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Guidelines for research on drugged driving

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Abstract

Aim—A major problem in assessing the true public health impact of drug-use on driving and overall traffic safety is that the variables being measured across studies vary significantly. In studies reported in a growing global literature, basic parameters assessed, analytical techniques and drugs tested are simply not comparable due to lack of standardization in the field. These shortcomings severely limit the value of this research to add knowledge to the field. A set of standards to harmonize research findings is sorely needed. This project was initiated by several international organizations to develop guidelines for research on drugged driving.

Methods—A September 2006 meeting of international experts discussed the harmonization of protocols for future research on drugged driving. The principal objective of the meeting was to develop a consensus report setting guidelines, standards, core data variables and other controls that would form the basis for future international research. A modified Delphi method was utilized to develop draft guidelines. Subsequently, these draft guidelines were posted on the internet for global review, and comments received were integrated into the final document.

Results—The Guidelines Document is divided into three major sections, each focusing upon different aspects of drugged driving research (e.g. roadside surveys, prevalence studies, hospital studies, fatality and crash investigations, etc.) within the critical issue areas of ‘behavior’, ‘epidemiology’ and ‘toxicology’. The behavioral section contains 32 specific recommendations; (2) epidemiology 40 recommendations; and (3) toxicology 64 recommendations.

Conclusions—It is anticipated that these guidelines will improve significantly the overall quality of drugged driving research and facilitate future cross-study comparisons nationally and globally.

Keywords

Alcohol; driving; DUI; illegal drugs; motor vehicle crash; trauma

BACKGROUND

Recent research [1–5] demonstrates that driving under the influence of drugs [DUID] other than alcohol is common, but not well documented. The consumption of psychoactive drugs, both medicinal (e.g. sedatives, anxi-olytics, hypnotics, antidepressant, antihistamine) and illicit drugs (e.g. amphetamine, cannabis, opioids, etc.) is a problem of growing interest in many

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countries in the world, because these substances are observed increasingly in impaired and injured drivers. Both illicit and licit drugs that affect the central nervous system (CNS) have the potential to impair driving performance. This has been an issue of great concern to many segments of society including: policy and decision-makers, members of the judiciary, politicians, police officers, road safety professionals, health professionals, manufacturers, owners of licensed premises, hospitality venues, employers in the public and private sectors, non-governmental organizations, insurance industry personnel and researchers, to name a few.

A major problem in assessing the true impact of drugs on driving and overall traffic safety is that the variables being measured across studies vary significantly. In research reported in a growing global literature, basic parameters assessed, analytical techniques and drugs tested are simply not comparable due to lack of standardization in the field. Often epidemiological research lacks statistical power, appropriate analytical methods, adequate control groups and/or testing of appropriate specimen matrices. Analytically, less sensitive and less specific methodology is often applied, assays are not validated fully and/or inappropriately high toxicology cut-off values are utilized. In behavioral and performance studies, appropriate pharmacokinetic data are often missing, making the data less meaningful, and experimental design is suboptimal. Although these inadequacies result from a variety of important factors, e.g. budget issues, limitations imposed by ethics committees, legislation, collaboration with police/hospitals, etc. we believe that many of these shortcomings could be avoided with internationally accepted research guidelines.

The International Council on Alcohol, Drugs and 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 be prepared. Furthermore, the ICADTS working group recommended that a consensus meeting of international researchers, representing the various aspects of the drugged driving research community (toxicologists, epidemiologists, behavioral scientists, trauma specialists, police, etc.), should be held as soon as possible to develop these standards to serve as a basis for future international DUID research. Such guidelines could enable researchers to harmonize the design of future experiments and encourage collection of data on core standardized variables that would facilitate cross-study comparisons.

As a result of the ICADTS working group recommendations, a 4-day 'experts' meeting, entitled 'Developing Standards for Research in Drugged Driving', was held in September 2006 at the Tufts University European Centre in Talloires, France. The meeting brought together international experts in drugged-driving to discuss harmonization of protocols for future research on drugged driving. The US National Institute on Drug Abuse (NIDA), European Commission (EU), European Drug Monitoring Centre (EMCDDA), French Society of Analytical Toxicology (SFTA), International Council on Alcohol, Drugs and Traffic Safety (ICADTS) and the International Association of Forensic Toxicologists (TIAFT) provided support for planning and implementation of this important project. 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 harmonize future international DUID research.

The organizing committee proposed to use the Delphi technique [6] 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. The Delphi method uses a highly structured, focused approach in order to establish a consensus opinion from 'experts'. The focus of consensus development targeted three areas of drugged driving research: epidemiology, behavior and toxicology.

The Delphi method is an iterative process, and aims initially 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 clarify progressively and expand on issues, identify areas of agreement or disagreement and establish priorities.

The modified Delphi method included the development of questionnaires in advance of the Talloires meeting to identify broad parameters for consideration within each area. For example, in the epidemiology group we asked: what are the basic problems encountered in epidemiology studies? What are the core parameters that should be included in any survey? How many subjects are needed? What should the selection criteria be? How does one avoid bias in the selection process? Should there be compensation for those who volunteer to participate in a study? Typically in the Delphi process, the answers to these broad questions raise more specific questions that then need to be answered. In the iterative process, the questions become more and more specific, ultimately producing consensus and specific recommendations.

The international experts were assigned to one of three areas, the behavioral, epidemiological or toxicology groups as follows:

Behavioral	Epidemiology	Toxicology
Jørg Mørland, Chair Norway	Alain Verstraete, Chair Belgium	Marilyn Huestis, Chair USA
Marie-Berthe Biecheler, France	Inger Marie Bernhoft, Denmark	Olaf Drummer, Australia
Steven Gust, USA	Patricia Dischinger, USA	Barry Logan, USA
Jan Ramaekers, Netherlands	Blandine Gadegbeku, France	Beitske Smink, Netherlands
Horst Schulze, Germany	Larry Gentilello, USA	
J. Michael Walsh, USA	Sjoerd Houwing, Netherlands	
	Brendan Hughes, UK	
	Dominique Lopez, France	

Responses to pre-meeting questionnaires were employed by the groups to identify specific issues, generate discussion and develop consensus on parameters. The 4-day meeting in Talloires included the first two iterative rounds of deliberation. The agenda promoted discussions within the issue groups and among all participants through plenary feedback meetings. The draft set of guidelines were posted on the websites of ICADTS and TIAFT for a 45-day review and comment period to reach many of the worlds 'experts' in drugged driving research. This provided a wider spectrum of opinions and the opportunity for others to make additional recommendations. In the last stage, comments received from the global research community were considered and integrated into the final document.

In an effort to demonstrate our basic philosophy that there is a need for standardization in this field, we have attempted to harmonize our terminology with the World Health Organization (WHO) lexicon of alcohol and drug terms [7] and the WHO manual on *Drinking and Driving* [8]. The following Guidelines Document is divided into three major sections, each focusing on a different aspect of drugged driving research (e.g. roadside surveys, prevalence studies, hospital studies, fatality and crash investigations, etc.) within the areas of behavior, epidemiology and toxicology. The behavioral section (1) contains 32 specific recommendations; (2) the epidemiology section 40 recommendations; and (3) the toxicology section 64 recommendations.

GUIDELINES FOR RESEARCH IN DRUGGED DRIVING

BEHAVIORAL SECTION

Recommendations (B1–32)

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:

Automotive behavior: well-learned skills (e.g.)

Tracking, steering (road tracking, critical tracking, compensatory tasks).

Vigilance or sustained attention (e.g. Mackworth Clock Test).

Control behavior: 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 behavior: 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, judgement (e.g. Tower of London task).

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 night-time) 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 upon the design of the study and the parameters to be studied.

Recommendation B7: Investigators should describe clearly 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, as well as the past driving history (e.g. DUI, moving violations, crashes, etc.)

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?: Recommendation B16:

Studies should conform with all legal and ethical regulations of their respective nations (e.g. Declaration of Helsinki, US Department of Health and Human Services, National Ethics Committees).

Recommendation B17: All studies should be designed to minimize the risks to subjects, investigators and the public in general.

Issue 4. What ‘core’ drugs/drug classes should be included in the toxicology test panel for behavioral studies?:

Recognizing that alcohol is the primary drug involved in impaired driving and that decades of research has yielded well-established knowledge of the effects of alcohol on behavior, our focus was directed towards drugs other than alcohol. A consensus was reached that behavioral studies focus typically on a particular drug of interest, and the number of doses of that drug. Reviewing the last 10 years of drugged driving research, we find that in addition to alcohol there are six classes of drugs that are seen most frequently in DUI arrests and motor vehicle crash victims: cannabis, benzodiazepines and other tranquilizing agents, opioids, stimulants [amphetamine, cocaine, methamphetamine, methylenedioxymethylamphetamine (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 (other than alcohol) on driving.

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, opioids, stimulants (amphetamine, cocaine, methamphetamine, MDMA), antidepressants and antihistamines, both alone and in combination with alcohol.

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, fentanyl) and novel stimulants (methylphenidate, modafinil), both alone and in combination with alcohol. Additional studies should be conducted to link the behavioral impairment with toxicological and other epidemiological factors where these data do not, as 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 concentrations, and when should these specimens be collected?: The exceptionally complex interactions of drug, dose, route of administration, CNS effects and ultimate outcome on behavior must be acknowledged.

Recommendation B21: Blood is the minimum specimen required to determine acute effects of drugs on behavior. Oral fluid may be of value, but with the present state of knowledge (e.g. the influence of sampling technique on the concentration of drugs in oral fluid) we believe that blood concentrations correlate better with behavior than oral fluid.

Recommendation B22: The behavioral effects of drugs should be related to dose and drug concentration in the brain. Currently, the best available indicator of drug concentration in brain is the concentration of 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?: Recommendation B26: At a minimum, performance should be assessed at T_{max} (when the drug concentration is at a maximum in the blood) to determine 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?: Little research has been conducted on the performance effects of chronic drug use. Specific issues relating to chronic use include: withdrawal, tolerance, multiple drug use, drug interaction, steady states and long-term (persistent) effects.

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.

Additionally, a matched control group of non-drug users should be considered (between group testing). Previous drug use should be determined as comprehensively as possible.

Issue 8. General issues related to the study design: 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: Both placebo controls and active verum [active substances that should elicit a response (e.g. impairment) in the test, i.e. opposite of placebo] are encouraged strongly.

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

EPIDEMIOLOGICAL SECTION

Recommendations (E1–40)—Recognizing that the type of research will dictate the required research parameters, our recommendations for epidemiological research are presented in 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: While we recommend that police officials are not involved directly in the collection of data, in order to conduct roadside/prevalence surveys more easily law enforcement authorities should be willing, funded, legally authorized and able to participate in traffic control while surveys are being conducted. Prior to the initiation of a study, procedures should be developed to handle obviously impaired drivers encountered while gathering data at roadside surveys.

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 assure 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?: 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 acceptable, as long as the results are reported clearly as being 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 data during the research study. Subjects should be provided with precise information regarding the purpose of the study and the minimal time required.

Recommendation E8: For roadside surveys a representative sample should be ensured by identifying subjects based on traffic patterns (night, day), timing, location, etc. 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 obtain 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, past driving record and other objective facts, etc.).

Recommendation E11: Refusal rates and characteristics of 'refusers' versus enrolled subjects should be examined. Provisions should be made to accommodate those who speak foreign languages. The validity of the study will depend on whether refusal-rates introduce bias.

Recommendation E12: The maximal 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.

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

1. Demographic data, including age, sex, level of education, nationality and driving history.
2. Type and age of vehicle.
3. Time and place of the data collection.
4. Toxicology on the core basic drug groups: alcohol, cannabis, cocaine, opioids, MDMA, amphetamines and benzodiazepines.

Issue 4. Legal/ethical issues in hospital studies: 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?:

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 to the hospital. This may introduce bias into 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 with hospital studies, researchers should pay attention to the parameters to be compared and try to screen for the same drug panels in the same biological fluid using the same laboratory techniques in both studies.

Recommendation E22: Researchers should obtain information regarding subjects' pre-hospital 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 involved in crashes.

Recommendation E27: Bias should be avoided in the selection process. Enrollment of subjects should be without any consideration of age, gender, race or language spoken.

Recommendation E28: Compensation for hospital study subjects should be avoided unless long questionnaires and interviews are required, and this should be conducted 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 obtain 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), information on the number of vehicles in the crash, vehicle type, time of crash, extent of injuries and other objective facts.

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 maximal 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.

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

1. Crash data (time/day of crash, whether injured party was the driver/passenger/pedestrian, single or multi-vehicle crash and police report).
2. Time the biological sample was taken (blood is the preferred specimen).
3. Toxicology on the core basic drug groups: alcohol (or ethanol), cannabis, cocaine, opioids, MDMA, 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 upon 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.

Issue 7. Legal/ethical issues in fatal crash/collision studies: 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?: 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 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?: Limitations may depend on costs, laws and regulations

Recommendation E38: At a minimum, data on the following parameters should be gathered:

1. Crash data (time/day of crash, whether injured party was the driver/passenger/pedestrian, single or multi-vehicle crash and police report).
2. Time the biological sample was taken (blood is the preferred specimen).
3. Toxicology on the core basic drug groups: alcohol or ethanol, cannabis, cocaine, opioids, MDMA, 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 upon 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 SECTION. Recommendations (T1–64)

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?

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, 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 recommend strongly that the most impairing and most prevalent drugs in each jurisdiction, county, state or country should be included to the maximum extent practical.

Recommendation T3: On-site 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 assay of different specific analytes.

Issue 2. Specimen collection

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: Ensure that blood is drawn from the opposite arm than any intravenous line to avoid contamination and dilution.

Recommendation T6: It is suggested that cut-off concentrations be at least as low as the lower end of the therapeutic range. For recreational drugs there are no therapeutic ranges; we suggest the use of analytical cutoff concentrations that are low, either state-of-the-art detection limits for multi-analyte analytical methods or concentrations that are likely to be reached 24 hours after use of a typical dose of the drug.

Recommendation T7: After collection, specimens 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 cut-offs in whole blood

Recommendation T8: Alcohol (cut-off, 0.1 g/l).

Recommendation T9: Opioids: morphine (cut-off 10 ng/ml), codeine (cut-off 10 ng/ml), 6-acetylmorphine (cut-off 10 ng/ml), methadone (cut-off 10 ng/ml), tramadol (cut-off 20 ng/ml).

Recommendation T10: Stimulants: amphetamine, methamphetamine, MDMA, 3,4-methylenedioxy-N-ethylamphetamine (MDEA/MDA) (cut-off 20 ng/ml); cocaine (cut-off 10 ng/ml) and metabolites (benzoylecgonine 50 ng/ml; cocaethylene 10 ng/ml, ecgonine methyl ester 10 ng/ml).

Recommendation T11: Cannabinoids: Δ 9-tetrahydrocannabinol (THC; 1 ng/ml), 11-nor-9-carboxy-THC (cut-off 5 ng/ml), 11-OH-THC (cut-off 1 ng/ml).

Recommendation T12: Benzodiazepines: diazepam (cut-off 20 ng/ml), oxazepam (cut-off 50 ng/ml), temazepam (cut-off 50 ng/ml), alprazolam (cut-off 10 ng/ml), clonazepam (cut-off 10 ng/ml), nordiazepam (cut-off 20 ng/ml), lorazepam (cut-off 10 ng/ml) and midazolam (cut-off 20 ng/ml).

Recommendation T13: Other hypnotics: zolpidem (cut-off 20 ng/ml), zopiclone (cut-off 20 ng/ml), diphenhydramine (cut-off 25 ng/ml) and doxylamine (cut-off 25 ng/ml).

Recommendation T14: Sedating antidepressants: amitriptyline (cut-off 25 ng/ml), nortriptyline (cut-off 25 ng/ml), doxepin (cut-off 25 ng/ml), imipramine (cut-off 25 ng/ml), desipramine (cut-off 25 ng/ml), trimipramine (cut-off 25 ng/ml), dothiepin (cut-off 25 ng/ml), mianserin (cut-off 25 ng/ml) and trazodone (cut-off 10 ng/ml).

Recommendation T15: Other medications e.g. butalbital (cut-off 100 ng/ml), carisoprodol (cut-off 500 ng/ml), fentanyl (cut-off 1 ng/ml), topiramate (cut-off 1 ng/ml), mirtazapine (cut-off 10 ng/ml), dextromethorphan (cut-off 20 ng/ml), buprenorphine (cut-off 1 ng/ml), flunitrazepam (cut-off 2 ng/ml) and illicit drugs e.g. phencyclidine (cut-off 10 ng/ml), lysergic acid diethylamide (LSD) (cut-off 0.5 ng/ml), ketamine (cut-off 10 ng/ml), cathinone (cut-off 20 ng/ml) and gamma hydroxy butyrate (GHB) (cut-off 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.

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 on-site test results or behavioral observations, collection should be conducted in accordance with suspected impaired driving.

Recommendation T18: There should be comprehensive testing of a minimum of 5% of specimens with negative on-site test results.

Issue 5. Suspected impaired driving research

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

Recommendation T21: Whole blood (10 ml) should be collected with anticoagulant and fluoride preservative.

Recommendation T22: If possible, additional specimens should be collected: oral fluid and urine.

Recommendation T23: Crash information should be recorded (e.g. time/day of crash, whether injured party was the driver/passenger/pedestrian, single or multi-vehicle crash, and police report) and the time of specimen collection should be documented.

Recommendation T24: Information on medications and total blood products, intravenous fluid or artificial blood/synthetic hemoglobin administered by emergency services and hospital should be documented.

Issue 7. Fatal injury research

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: Ante-mortem specimens should be obtained if available, especially in cases where there is a delay between the accident and death.

Issue 8. How long should specimens be retained after completion of the study?

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?

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. Oral fluid collection devices should be inert and not adsorb analytes of interest, or buffers included should elute analytes from collection device with minimal drug concentration dilution. Buffers should be selected that do not interfere with liquid chromatography–tandem mass spectrometry (LC/MS/MS) analysis.

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 cut-off concentrations in oral fluid?

Recommendation T34: Alcohol (cut-off, 0.1 g/l).

Recommendation T35: Opioids: morphine (cut-off 20 ng/ml), codeine (cut-off 20 ng/ml), 6-acetylmorphine (cut-off 5 ng/ml), methadone [2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP)] (cut-off 20 ng/ml), tramadol (cut-off 20 ng/ml).

Recommendation T36: Cocaine: cocaine and benzoylecgonine (cut-offs 10 ng/ml).

Recommendation T37: Amphetamines: amphetamine (cut-off 20 ng/ml), methamphetamine (cut-off 20 ng/ml), MDMA (cut-off 20 ng/ml), MDA (cut-off 20 ng/ml), MDEA (cut-off 20 ng/ml).

Recommendation T38: Cannabinoids: Δ^9 -tetrahydrocannabinol (THC; 2 ng/ml).

Recommendation T39: Benzodiazepines: appropriate cut-off 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 cut-off concentrations in oral fluid are yet to be established—zolpidem, zopiclone, diphenhydramine and doxylamine.

Recommendation T41: Sedating antidepressants: appropriate cut-off concentrations in oral fluid are yet to be established—amitriptyline, nortriptyline, doxepin, imipramine, desipramine, trimipramine, dothiepin, mianserin and trazodone.

Recommendation T42: Other medications: appropriate cut-off 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 post-mortem production)] relevant to the individual country or area.

Issue 11. What are minimum analytes to be tested and maximum cut-off 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.

Recommendation T43: Alcohol (cut-off, 0.1 g/l); 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: amitriptyline, nortriptyline, doxepin, imipramine, desipramine, trimipramine, dothiepin, mianserin and trazodone.

Recommendation T51: Other medications (e.g. butalbital, cocaethylene, carisoprodol, fentanyl, topiramate, nitrazepam, mirtazapine and dextromethorphan, buprenorphine (norbuprenorphine) and illicit drugs [e.g. PCP, LSD, ketamine, cathinone, and GHB (subject to post-mortem production)] relevant to the individual country or area.

Issue 12. Standards applied for tests conducted in the laboratory (i.e. performance criteria)

Recommendation T52: Assays should be properly validated. For appropriate validation criteria see the SOFT-AAFS Forensic Toxicology Guidelines. Available from: http://www.SOFT-Tox.org/?pn=publications&sp=laboratory_guidelines (accessed 18 June 2008).

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

Recommendation T54: Manufacturers should provide performance data for sensitivity, specificity, accuracy and recovery of analytes from the collection device at suggested cut-off concentrations for each lot of devices. The target analyte for each class of drugs and cross-reactivity of closely related compounds should be specified clearly.

Recommendation T55: Cut-off 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 on-site tests should be analyzed by mass spectrometry to evaluate false negative results.

Recommendation hT62: Each device should have a mechanism for assuring 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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