, there is a centralized system with a data repository documenting all deaths investigated by the Office of the Chief Medical Examiner. Autopsy rates vary depending upon the nature of the injury, but a complete autopsy is conducted for the majority of vehicle drivers. The primary exception is for single vehicle crashes in which the driver died in a hospital; for these cases, inspections are carried out instead of complete autopsies. Physical findings that create suspicion of drug use are recorded in the autopsy. In addition, detailed toxicology testing is carried out for illegal drugs and most prescription drugs, using blood samples. Although autopsy reports are considered "public record," the toxicology findings are not available to the public. However, it is possible to obtain these data for research purposes, if the proper safeguards with regard to confidentiality are met.

However, individual states also vary considerably in the rates of autopsy, the availability of data, and the amount of toxicology screening conducted. The National Association of Medical Examiners accredits

these offices and serves as a central resource for medical examiner information. Further information is available at their website, at http://www.name.org.

Data Linkage

As part of an ongoing effort by the National Highway Traffic Safety Administration (NHTSA) called the Crash Outcome Data Evaluation System (CODES) (NHTSA, 2006), states are encouraged to link available hospital, EMS, and police crash report data in order to create a comprehensive database for the study of crash-related injury epidemiology. A software program has been developed by NHTSA and made available to the CODES-funded states in order to facilitate linkage of these independent databases, which are maintained by separate agencies and have no unique identifier such as name or Social Security number (Runge, 2000). Despite this lack, however, it is possible to obtain linkages with a high probability of accuracy, based on variables such as the driver's date of birth, the date of the crash, and gender of the driver.

The resultant linked database provides a wealth of information relevant to the study of drug-related crashes. Since few drug tests are carried out by the police, by linking the data from the confidential toxicology databases to the police crash reports, we can then examine, for example, drug use among injured drivers or crash culpability among drivers with and without specific drugs or combinations of drugs and/or alcohol (Soderstrom et al., 1990; 1993; 2005). In addition, by linkage with the hospital discharge records, it is possible to determine the nature and severity of the injuries sustained in the crashes; this information is not available from the police crash report alone. It is also possible to compare the toxicology findings in the hospital with the substance use detection variable listed on the police crash report, in order to determine the sensitivity and specificity of drug use detection by the responding police officers (van Wijngaarden et al., 1995).

A study of crash culpability for drug use utilized the toxicology database linked with the crash reports for all drivers hospitalized at the R Adams Cowley Shock Trauma Center between 1997 and 2001 (Soderstrom et al., 2005). Since the number of cases in the database is quite large, it was possible to group patients with using alcohol only, cocaine only, etc. For those cases with no indication of culpability provided by the responding officer, an algorithm was developed for the determination of crash culpability, based on a modification of the methodology of Terhune (1982; 1986) and Perchonok (1978). Although the purpose of the analysis was to associate specific drugs with crash causation, in actuality it may only be concluded that drug use is associated with crash culpability, and not that the drug use was causal, since the toxicology measures are based on urine samples, which are actually measuring drug metabolites, possibly reflecting drug use initiated several days prior to the event. Based on the findings from the study, it is apparent that cocaine users were twice as likely to have caused their crash as non-cocaine users. Obviously, further research is required, using blood toxicology results, to confirm this finding and determine whether the cocaine use per se, or other factors common to cocaine users, resulted in higher crash rates.

Psychoactive Substance Use Diagnoses among a Population of Trauma Patients

Although the toxicology database provides important data on trends over time in drug use in the population of trauma patients, a positive toxicology finding is not a definitive indication of substance abuse, only use. For this reason, an in-depth investigation of the prevalence of alcohol/drug use diagnoses, the first of its kind, was conducted in the population of a large Level I trauma center; this study was conducted between 1994 and 1996. Substance use disorders were diagnosed by using the psychoactive substance use disorders (PSUD) section of the Structured Clinical Interview from the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R)* (SCID),

which uses DSM-III-R criteria to diagnose alcohol and drug abuse and dependence. The PSUDs were classified as current or lifetime.

Overall, 26% of all trauma patients included in the study had a current drug dependence diagnosis. Approximately 30% of male trauma patients were deemed to have a current drug dependence (either drug use alone or drugs in combination with alcohol). The highest prevalence rates were among those aged 21-39. For victims of "unintentional" trauma, a large proportion of whom are vehicle drivers, approximately 15% had a current drug and/or alcohol dependence diagnosis (Soderstrom et al., 1997).

The rate of drug dependence was significantly higher for those patients who tested positive for either alcohol or other drug use. Overall, among those patents with both a positive BAC and positive urine drug screening test, 36.5% were noted to have a current drug dependence with or without alcohol dependence. While 38.7% of patients with positive urine screening tests for drugs other than alcohol and nicotine were currently drug dependent, an additional 3.9% of drug-negative patients had current diagnoses of drug dependence.

Summary

With increasing interest in the success of brief intervention for alcohol abuse among trauma patients (Gentilello et al., 1999; D'Onofrio et al., 2002; Soderstrom et al., 2005), there is a renewed push by the American College of Surgeons to require screening for drugs and alcohol. As a byproduct of this screening, which is done primarily for clinical purposes, it is possible to monitor trends in alcohol and drug use among populations served by the trauma center. If such data collection were conducted in a standardized fashion at a representative sample of trauma centers nationwide, it would provide a "snapshot" of regional drug usage, assisting not only trauma clinicians but public health practitioners and state and local health departments.

However, in order to quantify the prevalence of drugs used, it is crucial that the data be collected in such a way as to be able to distinguish between those not tested and those who were tested but have negative findings. For many trauma registries, this is currently not the case; rather, results are recorded if positive, leaving the denominator of the number of cases tested in question. Also, if data are to be collected from multiple trauma centers, it is crucial that the toxicology testing be carried out in the same manner, with the same quality control standards.

Since the purpose of this paper is to address issues related to drugged driving, it is also possible to obtain some very valuable information by linking police crash reports with the toxicology findings. This, of course, must be done in a confidential manner, ensuring the fact that all identifiers are removed once the linkage is accomplished. The resultant database provides a wealth of information on the types of crashes associated with drug use, time of day, day of week, etc. In addition, crash culpability may be assessed, using either the judgment of the responding police officer or an algorithm based on various factors about the crash. While drug tests utilizing urine do not reflect crash causation, since metabolites may persist for days, it may be concluded that persons using various drugs or drug combinations are currently more involved in specific types of crashes, or are more likely to have caused certain crashes.

As the ultimate goal of this research is to prevent death and disability from motor vehicle crashes, another important function of these data is to provide some basis for the initiation of alcohol and drug treatment in the tertiary care setting. In a long-term mortality study of former trauma center patients, it was noted that those with a one-time positive toxicology finding (alcohol and/or drugs) upon admission to the trauma center were significantly more likely to die of a subsequent injury in the following decade (Dischinger et al., 2001). Admission to the trauma hospital may be the "red flag" or first indication of an underlying substance abuse problem. Again, the presence of drugs or alcohol in blood or urine does not prove

causality for the injury-causing crash, but it does provide a basis for discussion with the patient in order to prevent future repeated injury. If further screening provides the evidence for diagnosis of a substance abuse problem, steps towards intervention may be initiated. Although evidence for the success of brief intervention techniques for alcohol in the trauma center setting is mounting, it is not known whether similar initiatives might also be effective for certain groups of drug users.

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Ethical, Legal, and Human Subjects Issues in Drugged Driving Research

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Introduction
Traffic safety research in the field of the risks of drug driving is only possible if drivers' impairment can be based on concentrations of substances in various body fluids. However, before taking body fluids for research purposes, the responsible project manager has to identify the needs for considering ethical, legal, and human issues.

Reflections on these needs are described in this paper, and examples are given regarding actual research projects where ethical, legal, and human issues have been a subject. The examples regarding how to handle these issues come from the project IMMORTAL (Impaired Motorists, Methods of Roadside Testing and Assessment for Licensing) of the European Commission's 5th Framework Programme for research projects (www.immortal.or.at).

When planning a research project on drugged driving, there are various codes of ethics to be taken into account:

- Declaration of Helsinki (1964), amended in Edinburgh (2000)
- Ethics Code by the Ethics Committee of the American Psychological Association (2002) June 2001, final
- Recommendations of the European group on ethics in science and new technologies to the European Commission (2003)

Data collections that need ethical considerations
When planning a research project that involves the participation of human beings and human biological samples, various factors regarding ethical aspects have to be considered. For project proposals within the European Commission's 6th Framework Programme for research, a checklist (see Science and Society in Europe >Ethics >Ethical Rules at http://ec.europa.eu/research/ must be filled in. If some of the answers indicate, for example, research on human beings, human biological samples, or sensitive personal data, a special section in the project proposal must be devoted to explanations on how to cope with these ethical issues.

If participation is voluntary, the test person will normally need to give an informed consent in writing. However, if it can be guaranteed that the research has no implications for the person, that the information to be used in the research is anonymous, and that no personal data are included, it might happen that a written consent is not necessary. As explained below, this has been the case in the roadside surveys in the Netherlands and Norway in IMMORTAL (Assum et al., 2005), and also in Denmark in previous research (Behrensdorff, 2001).

Hospital studies by means of blood samples from live test persons would also normally demand ethical approval. As explained below, this has been the case in the hospital studies in the Netherlands and Norway in IMMORTAL, although no personal information was included in the data collection. However, in a similar future hospital study in Denmark as part of the upcoming DRUID project, a request to the Central Medical Ethics Committee in Denmark resulted in the answer that this study will not need any approval from the committee. In other words, no informed consents are needed. Of course, the persons will be informed in writing that an anonymous blood sample has been taken for research purposes.

Experiments that require recruited test persons need ethical approval although participation in voluntary, because the names of the test persons will be known by the research team.

However, if the participation in mandatory, for example, in a roadside survey, the police can force the test person to participate by delivering a sample. In this case, the problem is for the police to handle their legal obligations regarding suspicion of drug driving and, at the same time, include the sample and other information in the research data.

As explained, national ethical rules might vary. This is also true for application forms to medical ethics committees as well as other requirements regarding an application. Finally, the demands to the research team that are stated in the approval might also vary, for example, how to inform the test persons or demands for information from other bodies, such as the national data protection agency.

Studies in IMMORTAL that needed considerations regarding ethical issues
The following types of studies regarding the risks of drug driving were carried out in IMMORTAL:

- Experiments, both on-road and simulator studies
- Epidemiological studies, including roadside surveys, hospital surveys, and qualitative interviews

The following types of samples were collected:

- Saliva
- Urine
- Blood

The studies within the IMMORTAL project were carried out according to the code of ethics on human experimentation established by the declaration of Helsinki (1964) and amended in Edinburgh (2000).

Experience from IMMORTAL project
Two on-road experiments (driving after intake of ecstasy or amphetamines, driving after intake of ecstasy and alcohol) and a simulator experiment (driving after intake of a cocktail of three types of over-the-counter medicine) were carried out (Ramaekers et al., 2004). Test persons were recruited through advertisement. All subjects gave their informed consent in writing. Approval for the on-road studies was obtained from the university's Medical Ethics Committee and the District Attorney of the City of Maastricht. A permit for obtaining, storing, and administering ecstasy was obtained from the Dutch drug enforcement administration. Ethical approval for the simulator study was obtained from the Leeds University Psychology Department. All subjects were informed that they could withdraw at any point in the experiment, and they were paid for their participation.

Roadside survey in the Netherlands, Norway, and United Kingdom
Roadside surveys to measure the prevalence of drugs in the general driving population were carried out in three countries within the IMMORTAL project (Assum et al., 2005).

In the Netherlands, drivers were stopped randomly by the police and asked for a compulsory breath test. Following this, the police asked the drivers to cooperate with a research team on a voluntary basis. Two interviewers asked questions, and a nurse collected saliva/urine/blood samples. In Norway, a similar procedure was used regarding a compulsory breath test. However, in Norway, the police also asked questions and collected saliva samples. Ethical approval was not needed for these studies.

In the roadside survey in UK (Scotland), drivers were also stopped randomly by the police. However, ethical approval was needed before the study could be carried out. The police officer asked drivers to cooperate with a research team on a voluntary basis and read out a prepared briefing to the driver. If

informed consent was obtained from the driver for participation in the study, the police officer passed the driver over directly to a survey staff of three persons who asked questions and took saliva samples. In all three countries, specimens and questionnaires were uniquely numbered and anonymous.

Hospital surveys in the Netherlands and Norway
Hospital case studies to measure the prevalence of drugs in injured drivers were carried out in two countries within the IMMORTAL project (Assum et al., 2005).

In the Netherlands, blood samples were taken from seriously injured drivers admitted to one pre-selected hospital and a doctor filled in a questionnaire on the crash. All patients or (in the Netherlands) their legal representatives were asked for informed consent in order to be included in the study. The Medical Ethics Committee of the hospital approved the study protocol in the Netherlands, and the regional medical-ethical committee for eastern Norway approved the study in Norway. All data were processed anonymously.

On the contrary, in UK (Scotland) although considerable efforts were made to obtain ethical approval to collect hospital samples from injured drivers, this proved not to be possible. The main argument from the ethics committee was that drivers who have been involved in a crash may not be in any condition mentally to give informed consent to a body fluid sample being taken; the procedure would therefore be ethically unacceptable.

Hospital survey with interviews in Denmark
A qualitative study on injured drivers' drug use and drugs as an accident factor was carried out in Denmark (Bernhoft, 2005). Injured drivers who appeared in the emergency room of two pre-selected hospitals in Denmark were informed about the study and that they might be contacted for an interview at a later stage if they had used medicines or other drugs before the crash. The personnel in the hospital gave both oral and written information to the patient; in the case of a written consent, a saliva sample was taken and a questionnaire was filled in with information on alcohol and medicine intake before the crash. Information on the crash was copied from the driver's registration in the hospitals. Regarding seriously injured drivers, the same procedure was used, but blood samples might be taken before the consent was given. An approval was obtained from the Medical Ethics Committees in each of the hospital areas. As a consequence of obtaining information on personal data, such as National Insurance number, name, address, and phone number, it was demanded by the Medical Ethics Committee that the project should also be announced to the Danish Data Protection Agency. This notification gave permission to use the data solely for scientific purposes.

Specimen, registration sheet, questionnaire, and informed consent were uniquely numbered. Names and addresses and other personal data were included in the information. Registration sheets, questionnaires, and informed consents were submitted to the project manager. Specimens were submitted to the laboratory for analysis. Patients who had used medicines or other drugs were subsequently contacted by phone in order to give an interview, for example, about the accident and their drug habits. Confidentiality was guaranteed regarding the information obtained in the interview and used in the reporting.

Various considerations regarding the IMMORTAL studies
When carrying out experiments, the names of the test persons will be known by the research team, the test persons will undergo medical inspections before taking part in the study, and they will be asked to take specific doses of various substances—legal or illegal, controlled by the research team. In case of side effects**,** these must be handled by the research team. Therefore, ethical approval is mandatory.

Roadside studies can only be carried out with help of the police to stop drivers. It is quite easy for a research team to obtain a voluntary sample shortly after the driver has been stopped, on the assumption

that the driver is willing to take part in the study. However, if the police officer is taking the samples and suspects some of the drivers for impaired driving, then the most difficult issue is to guarantee that all samples from the suspected drivers are included in the research data.

Therefore, we recommend involving research teams to take the samples. If random drug sampling is allowed, however, an approach might be to ask the police to take two samples from each driver, one for the police investigation and one for the research purpose.

In hospital studies aimed at calculating the prevalence of drugs in injured drivers, the most difficult part of the process is to ensure that samples are taken from all patients who fulfill the requirements for being included in the study, that is, they were drivers in a crash. The hospital staff would concentrate more on the treatment than on giving information to the patient about the research and taking another sample for research purposes. It is therefore recommended to have a team of personnel, all day and night, dedicated to collecting samples and other information for the research.

An approval from the ethics commission would normally imply that the patient gives the informed consent before the sample is taken. However, this means that the sample might be taken a long time after the patient was brought to the hospital, and thus giving insufficient information on the impairment at the time of the crash. As was seen in Norway, some patients will be brought to treatment in other departments before giving samples.

Therefore, a better study layout would be to take the sample as quickly as possible after the patient has arrived in the hospital and ask for informed consent at a later stage but before the sample is analyzed, as it was done in the Netherlands. However, this means that a link must be established between the uniquely numbered sample and the name of the patient.

In order to be able to use the result of analysis of the specimen as an indication for drug concentration at the time of the crash, information must be included in the research data for the test persons about medication that has been given as part of the treatment before sample taking, either in the ambulance before arriving at the hospital or in the hospital.

Instead of signing a consent indicating willingness to take part in a study, the partner from Norway tried to get approval from the ethics committee on a procedure asking patients to sign a form—a negative consent—if they were NOT willing to take part in the study. This would have been a much easier way to collect data, but the committee did not approve this design.

Demands for an application to the Ethics Committee in Denmark (Interviews of injured drivers)
As an example of information to be included in an application to the Ethics Committee, the demands in Denmark regarding the application for interviewing injured drivers (Bernhoft, 2005) are listed below. The application had to be signed by the project manager and the leading doctor in the emergency department of the hospital. The following information was included in the application:

- Scientific description of the project
- Popular description of the project
- Ethical considerations regarding test persons
- Information leaflet about the study to the patients
- Information leaflet about the participants' right to withdraw from the project at any time
- Guidelines to the hospital personnel on how to inform the test persons
- Consent to be filled in by the test person and the study-responsible person
- Copies of questionnaires/interview guides if any

In order to be able to cooperate with the hospital, various manuals were prepared, including among others, the following:

Manual for selection of potential test persons

- Patient from traffic accident
- Driver of a car
- Time from accident to sample taking (Max. 3 hours)

Manual for information of patients

- Oral information about the project and the patient's right to withdraw at any time
- Delivery of leaflet about the project
- Delivery of a leaflet about the rights to withdraw
- Obtaining a written consent

Manual for providing a blood sample for the survey and delivery for analysis

- Questionnaire about alcohol and drug use before the crash
- Identification of case number on the tube, but no personal data
- Storage of the sample
- Submission of the sample to laboratory for analysis

Legal issues

The most important issue in research of drug driving is to respect the confidentiality rule in relation to persons who take part in research. The information available for the researchers might include information on their breaking of the law and must be kept apart from the legal authorities.

Regarding roadside surveys, they cannot be carried out without assistance from the police. But it is crucial for a research project that the data collection is not biased due to police investigation of some of the potential test persons for the survey. So, how can we ensure that we will receive samples from all randomly selected drivers for the research? There are three different situations:

1. Roadside survey in a country where neither random breath testing nor random drug testing is allowed. The normal procedure would be that the police will stop the drivers and researchers will collect the samples for the research purpose. The police will only be involved in stopping the cars. This layout will ensure anonymity of the test persons and ensure that all test persons are included in the scientific study.

2. Roadside survey in a country where random breath testing is allowed, but random drug testing is not allowed. The normal procedure would be that the police will stop the drivers and ask for an alcohol breath test. After this, researchers will collect samples for drug analysis. However, in case of a suspicion of drink driving, the normal police procedure regarding an offence will be carried out. The important point in this situation is to ensure that the researchers get the opportunity to ask the drivers suspected of drink driving to deliver a sample for drug analysis. If this is possible, then the layout will ensure anonymity of the test persons and ensure that all test persons are included in the scientific study. In the roadside survey in Norway, as part of IMMORTAL, the police also collected the saliva samples for drug analysis. We know that a few alcohol-positive drivers were not included in the research.

3. Roadside survey in a country where both random breath testing and random drug testing are allowed. The procedure in such a country would be that the police will stop drivers and test both for alcohol and other drugs. In case of suspicion, the normal police procedure will take place. In order to get samples from all stopped drivers, you will need to cooperate with the police in collecting an extra sample

for the research purpose of prevalence of drug driving. These samples must be uniquely numbered, corresponding to the number in connection to information about age, gender, and alcohol reading.

DRUID

As part of the project preparation, a checklist was sent to all partners with the following questions:

- Have you carried out this type of study before?
- Do you need ethical approval?
- Have you gotten ethical approval for former studies?
- How long does it take to get the approval?
- Will informed consents be mandatory?
- Do you need to inform the Data Protection Agency?

Furthermore, Science and Society in Europe http://ec.europa.eu/research/ formed the basis for considerations on ethical issues that were included in the project proposal.

When the project starts, the coordinator has to produce an Ethics Manual. The manual shall define the procedures to be followed in DRUID and will include a template on "Ethical and legal issues" to be filled in by all partners who are going to apply for an ethical approval. The purpose of the template is to serve as a guideline for the partners regarding their applications to ethics committees. The information from the partners will be based on national ethical and legal policies and should include information on project-specific issues. The templates must be filled in by the partners during the first 3 months of the project.

Furthermore, an Ethical Advisory Board will be set up by the European Commission. The Board will receive relevant national regulations from the partners and applicable standards regarding ethical issues. The Board will also receive the Ethics Manual of DRUID for approval. Finally, the Board will review the protocols and informed consent procedures. The Coordinator will provide the Board with annual reports of the activities in DRUID and thus ensure that the projects are carried out in compliance with international ethics conventions.

Conclusion

When planning research on drug driving, you should contact the National Ethics Committee in order to know their requirements for application. National rules might differ, so you cannot rely on practice from other countries. You need to check the national rules for application.

In order to guarantee a good study design, you will need to provide manuals for all involved parties, that is, police, research teams, hospital personnel, and toxicologists. You also have to produce information leaflets for the test persons.

In roadside surveys, police officers are needed to stop drivers. However, depending on national drink and driving laws, you will need to discuss with the police how to include offended drivers in the research.

For hospital studies, hospital personnel are needed to take samples form injured drivers. But because personnel in hospitals change rapidly, you must name specific persons in the hospitals to be in charge of the survey for the whole data collection period.

But the most important issue for all types of studies is to guarantee confidentiality and anonymity of the test persons throughout the research and in all reports.

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GUIDELINES
FOR
DRUGGED DRIVING RESEARCH

BEHAVIORAL (B) Section – Recommendations

Issue 1 – What Behaviors Should Be Measured in Drugged Driving Research?

There are three core levels of behavior that should be measured to predict crash risks/accidents:

- Automative behaviors – Well-learned skills (e.g.)
  - Tracking, steering (road tracking, critical tracking, compensatory tasks)
  - Vigilance or sustained attention (e.g., Mackworth Clock Test)
- Control behaviors – Maintaining distance, passing, etc.
  - Motor performance, maneuvers (reaction time, car-following tasks)
  - Divided attention (dual attention tasks)
  - Perception (time to collision type tasks)
- Executive planning – Interactive functions with ongoing traffic
  - Risk taking, impulsivity (e.g., stop signal, Iowa gambling tasks)
  - Information processing, attention (choice reaction-time, selective or focused attention tasks)
  - Cognition, judgment – (e.g., Tower of London task)

Issue 1 Recommendations

Recommendation B1 – Researchers should use tests that have been validated to be sensitive to drug effects on driver performance, and to the extent possible, have demonstrated predictive validity of driving impairment. However, new behavioral tests that appear promising may be included along with other well-validated tasks.

Recommendation B2 – Alcohol effects on performance can serve as a standard reference to quantify impairment for many other drugs.

Recommendation B3 – Performance batteries should include a sustained attention task in order to assess drug-vigilance interactions as a function of time working on the task. The duration of the attention task will depend on the half-life of the drug being studied.

Recommendation B4 – A major goal of future research should be the development of specific criteria defining fitness to drive.

Recommendation B5 – Further research to develop a standardized battery of tests is encouraged. Environmental conditions (especially daytime and nighttime) should be considered when relevant.

Recommendation B6 – Research to validate new handheld devices being developed for real-time (e.g., roadside, ambulatory) testing is also strongly encouraged.

Issue 2 – How Many Subjects Are Needed in Drugged Driving Studies?

The number of subjects needed to determine the behavioral effects of drugs will depend on the design of the study and the parameters to be studied.

Issue 2 Recommendations

Recommendation B7 – Investigators should clearly describe the study population and all subject selection criteria.

Recommendation B8 – A power analysis is needed to determine the required number of subjects. This will be a factor of the sensitivity of the test and the experimental study design.

Recommendation B9 – The demographics of the subject population should be representative of the target population.

Recommendation B10 – It is important to know the current and past drug-use history of all test subjects.

Recommendation B11 – Ideally, medicinal drug studies would be conducted in patient populations. However, healthy volunteer populations can be acceptable as well, unless it is evident that drug effects in this group differ from those in patients.

Recommendation B12 – Studies involving illicit drugs should be limited to subjects who are current/previous users and are healthy enough to participate. Those applicants who have medical risks should not be included.

Recommendation B13 – In the subject selection process, genetic testing should be considered as it can indicate differential sensitivity to drugs.

Recommendation B14 – Studies in individuals involved in DUI accidents are encouraged, e.g., to identify potential behavioral measures to distinguish crash-involved from non-crash-involved drivers, or to analyze behavioral factors identified in epidemiological crash analyses.
Recommendation B15 – Incentives/compensation to subjects for participation in a research project should be based on the time and inconvenience (not discomfort) involved.

Issue 3 – What Ethical and Legal Issues Should Be Considered?

Issue 3 Recommendations

Recommendation B16 – Studies should conform with the legal and ethical regulations of their respective nations (e.g., Declaration of Helsinki, U.S. Department of Health and Human Services, National Ethics Committees).
Recommendation B17 – All studies should be designed to minimize the risks to the subjects, the investigators, and the general public.

Issue 4 – What "Core" Drugs/Drug Classes Should Be Included in the Toxicology Test Panel for Behavioral Studies?

A consensus was reached that behavioral studies typically focus on a particular drug of interest and a number of doses of that drug. Reviewing the last 10 years of drugged driving research, we find that there are six classes of drugs that are most frequently seen in DUI arrests and motor vehicle crash victims: Cannabis; benzodiazepines and other tranquilizing agents; opiates; stimulants (amphetamine, cocaine, methamphetamine, MDMA); antidepressants; and antihistamines. Therefore, we believe it is important to test for these drugs in studies designed to examine the behavioral effects of drugs on driving.

Issue 4 Recommendations

Recommendation B18 – In studies designed to assess the impact of drugs on driving, we recommend that the core drug-test panel should include cannabis; benzodiazepines and other tranquilizing agents; opiates; stimulants (amphetamine, cocaine, methamphetamine, MDMA); antidepressants; and antihistamines.
Recommendation B19 – Studies should also be done with novel drugs. Drugs of interest include new synthetic drugs in the opioid class (i.e., oxycodone, hydromorphone, fentanyls) and novel stimulants (methylphenidate, modafinil). Additional studies should be conducted to link the behavioral impairment with toxicological and other epidemiological factors where this data does not yet exist.
Recommendation B20 – Of particular interest and importance are studies of drug/drug or drug/alcohol combinations because of increased risk associated with these combinations in crash risk studies.

Issue 5 – What Are the Best Specimens To Use To Correlate Behavioral Impairment With Drug Levels, and When Should These Specimens Be Collected?

There is a consensus acknowledging the complex interactions of the drug, the dose, the route of administration, the CNS effects, and the ultimate outcome on behavior (Figure 1).

Issue 5 Recommendations

Recommendation B21 – Blood is the minimum specimen required to determine acute effects of drugs on behavior.
Recommendation B22 – The behavioral effects of drugs should be related to dose and drug concentration in the brain. Currently, the best available indicator of the drug concentration in the brain is the concentration of the drug in blood. Studies that will look at the correlation between blood concentration and brain activity are encouraged.
Recommendation B23 – Urine specimens are particularly valuable to document or exclude prior drug consumption.
Recommendation B24 – Hair specimens may be useful in studies of chronic use.
Recommendation B25 – It is advisable to take a sufficient number of blood samples to characterize the full pharmacokinetic (PK) profile after a single drug dose.

Issue 6 – How Long After Drug Administration (Time Interval) Should Performance Be Tested?

Issue 6 Recommendations

Recommendation B26 – At a minimum, performance should be assessed at Tmax (when the drug concentration is at a maximum in the blood) to determine the acute effects. Ideally, behavioral assessments should be conducted repeatedly over time to capture and fully characterize the entire PK/pharmacodynamic profile including residual or hangover effects.

Recommendation B27 – It is advisable to always include blood samples with performance testing.

Issue 7 – Are There Special Considerations Researchers Should Be Aware of With Regard to Chronic Drug Users and Behavior?

Not much research has been conducted on the performance effects of chronic drug use. Specific issues relating to chronic use include withdrawal, chronic tolerance, multiple drugs/drug interaction, steady states, and long-term (persistent) effects.

Issue 7 Recommendation

Recommendation B28 – In studies designed to assess the chronic use of drugs, performance tests should be repeated during a relevant time period (within-group testing). Ideally, a drug-free baseline measurement should be performed before chronic drug administration. In addition, a matched control group of non-drug users should be considered (between group testing). Prior drug use should be determined as comprehensively as possible.

Issue 8 – General Issues Related to the Study Design

Issue 8 Recommendations

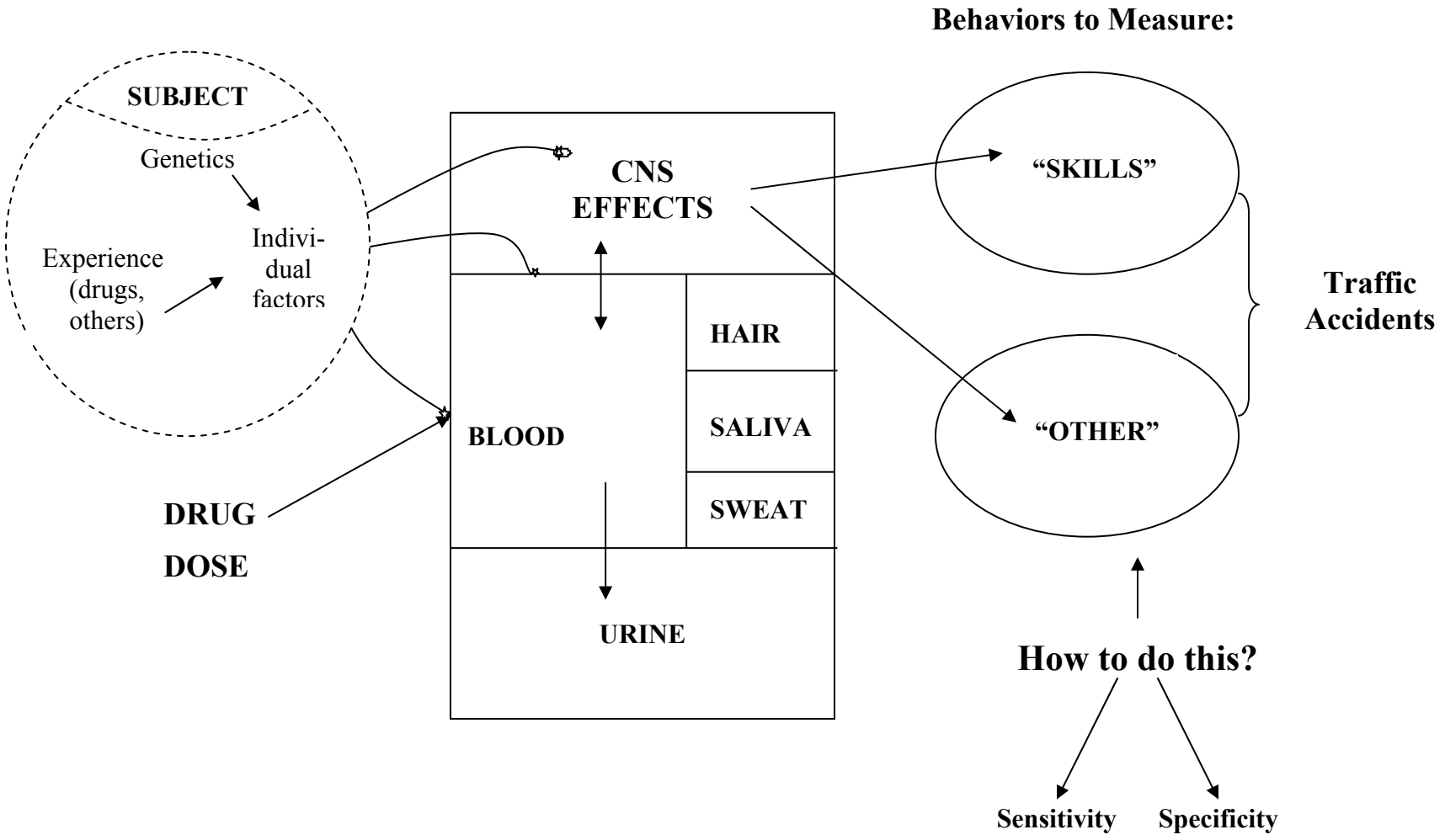
Recommendation B29 – It is advisable to include multiple doses in performance studies in order to define dose and concentration-effect relations on behavior.

Recommendation B30 – Dose ranges employed in experimental studies should preferentially cover the full therapeutic range (medicinal drugs) or reflect real-world drug-use patterns (drugs of abuse).

Recommendation B31 – Placebo-controlled and active verum are strongly encouraged.

Recommendation B32 – Performance baselines should be established (i.e., subject trained to plateau levels) prior to study onset in order to eliminate learning effects.

FIGURE 1


Behaviors to Measure:
SUBJECT
Genetics
Indivi-
dual
factors
Experience
(drugs,
others)
DRUG
DOSE
CNS
EFFECTS
HAIR
SALIVA
SWEAT
BLOOD
URINE
"SKILLS"
"OTHER"
Traffic
Accidents
How to do this?
Sensitivity
Specificity

EPIDEMIOLOGICAL (E) Section – Recommendations

Recognizing that the type of research will dictate the required research parameters, our recommendations for epidemiological research are presented in the following three parts which follow parallel formats:

Part I – Roadside Surveys/Prevalence Studies
Part II – Hospital Studies
Part III – Fatal Crash/Collision Studies

Part I – Roadside Surveys/Prevalence Studies

Issue 1 – Legal/Ethical Issues in Roadside Surveys/Prevalence Studies

To conduct roadside/prevalence surveys more easily, law enforcement authorities should be willing, funded, legally authorized, and able to participate in them. Prior to the initiation of a study, procedures should be developed to handle obviously impaired drivers encountered while gathering data at roadside surveys.

Issue 1 Recommendations

Recommendation E1 – Communication should be made with relevant authorities (local, regional, and national organizations) to ensure compliance with institutional and research requirements and protection of study subjects.

Recommendation E2 – In order to ensure identification but also ensure anonymity, collected specimens should be identified by a coded identification number only, not a name.

Recommendation E3 – Recording any information that would allow others to trace back and identify the subject should be avoided.

Recommendation E4 – A leaflet describing the purpose of the research (including information on confidentiality and anonymity) should be given to all subjects included in the study.

Issue 2 – What Are the Subject and Study Design Issues That Should Be Considered in Conducting Roadside Surveys/Prevalence Studies?

Issue 2 Recommendations

Recommendation E5 – A power analysis should be used to ensure that a sufficient number of subjects are included in the study design to be representative of the general population of drivers of motorized vehicles.

Recommendation E6 – In general, subjects should be selected on a random basis recognizing that there may be problems with professional drivers (e.g., taxi, truck drivers, etc.). A subsample is possible as long as you clearly state that the results are limited to that subset.

Recommendation E7 – Bias should be avoided in the subject selection process. Refusals can be reduced by ensuring confidentiality and privacy of the data during the research study. Subjects should be provided with precise information regarding purpose of the study and minimal time required.

Recommendation E8 – A representative sample should be ensured by identifying subjects based on traffic patterns (night, day), timing, location, etc., and during the study planning or piloting phases, potential biases should be identified and accounted for in the study design/analysis.

Recommendation E9 – According to each country's ethical rules, volunteer subjects should receive fair compensation based on the amount of time spent participating in the research (a minimal burden should not result in financial compensation).

Recommendation E10 – In order to examine possible bias, when an individual refuses to participate in the research project, the researcher should endeavor to get as much objective information as possible on the person who refuses, including core demographic data similar to enrolled participating subjects (e.g., gender, age range).

Recommendation E11 – Refusal rates and characteristics of refusers versus enrolled subjects should be examined. The validity of the study will depend on whether refusal rates introduce bias.
Recommendation E12 – The maximum allowable refusal rate in roadside surveys/prevalence studies will depend upon the purpose of the study and the prevalence of drug use.

Issue 3 – What Are the Core Data Parameters for Roadside Surveys/Prevalence Studies?
Limitations may depend on costs, laws, and regulations.

Issue 3 Recommendation

Recommendation E13 – At a minimum, data on the following parameters should be gathered:

1. Demographic data including age, sex, level of education, and nationality.
2. Type and age of vehicle.
3. Time and place of the control.
4. Toxicology on the core basic drug groups: Alcohol, cannabis, cocaine, opiates, XTC, amphetamines, and benzodiazepines.

Part II – Hospital Studies

Issue 4 – Legal/Ethical Issues in Hospital Studies

Issue 4 Recommendations

Recommendation E14 – A leaflet describing the purpose of the research (including information on confidentiality and anonymity) should be given to all subjects included in the study.
Recommendation E15 – Standards for obtaining informed consent in hospitalized injured patients are different from other settings because of the frequent presence of head injuries, shock, intubation, severe intoxication, and other medical issues. Therefore, options for obtaining deferred or surrogate consent should be explored and clarified prior to beginning the study.
Recommendation E16 – Information obtained for research purposes should be separated from police/medical records.

Issue 5 – What Are the Subject and Study Design Issues That Should Be Considered in Conducting Hospital Studies?

Issue 5 Recommendations

Recommendation E17 – Laws and regulations should be reviewed to determine whether consent is needed to draw a blood sample.
Recommendation E18 – In the study design, researchers should determine whether to draw blood before or after consent. Pollution, or dilution of blood sample with plasma expanders or drugs, should be noted.
Recommendation E19 – Blood samples should be collected as soon as possible after the accident or injury. The interval between the accident/injury and the time the sample is drawn is a critical element. Time of accident and time samples are collected should be recorded.
Recommendation E20 – Patients who are intoxicated are more likely to be transported to the hospital. When transferred to the emergency room, intoxicated patients are more likely to be admitted at the hospital. This may introduce bias in the sample. To the extent possible, other sources of data should be examined to try to determine the extent of this bias.
Recommendation E21 – If attempting to link roadside/prevalence studies and hospital studies, researchers should pay attention and try to screen for the same drug panels in the same biological fluid using the same lab techniques in both studies.
Recommendation E22 – Researchers should obtain information regarding subjects' prehospital medication during the transfer of the patient from the place of the crash to the hospital.
Recommendation E23 – If possible, dedicated research staff responsible for data coordination should be present in the hospital 24 hours/day, 7 days/week.
Recommendation E24 – Studies should try to cover more than one hospital, as those limited to a single hospital may not see a representative sample of all crash drivers and other motor vehicle crash victims.
Recommendation E25 – In the study design, researchers should consider the problems associated with the testing of live drivers; lack of facilities to conduct screenings; and lack of collaboration with police.

Recommendation E26 – A power analysis should be used to ensure that a sufficient number of hospital study subjects are included in the study design to be representative of the general population of drivers of motorized vehicles.
Recommendation E27 – Bias should be avoided in the selection process. The enrollment of subjects should be without any consideration of age, gender, or race.
Recommendation E28 – Compensation for hospital study subjects should be avoided unless long questionnaires and interviews are required, and this should be done in accordance with each country's ethical rules.
Recommendation E29 – In order to examine possible bias, when an individual refuses to participate in the hospital research project, the researcher should endeavor to get as much objective information as possible on the person who refuses, including core demographic data similar to enrolled participating subjects (e.g., gender, age range, etc.).
Recommendation E30 – Hospital study refusal rates should to be examined. The validity of the study will depend on whether refusal rates introduce bias.
Recommendation E31 – The maximum allowable refusal rate in hospital studies will depend upon the purpose of the study and the prevalence of drug use.

Issue 6 – What Are the Core Data Parameters for Hospital Studies?
Limitations may depend on costs, laws, and regulations.

Issue 6 Recommendations

Recommendation E32 – At a minimum, data on the following parameters should be gathered:

1. Time of crash.
2. Time the biological sample was taken (blood is the preferred specimen).
3. Toxicology on the core basic drug groups: Alcohol, cannabis, cocaine, opiates, XTC, amphetamines, and benzodiazepines.

Recommendation E33 – In addition to the core substances (see Recommendation 32), the scope of the drug panel could be expanded to include other drugs based on the consumption patterns of the country and region(s) in question.
Recommendation E34 – Based on the purpose of the study, consent should be obtained to link emergency department toxicology reports with other relevant databases (e.g., police report, trauma registries, pre-hospital ambulance records, criminal records, injuries of other passengers). Consent may not be needed if data are linked and all identifiers are removed.

Part III – Fatal Crash/Collision Studies

Issue 7 – Legal and Ethical Issues in Fatal Crash/Collision Studies:

Issue 7 Recommendation

Recommendation E35 – The study design should consider the implications of anonymity and confidentiality not being guaranteed if results of the analysis are positive (implications for health/life insurance, etc.).

Issue 8 – What Are the Subject and Study Design Issues To Consider When Conducting Fatal Crash/Collision Studies?

Issue 8 Recommendations

Recommendation E36 – All subjects should be included according to the definition of what constitutes a "fatal crash/collision" in the study design.
Recommendation E37 – To avoid bias in the selection process, prosecutors, coroners, and hospital pathologists should be involved in the study to ensure all toxicology and autopsy analyses are completed. Training of all these parties is essential as well as collaboration with the police attending the accident.

Issue 9 – What Are the Core Data Parameters for Fatal Crash/Collision Studies?
Issue 9 Recommendations
Recommendation E38 **–** At a minimum, data on the following parameters should be gathered: 1. Time of the crash. 2. Time the biological sample was taken (blood is the preferred specimen). 3. Toxicology on the core basic drug groups: Alcohol, cannabis, cocaine, opiates, XTC, amphetamines, and benzodiazepines. ***Recommendation E39*** – In addition to the core substances (see Recommendation E38), the scope of the drug panel could be expanded to include other drugs based on the consumption patterns of the country and region(s) in question.
Recommendation E40 **–** Based on the purpose of the study, consent should be obtained to link toxicology results with other relevant databases (e.g., police report, trauma registries, pre-hospital ambulance records, criminal records, injuries of other passengers).

TOXICOLOGY (T) Section – Recommendations

Recommendations 1 – 15 are specific to Epidemiological Studies.
Recommendations 16 – 18 are specific to Checkpoint/Survey Research.
Recommendations 19 – 20 are specific to Suspected Impaired Driving Research.
Recommendations 21 – 24 are specific to Injury/Trauma Research.
Recommendations 25 – 28 are specific to Fatal Injury Research.
Recommendations 29 – 64 are General .

Issue 1 – What Are the Best Specimens to Collect for Epidemiological Studies?

Issue 1 Recommendations

Recommendation T1 – Whole blood is always preferable for interpreting potential drug effects.
Recommendation T2 – In studies designed to assess the prevalence of drug use in drivers and/or the risk of driving performance impairment, then the broadest spectrum of licit and illicit drugs should be monitored. It is understood that there are financial consequences to this recommendation and both cost and sample volumes may be limiting factors. However, we strongly recommend that the most impairing and most prevalent drugs in each jurisdiction, county, state, or country should be included to the maximum extent practicable.
Recommendation T3 – Onsite oral fluid and/or urine tests evaluate a narrow spectrum of drugs at varying sensitivities that may limit drug detectability, and each matrix may require analysis of different specific metabolites.

Issue 2 – Specimen Collection

Issue 2 Recommendations

Recommendation T4 – The time interval between driving and specimen collection should be taken into account in the interpretation of test results. Specimen collection should be as soon as possible (preferably within 3 hours), and the time of collection and time between stop and collection recorded.
Recommendation T5 – It is essential to ensure that blood is drawn from the arm opposite an intravenous line to avoid contamination and dilution.
Recommendation T6 – It is suggested that cutoff concentrations be at least as low as the lower end of the therapeutic range.
Recommendation T7 – After collection, specimen should be refrigerated as soon as possible. Analyte stability should be considered with regard to storage and shipment of specimens.

Issue 3 – Recommended Analytes Tested and Maximum Cutoffs in Whole Blood

Issue 3 Recommendations

Recommendation T8 – Alcohol (cutoff, 0.1 g/L).
Recommendation T9 – Opioids: Morphine (cutoff 10 ng/mL), codeine (cutoff 10 ng/mL), 6-acetylmorphine (cutoff 10 ng/mL), methadone (cutoff 10 ng/mL), tramadol (cutoff 20 ng/mL).
Recommendation T10 – Cocaine: Cocaine (cutoff 10 ng/mL) and metabolites (benzoylecgonine 50 ng/mL; cocaethylene 10 ng/mL, ecgonine methyl ester 10 ng/mL).
Recommendation T11 – Cannabinoids: Δ9-tetrahydrocannabinol (THC; 1 ng/mL), 11-nor-9-carboxy-THC (cutoff 5 ng/mL), 11-OH-THC (cutoff 1 ng/mL).
Recommendation T12 – Benzodiazepines: Diazepam (cutoff 20 ng/mL), oxazepam (cutoff 50 ng/mL), temazepam (cutoff 50 ng/mL), alprazolam (cutoff 10 ng/mL), clonazepam (cutoff 10 ng/mL), nordiazepam (cutoff 20 ng/mL), lorazepam (cutoff 10 ng/mL), and midazolam (cutoff 20 ng/mL).
Recommendation T13 – Other hypnotics: Zolpidem (cutoff 20 ng/mL), zopiclone (cutoff 20 ng/mL), diphenhydramine (cutoff 25 ng/mL), and doxylamine (cutoff 25 ng/mL).

Recommendation T14 – Sedating antidepressants: Amitryptyline (cutoff 25 ng/mL), nortriptyline (cutoff 25 ng/mL), doxepin (cutoff 25 ng/mL), imipramine (cutoff 25 ng/mL), desipramine (cutoff 25 ng/mL), trimipramine (cutoff 25 ng/mL), dothiepin (cutoff 25 ng/mL), mianserin (cutoff 25 ng/mL), and trazodone (cutoff 10 ng/mL).
Recommendation T15 – And other medications [e.g., butalbital] (cutoff 100 ng/mL), carisoprodol (cutoff 500 ng/mL), fentanyl (cutoff 1 ng/mL), topiramate (cutoff 1 ng/mL), mirtazapine (cutoff 10 ng/mL), and dextromethorphan (cutoff 20 ng/mL), buprenorphine (cutoff 1 ng/mL), flunitrazepam (cutoff 2 ng/mL) and illicit drugs (e.g., phencyclidine (PCP; 10 ng/mL), LSD (cutoff 0.5 ng/mL), ketamine (cutoff 10 ng/mL), cathinone (cutoff 20 ng/mL), and GHB (cutoff 5000 ng/mL; subject to postmortem production) relevant to the individual country or area.

Issue 4 – Checkpoint/Survey Research
Specimen Collection and/or Testing Issues

Issue 4 Recommendations

Recommendation T16 – For checkpoints, oral fluid (preferably 1 mL) and if possible, 10 mL whole blood with anticoagulant and fluoride preservative.
Recommendation T17 – If impairment is suspected based on onsite test results or behavioral observations, conduct collection in accordance with suspected impaired driving.
Recommendation T18 – There should be comprehensive testing of a minimum of 5% of specimens with negative onsite test results.

Issue 5 – Suspected Impaired Driving Research

Issue 5 Recommendations

Recommendation T19 – If possible, 10 mL whole blood (with anticoagulant and fluoride) otherwise urine (preferably 30 mL) or oral fluid (preferably 1 mL), depending upon legal requirements of study.
Recommendation T20 – Police reports with driving behavior, breath alcohol test results and documentation of interviews, admitted drug use, field impairment tests, medical examinations, and presence of paraphernalia should be collected for research purposes.

Issue 6 – Injury/Trauma Hospital Research

Issue 6 Recommendations

Recommendation T21 – Whole blood (10 mL) should be collected with anticoagulant and fluoride preservation.
Recommendation T22 – If possible, additional specimens should be collected: oral fluid and urine.
Recommendation T23 – Estimated time of crash and the time of specimen collection should be documented.
Recommendation T24 – Information on emergency services and hospital medications administered, and total blood products, intravenous fluid, or artificial blood/synthetic hemoglobin provided should be documented.

Issue 7 – Fatal Injury Research

Issue 7 Recommendations

Recommendation T25 – Peripheral blood (10 mL) with anticoagulant and fluoride preservative should be collected.
Recommendation T26 – If possible, additional specimens should be collected: urine (preferably 10 mL), vitreous fluid (preferably 1 mL left and right eyes).
Recommendation T27 – Estimated time of crash, time of death, and time of autopsy (specimen collection) should be recorded.
Recommendation T28 – Obtain ante-mortem specimens if available, especially in cases where there is a delay in time of death.

Issue 8 – How Long Should Specimens Be Retained After Completion of the Study?

Issue 8 Recommendation

Recommendation T29 – Unless there are statutory limitations, specimens should be kept until issuance of all study reports.

Issue 9 – What Standards Should Be Applied to Collection Devices?

Issue 9 Recommendations

Recommendation T30– Whole blood should be collected in a sterile vacutainer-type tube with sodium fluoride and anticoagulant, and an inert stopper/container.

Recommendation T31 – Oral fluid devices should have some type of indicator that illustrates a sufficient amount of oral fluid has been collected to allow analysis. If possible, collection should occur without the use of stimulating agents.

Recommendation T32 – Urine collection devices should be inert and not adsorb analytes of interest.

Recommendation T33– Manufacturers should provide recovery data for all relevant drugs for each lot of devices and attempt to minimize variation between available lots.

Issue 10 – What Are the Minimum Analytes To Be Tested and Maximum Cutoff Concentrations in Oral Fluid?

Issue 10 Recommendations

Recommendation T34 – Alcohol (cutoff, 0.1 g/100mL).

Recommendation T35 – Opioids: Morphine (cutoff 20 ng/mL), codeine (cutoff 20 ng/mL), 6-acetylmorphine (cutoff 5 ng/mL), methadone [EDDP] (cutoff 20 ng/mL), tramadol (cutoff 20 ng/mL).

Recommendation T36 – Cocaine: Cocaine and metabolites-benzoylecgonine (cutoff 10 ng/mL).

Recommendation T37 – Amphetamines: Amphetamine (cutoff 20 ng/mL), methamphetamine (cutoff 20 ng/mL), MDMA (cutoff 20 ng/mL), MDA (cutoff 20 ng/mL), MDEA (cutoff 20 ng/mL).

Recommendation T38 – Cannabinoids: Δ9-tetrahydrocannabinol (THC; 2 ng/mL).

Recommendation T39 – Benzodiazepines: Appropriate cutoff concentrations in oral fluid are yet to be established, but are likely to be much lower than blood concentrations: diazepam, oxazepam, temazepam, alprazolam, clonazepam, nordiazepam, chlordiazepoxide, lorazepam, and midazolam.

Recommendation T40 – Other hypnotics: Appropriate cutoff concentrations in oral fluid are yet to be established: zolpidem, zopiclone, diphenhydramine, and doxylamine.

Recommendation T41– Sedating antidepressants: Appropriate cutoff concentrations in oral fluid are yet to be established: amitryptyline, nortriptyline, doxepin, imipramine, desipramine, trimipramine, dothiepin, mianserin, and trazodone.

Recommendation T42 – And other medications: Appropriate cutoff concentrations in oral fluid are yet to be established (e.g., butalbital, cocaethylene, carisoprodol, fentanyl, topiramate, nitrazepam, mirtazapine, and dextromethorphan, buprenorphine [norbuprenorphine] and illicit drugs (e.g., phencyclidine [PCP], LSD, ketamine, cathinone and GHB [subject to postmortem production] relevant to the individual country or area).

Issue 11 – What Are Minimum Analytes To Be Tested and Maximum Cutoff Concentrations in Urine?

Urine specimens provide a basis for further investigations in blood of relevant drug classes. Detection limits should be as low as analytically feasible.

Recommended minimum analytes to be tested in urine:

Issue 11 Recommendations

Recommendation T43 – Alcohol (cutoff, 0.1 g/100mL); report concentration in the matrix used.

Recommendation T44 – Opioids: Morphine, codeine, 6-acetylmorphine, methadone (EDDP), tramadol. If appropriate for the specific country or area, add oxycodone, hydrocodone, hydromorphone.

Recommendation T45 – Cocaine: Cocaine and metabolites (benzoylecgonine).

Recommendation T46 – Amphetamines: Amphetamine, methamphetamine, MDMA, MDA, MDEA.

Recommendation T47 – Cannabinoids: 11-nor 9-carboxy-THC.
Recommendation T48 – Benzodiazepines: Diazepam, oxazepam, temazepam, alprazolam, clonazepam, triazolam, nordiazepam, chlordiazepoxide, lorazepam, midazolam, and flunitrazepam.
Recommendation T49 – Other hypnotics: Zolpidem, zopiclone, diphenhydramine, and doxylamine.
Recommendation T50 – Sedating antidepressants: Amitryptyline, nortriptyline, doxepin, imipramine, desipramine, trimipramine, dothiepin, mianserin, and trazodone.
Recommendation T51 – And other medications (e.g., butalbital, cocaethylene, carisoprodal, fentanyl, topiramate, nitrazepam, mirtazapine, and dextromethorphan, buprenorphine [norbuprenorphine]) and illicit drugs (e.g., phencyclidine [PCP], LSD, ketamine, cathinone, and GHB (subject to postmortem production) relevant to the individual country or area.

Issue 12 - Standards Applied for Tests Conducted in the Laboratory (i.e., Performance Criteria)

Issue 12 Recommendations

Recommendation T52 – Assays should be properly validated. References describing appropriate validation criteria include the SOFT-AAFS Forensic Toxicology Laboratory Guidelines, Peters et al. (Amphetamine method validation), ISO 17025, FDA.
Recommendation T53 – For research purposes, it is not necessary to perform an immunoassay screening test if tandem mass spectrometry or full-scan mass spectrometry is used to identify and quantify analytes of interest.

Issue 13 – Standards for Tests Conducted at Point of Collection

Issue 13 Recommendations

Recommendation T54 – Manufacturers should provide performance data for sensitivity, specificity, accuracy, and recovery of analytes from the collection device at suggested cutoff concentrations for each lot of devices. The target analyte for each class of drugs and cross-reactivity of closely related compounds should be clearly specified.
Recommendation T55 – Cutoff concentrations should be specified for undiluted oral fluid.
Recommendation T56 – Additional specimen volume should be available for confirmatory laboratory-based analysis and allow appropriate chain of custody measures, if necessary.
Recommendation T57 – The assay should be able to perform acceptably, reproducibly, and reliably at cold and hot temperatures and in inclement weather.
Recommendation T58 – Test results should be available within 5 minutes if possible.
Recommendation T59 – Preferably, the assay should be convenient, robust, and require the least number of reagents and steps possible.
Recommendation T60 – Preferably, there will be a small handheld instrument for objective endpoint determination.
Recommendation T61 – A minimum of 5% of negative onsite tests should be analyzed by mass spectrometry to evaluate false negative results.
Recommendation T62 – Each device should have a mechanism for ensuring accurate device performance.
Recommendation T63 – In addition, each analyst should include at least one positive and negative quality control sample for each analyte once each day to verify performance.
Recommendation T64 – Minimum drug classes that should be included are cocaine, THC, amphetamines, benzodiazepines, and morphine. Additional analytes or classes to include are carisoprodol, zolpidem, buprenorphine, methadone, and tramadol.

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