DOT HS-803 879

DRUGS AND DRIVING
A SELECTED BIBLIOGRAPHY
SUPPLEMENT ONE

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16. Abstract

This report presents a first supplement to Drugs and Driving: A Selected Bibliography (HS - 802 188), a bibliography of literature dealing with the relationship between drug use (other than alcohol alone) and highway safety. This supplement both updates the parent volume and expands coverage in certain research areas related to the field of drugs and highway safety. In particular, literature pertaining to drug usage patterns and drug analytical methodology has been included. A detailed description of the literature scope and document selection process is provided.

The bibliography consists of four appendices, including a Topical Index, an Author Index, a Title Index, and Abstracts of nearly 400 articles. A revised topical index was developed to improve user access to document abstracts. Within the topical index are cross-referenced lists of drugs by name and by usage.

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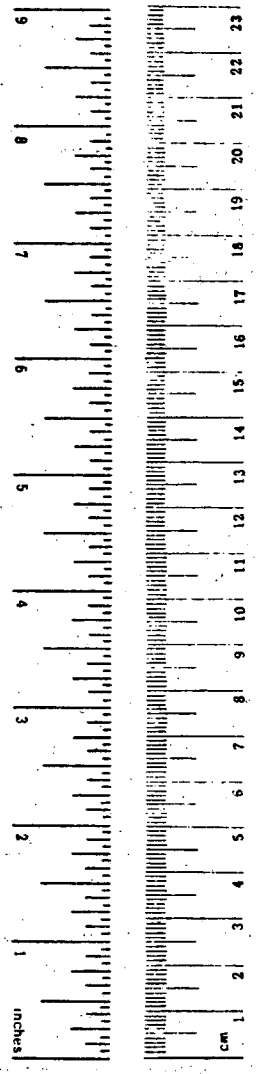
METRIC CONVERSION FACTORS

Approximate Conversions to Metric Measures

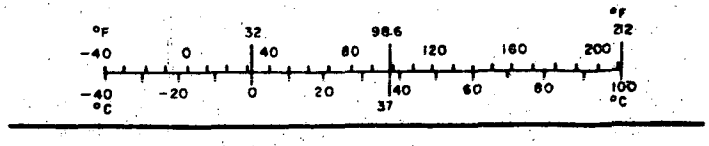
Symbol	When You Know	Multiply by	To Find	Symbol
	LENGTH			
in	inches	*2.5	centimeters	cm
ft	feet	30	centimeters	cm
yd	yards	0.9	meters	m
mi	miles	1.6	kilometers	km
	AREA			
in^2	square inches	6.5	square centimeters	cm^2
ft^2	square feet	0.09	square meters	m^2
yd^2	square yards	0.8	square meters	m^2
mi^2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

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



Approximate Conversions from Metric Measures

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



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The multidisciplinary projects that supported this bibliographic effort involved many individuals. The principal investigators thank all who assisted.

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Alan C. Donelson, Ph.D.
Principal Investigator

DRUGS AND DRIVING:
A SELECTED BIBLIOGRAPHY
SUPPLEMENT ONE

CONTENTS

1.0 INTRODUCTION

This report presents a first supplement to Drugs and Driving: A Selected Bibliography (HS-802 188), a bibliography of literature dealing with the relationship between drug use (other than alcohol alone) and highway safety.

The bibliographic supplement is the product of an extended literature search conducted under the sponsorship of the U.S. Department of Transportation, National Highway Traffic Safety Administration, as part of efforts under contracts DOT-HS-5-01217 and DOT-HS-7-01530.

This supplement both updates the parent volume and expands coverage in certain research areas related to the field of drugs and highway safety. In particular, literature pertaining to drug usage patterns and drug analytical methodology has been included. The general criterion for the inclusion of a document was apparent relevance to drugs/highway safety and to contract objectives. For example, increased concern over methodological issues is reflected in this compilation.

A key phrase in current drug/driving research is problem definition. The issue of drugs and driving continues as a worthy research topic; the existence of a "drug/driving problem," however, remains a presumption. Of course, the presumption is necessary as a research hypothesis. But the reader is cautioned not to presume the actual existence of a drugs-and-driving problem. The true problem now is determining whether there is a problem and, if there is, identifying its nature and extent.

The report is intended as a resource document. Its purpose is to aid current efforts in determining the relationship of drugs and highway safety. The primary objective is not analysis of research, but rather presentation of literature. The contents of the report

are representative, but not inclusive, of the available literature. No representation of scientific validity of all the materials included is made.

1.1 Background

The University of Michigan Highway Safety Research Institute (HSRI) received two contracts dealing with the area of drugs and driving from the National Highway Traffic Safety Administration (NHTSA). The contracts were two of a series that forms a comprehensive program for the examination of this issue. The following paragraphs present the context and rationale for this research. Specifically, they describe contract objectives and the relation of the literature search to them.

A contract received by Indiana University (IU) from NHTSA in June 1974 preceded the projects that supported the present document. Contract DOT-HS-4-00994, entitled "Drug/Driving Research Review and Symposium," reviewed the relationship between the use and abuse of drugs (other than alcohol alone) and highway safety. The principal investigators for this project were Kent B. Joscelyn and Roger P. Maickel. The study developed the basis from which the later contracts received by HSRI derived.

The central objectives of the study may be summarized as follows:

- Ascertain and document on the basis of existing research literature the relationship between drug use (other than alcohol alone) and highway safety.
- Ascertain the "state of the art" of research in the field of drugs and highway safety.
- Define areas in drugs and highway safety that require further research and suggest, insofar as present knowledge permits, possible drug/driving countermeasures that can be implemented in the immediate future.

The research plan to achieve these objectives contained several elements. A literature search identified published literature to be included in the study. An international symposium provided a forum to determine

the state of the art in current knowledge and to develop directions for future research. Finally, a research review collated and synthesized the information obtained in the literature search and symposium. The project produced a series of reports:

- Report of an International Symposium on Drugs and Driving (DOT HS-802 187);
- DRUGS AND DRIVING: A Selected Bibliography (DOT HS-802 188); and
- DRUGS AND DRIVING: A Research Review (DOT HS-802 189).

In Contract DOT-HS-5-01217, entitled "The State of Knowledge and Information Needs in Alcohol/Drugs and Highway Safety," the examination of drugs and highway safety was part of a larger project involving alochol-related objectives. The general objectives of this project related to drugs (other than alcohol alone) were:

- to critically review, evaluate, and summarize existing knowledge concerning the drug/crash problem; and
- to recommend further research on the drug/crash problem that is a priority need and is likely to produce the most significant results.

In pursuing these objectives, the role of drugs in highway crashes was examined from the following topical standpoints:

- problem definition
- measurement of agent effects
- measurement of agent presence
- relationship between agent presence and impairment
- countermeasures

The critical review of existing information in these areas led to the summarization of current knowledge and recommendations for future directions in research. As part of the literature examination and review process, a literature search was performed. The document

identification and collection activity was broad-based to (1) supplement the existing information base and (2) satisfy literature requirements in hitherto unsearched areas.

The second contract, DOT-HS-7-01530, was received by HSRI in November 1976. The general objectives of this contract, entitled "Drug Research Methodology," were:

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

The main focus of the project was on solutions to problem issues in drugs and highway safety. Specifically, the overall task was to identify and develop methodologies for research in the area of drugs and driving. The central objectives of the study were:

- to identify those problem areas that should be addressed in drug methodology;
- to provide workable and detailed solutions that could be implemented with current technology; and
- to provide a listing of priority items of experimental research that NHTSA could address in the foreseeable future.

The last two objectives were directed toward the determination of the extent drugs contributed to traffic crashes.

Under this second contract, a workshop approach was used to examine problem issues in four specific but interrelated areas:

- Identification of Drugs of Interest
- Drug Analytical Methodology
- Epidemiological Research Methodology
- Experimental Research Methodology

A specific task under Contract DOT-HS-7-01530 ("Drug Research Methodology") was to update the literature review performed for NHTSA

under Contract DOT-HS-4-00994, described above. Under the latter contract, formal literature search activity ceased after April 1975. DRUGS AND DRIVING: A Selected Bibliography (DOT-HS-802 188) was produced from the Research Report File. This document (hereafter referred to as Selected Bibliography) included abstracts of articles identified under Contract DOT-HS-4-00994 and indexed by topic, title, author, drug, and accession number. The hard copy file of documents, now maintained at HSRI, was enlarged by subsequent literature search efforts under Contract DOT-HS-5-01217, also described above. Thus, the literature search task for Drug Research Methodology continued the previous efforts and produced this first supplement to the Selected Bibliography. (To avoid confusion, the present report will be referred to as Supplement One.)

The literature search also served specific objectives of Contract DOT-HS-7-01530:

- to identify, collect, and review recent literature related to drugs and highway safety; and
- to provide common review material to workshop participants prior to each workshop.

The format of a bibliography provided a means for organizing and indexing this type of material. Supplement One presented a selection of abstracted literature earlier for HSRI staff, NHTSA, and the workshops, and now for more general distribution.

1.2 Report Organization

This report consists of a series of introductory sections and a set of appendices that organize and present reference materials on drugs and driving.

Section 2.0 describes the technical approach used in the compilation of the bibliographic supplement. The scope of the literature search is defined in terms of major topic areas, and criteria for exclusion of related material are specified. A series of subsections outlines the literature search methods, notes limitations on the literature search, and describes the abstract collection.

Section 3.0 describes the organization of the bibliographic material in the appendices. Explanation of the various indices is provided, and guidelines for efficient use of the bibliography are included.

2.0 TECHNICAL APPROACH

The general approach used in compiling this bibliographic supplement was similar to that used under contract DOT-HS-4-00994 in producing the parent volume. The literature search comprised both manual and computer-assisted techniques. The scope of the search was broadened somewhat compared to the previous effort, so that additional sources were used.

The technical approach was designed to meet three main objectives:

- to maintain comprehensive files of literature specifically dealing with drugs-and-driving issues;
- to broaden the topical scope of the bibliography, including literature pertaining to specific research requirements and information needs in the field of drugs/highway safety; and
- to provide access to the main bodies of relevant literature and especially to major area reviews.

Of primary concern was the inclusion of all documents directly related to the topic area of drugs and driving. The expanded scope of bibliographic coverage proportionately increased the representation of support areas indirectly related to the field of drugs/highway safety. The collected material is not all-inclusive of the available literature in these areas. However, an attempt was made to identify and collect major reviews of subtopical areas, and to provide ready access to peripheral research relevant to the central objectives of drugs/highway safety. The identification and collection of other bibliographies and research compilations supported this objective.

As in the Selected Bibliography, literature search activity encompassed technical and non-technical sources in addition to scientific literature bases. Thus, the bibliography contains entries from the general literature, as well as from the archival literature. As pointed out in the parent volume, caution must be exercised in using

the bibliographic references. The reader is reminded here to consult each original article of interest, to determine its degree of relevance for special concerns, and to assess independently its scientific validity.

In the attempt to include research areas indirectly related to drugs and highway safety, several massively documented areas were touched upon. The sheer volume of available material necessitated the development of exclusionary criteria. The following sections present a detailed description of the literature search and selection process which led to the production of this bibliography.

2.1 Literature Search Scope and Document Selection

This section discusses the major topic areas in which literature was identified for inclusion in the bibliography. It defines the scope of the literature search in terms of specific research areas, and describes the criteria used to exclude documents of minor importance.

The topical expansion in bibliographic coverage is intended to more adequately represent the multidisciplinary nature of the field of drugs/highway safety. Epidemiology and experimentation are two general approaches that characterize this field. Within these distinct research branches are specific research requirements, information needs, and methodological issues. There are also areas of related needs, due to the complementary nature of these research approaches. In the following subsection, a brief background discussion of research in drugs/highway safety is presented to develop the rationale of the literature search.

2.1.1 Research in the Field of Drugs and Highway Safety.

As stated from the outset, the existence of a "drugs-and-driving problem" remains a presumption. The role of drugs in traffic crash causation is still hypothetical and unconfirmed. Broadly speaking, determining

the relationship of drugs and highway safety requires systematic research that can engage a many faceted study of drug interactions with individual, vehicular, and environmental factors related to driving. A multidisciplinary approach is embodied in the field of drugs and highway safety. As an applied research field, drugs and highway safety involves the conjunction of pharmacology and pharmaco-behavioral sciences with highway safety research and its allied concerns.

The central objectives of research in drugs and highway safety concern problem definition and countermeasure development. The "state of the knowledge" is such that much basic and applied research is required to determine adequately the nature and extent of any drugs-and-driving problem. If a problem is identified, additional research will be necessary to develop and to evaluate alternative approaches to deal with it. Ancillary research areas contribute significantly in the overall endeavor. For example, research in these areas provides:

- information on which to base decisions regarding experimental design or countermeasure development;
- methodological support in exploratory research or in project evaluation; and
- technological support in the execution of experiments or in the implementation of countermeasures.

Because their capability in meeting the research requirements of drugs/highway safety warrants periodic assessment, access to this special literature is desirable.

Bodies of literature relevant to the information needs of drugs/highway safety research can be delineated in terms of major research areas and supporting fields. In the following subsection, the scope of the literature search is defined.

2.1.2 Scope of Literature Search. The "state of knowledge" evaluation and the analysis of information needs required a broad-based literature review. To facilitate description of the literature search, the relevant literature of discrete research areas is described below. Criteria for exclusion of documents are specified within each area.

2.1.2.1 Epidemiological Literature. The epidemiological approach to the study of drugs and driving includes both direct and indirect lines of research. The direct assessment of accident risk attributable to drug use by drivers involves field surveys. Methodological issues involve study design and drug analytical methodology. All literature directly related to the epidemiological study of drugs and driving was collected upon identification.

The indirect assessment of drug use by the general or special populations aids in the estimation of drug risk potential. Thus, literature pertaining to drug usage patterns was identified and collected. Toxicological studies which indicated those drugs likely to be misused or used to excess were also deemed relevant. Reports describing drug user characteristics were considered important in the identification of target groups for countermeasure activity. Reports of this nature were excluded if the drugs or specific topic areas were inappropriate to the indirect assessment of accident risk in driving.

Literature dealing with basic issues in epidemiologic research was also included in the bibliography if the documents were related to the study of drug-related problems in society. Reports describing general drug screening were collected as described below.

2.1.2.2 Experimental Literature. In the experimental approach to the study of drugs and driving, the significance of drug effects is assessed under controlled conditions. Types of experiments

range from those closely related to the actual driving task (e.g., driving simulation) to those in which simple tests of human performance are utilized (e.g., choice reaction time). All identified studies involving the perceptual, sensory, and psychophysical evaluation of drug effects in man were included in the bibliography. While some reports did not mention driving per se, these were included on the basis of their similarity to research generally conducted in the field of drugs/highway safety. Experimental investigations which attempted to characterize the nature of drug effects in man were also included if, in the judgment of the compiler, they might support the analysis of driver impairment by drugs. Reports dealing with drug effects in animals were generally excluded; exceptions included studies that contributed to the understanding of the nature of drug effects in man, and reports that simultaneously dealt with drug effects in man and/or with drug analytical methodology.

Papers dealing with methodological issues in behavioral research were included on the basis of their relevance to the experimental assessment of drug effects on human performance. Reviews of behavioral research methodologies were also collected when identified.

2.1.2.3 Literature Concerning Drug Analytical Methodology. In the epidemiological study of drugs in drivers, analytical capability is required for the detection, identification, and quantification of drugs in body fluids. Depending on specific study objectives, a general drug screening system may be employed for the purpose of drug detection and preliminary identification. Confirmatory drug analysis methods usually permit quantitation. Specific screening techniques, useful in the systematic approach to drug screening in body fluids, also have an important place in drug analytical methodology.

All identified reports describing general drug screening methodology were included in the bibliography. Documents dealing with specific screening methodology and confirmatory/quantitative methods were included (1) if the drugs were determined in biological liquids and (2) if the drugs were of possible interest in the field of drugs/highway safety. Since the body of literature pertaining to drug analysis is massive and ever expanding, particular emphasis was placed on the identification and collection of method reports in which drug levels were determined in human subjects.

Technical assessments of the "state of the art" in drug analysis are important to the area of countermeasure development. Evaluations of drug analytical methodology and intercomparisons of specific methods are useful in the design of research involving drug analysis. Therefore, reviews of analytical techniques and their application to drug analysis were included in the bibliography.

Epidemiological study of drugs in drivers may also require the use of independent laboratories for the purpose of drug analysis. Laboratory evaluation may become important in this regard. Papers dealing with quality control and proficiency testing were included as a separate topic area.

2.1.2.4 Drug Concentration-Effect Literature. The adequate interpretation of epidemiologic data pertaining to drug levels in accident- and nonaccident-involved drivers requires a substantial information base relating drug concentration in body fluids to drug effect. Greatest interest in the significance of drug blood levels has been evident in the area of clinical pharmacology. Relatively few reports could be identified in the experimental literature which correlated drug levels with performance of driving-related skills.

Most identified reports dealing with correlations between drug levels in body fluids and drug effects were included in the bibliography. Although some investigations used measures of drug effect unrelated to the driving task per se, other considerations contributed to their relevancy. These reports cited drug analysis methods adequate for the determination of therapeutic drug levels and reported drug blood concentrations resulting from common dosage levels. They also described effects of therapeutic drugs that might increase a driver's risk of accident. Reports that inadequately described these aspects of clinical investigation were excluded from the bibliography.

2.1.2.5 Drug Concentration Literature. Data pertaining to the therapeutic or toxic blood levels of drugs in body fluids are important for the following reasons:

- approximate drug levels representing threshold ranges for therapeutic, impairing, and toxic effects are indicated;
- the sensitivity required of analytical methodology for the detection, identification, and quantification of drugs in body fluids is specified prior to selection of drug analysis methods;
- the time course of pharmacokinetic phases of absorption, distribution, metabolism, and excretion is described as reflected in blood levels of parent drug and (some) metabolites; and
- the inter-subject (inter-patient) variability in drug blood levels after single- and/or multiple-dose administration is indicated.

The relevance of these data is found in the interpretation of drug levels from both epidemiological and countermeasure standpoints; in the designing of countermeasures; in the designing of drug screening methodology and the selection of adequate confirmatory/quantitative methods; and in the assessment of drug concentration as a valid measure of drug effect.

Literature reports containing drug level data are diverse in nature and type. Compilations presenting comprehensive tabulations of drug concentration ranges were identified and collected. Less inclusive reports of a toxicological nature were also included in the bibliography. Reports of epidemiological findings representing drug levels determined in non-driver groups were included only if the drugs themselves were of interest in drugs/highway safety.

Specific reports of human drug concentration data were also considered within the scope of this topic area. Often in the clinical or experimental context, drug concentrations in the blood would be determined following acute and chronic drug administration. Many of these documents were included as a result of relevance to other areas. However, purely pharmacokinetic and/or drug metabolism studies involving drugs of interest were also identified and collected. Reports of specific analytical methods for these drugs would also contain the determination of drug levels in body fluids as a demonstration of method applicability. Many of this latter type of document were identified and collected in the search of literature pertaining to drug analysis. While these studies typically involved small groups of subjects, the preliminary indication of drug level variability was considered useful in drug/driving research.

2.1.2.6 Miscellaneous Topic Areas. Several other topic areas were included within the scope of the literature search.

Socio-legal studies dealing with drug-related problems in society were included if a relation to the drugs and driving problem was evident. Literature pertaining to the development, evaluation, and implementation of drug countermeasures was identified and collected. Reports dealing with alcohol only were generally excluded. Exceptions included documents dealing with general countermeasure issues applicable also to other drugs.

General pharmacological effects of drugs whose use by drivers may present increased accident risk were also of interest. Document abstracts in this bibliography include literature on drug interactions, studies of the sites and mechanisms of drug action, and reports dealing with the time-dependency of drug effects. As an information base for the interpretation of drug levels, reviews and individual reports were compiled which discussed factors influencing the drug concentration-effect relationship. Documents in the area of general pharmacology were excluded if the reports were only of slight significance.

The following section briefly outlines the literature search methods used in the compilation of this bibliography.

2.2 Literature Search Methods

The literature search procedure involved the following steps:

- identification;
- collection; and
- review.

Following these steps, documents were abstracted (if not already abstracted) and included in the bibliography according to selection criteria.

The next sections of this report detail literature search methods.

2.2.1 Manual Literature Search. On the basis of previous efforts in compiling the Selected Bibliography, a list of journals was developed in which relevant documents had been frequently identified. Journal issues published since the cessation of formal literature search activity under contract DOT-HS-4-00994 were searched for related material. Journals pertaining to research areas newly included within the scope of the bibliography were searched according to the specific topic area.

Author indices were used to identify recent reports by active researchers in the field of drugs/highway safety. Other bibliographies and selected abstract services were also searched. Citations included in major topical and subtopical reviews were also identified and collected.

2.2.2 Computer Assisted Searching. Several computer-based information retrieval services were used as appropriate in the literature search. The data bases available to the research staff included the following systems:

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

2.2.3 Other Search Methods and Efforts. The topic area of drugs and driving is one of the search topics of the HSRI Information Center. The continuing surveillance of the literature conducted by the Information Center staff includes periodic computer searches of the relevant literature. Upon identification, all publications on this topic are automatically collected.

In addition to the formal search methods described above, the staff is in personal communication with leading researchers in the field. Previously unidentified material and conference papers were frequently received during the course of the literature search by research staff and the HSRI Information Center.

In the following section, limitations on the literature search are described and the effectiveness of criteria for document selection is briefly discussed.

2.3 Limitations of Literature Search and Document Selection Procedures.

In the Selected Bibliography the authors discussed general and specific limitations applying to that volume. Some limitations in the original work apply equally to Supplement One. The expanded search relative to the Selected Bibliography engendered other problems. This section describes factors that influenced the comprehensiveness and the quality of material included. The discussion incorporates points made previously in the Selected Bibliography.

The omission of relevant material is inevitable. A number of factors war against the ideal of all-inclusiveness, and many lie well beyond the control of compilers. For example, the literature search task occupied a subsidiary position relative to other contract objectives. Available resources--both staff time and funding level--limited the search and collection of literature. This nearly universal restriction was ameliorated by efficient planning and by the previous effort devoted to the Selected Bibliography. In many areas, including the general topic of "drugs and driving," the literature search was a simple update of that comprehensive collection.

A fundamental limitation arises from the nature of the literature base pertaining to the field of drugs and highway safety. Drugs and highway safety is an applied field of loosely knit research areas. The determination of drug influence on traffic crash causation requires a systematic, multidisciplinary approach. "Drugs and driving," however, remains an isolated, special topic in journals serving the respective disciplines. Thus, the relevant documents to be identified are scattered throughout many journals and other literature sources. Multidisciplinary fields provide other pitfalls for broad-based literature searches. Although many research areas as such are reasonably well-defined, their relation to drugs and highway safety often is not.

Many reports occupy a gray area of semi-relevance in which the personal biases of reviewers hold sway. Time and cost limits forced cursory searches of some relatively large research areas, e.g., drug analysis methods.

The weaknesses and limitations of literature search methods exacerbate problems in dealing with the literature of drugs and highway safety. To search every likely publication for relevant material is impossible. The manual search is made manageable by by selection of lists of journals and authors, abstract services, and other bibliographies. These tools aid in examining source material. The weaknesses and strengths of each index and list, however, are carried forth into the search. Titles and indices included by document sources themselves may be incorrect; compilations of abstracts or bibliographies reflect the (unknown) biases of their compilers. The use of computer-assisted techniques supplemented the literature search by manual means. The ability to elicit relevant output from information storage, search, and retrieval systems depends on the selection of key works or topic indicators as well as on the way a document was identified originally in the system. Broad topics and specific issues appeared refractory to automated searches.

The fact that one can't find what isn't there also limits the apparent inclusivity of both bibliographies. The coverage of material published or issued within two years of the literature search is most likely incomplete. The publication process is itself lengthy; there is a significant "lag time" between completion and reporting of research findings. The indexing and dissemination of abstracts as well as the entry of material into computer systems takes even longer since it follows initial publication. Foreign language publications share these and exhibit other problems. Mistranslations of titles and inaccurate or uninformative abstracts of article content combine with cost and availability factors in hindering the inclusion of foreign documents.

In addition to the directing influence of contract objectives, the personal biases of individual searchers and reviewers also affect the selection of documents. For example, a judgmental selection was necessary in peripheral research with massive documentation. Exclusionary criteria, described in section 2.1.2, aided in this process. Nevertheless, the distribution of reports within and among research areas reflects the impact of human value judgments.

The quality of selected documents is another matter requiring a cautionary note. A wide range of sources contributed the full spectrum of articles and reports: technical and non-technical, general and archival, scientific and popular documents are included in this collection. Limitations of the literature base itself become important to the user, who must also evaluate the material.

In general, the published archival literature is viewed as factually accurate and reliable. This is due in part to a significant level of peer review during the editorial process. The rigor with which submissions are reviewed, however, varies. Data presentation, experimental design, and methodological accuracy may still be of questionable validity. Statements made or conclusions drawn in discussion sections are usually those of the authors and are subject to bias and error. The technical literature includes reports published by government agencies, commercial organizations, private research foundations, and universities. Selections of this nature must be examined carefully since, for the most part, they represent literature that has not been subjected to any peer review process. For example, an independent assessment of methodology should always be made. The popular literature requires still more caution, since simplifications for the lay audience may blur critical distinctions, either intentionally or unwittingly. Articles written to persuade often downplay facts contrary to chosen sides of emotional issues. Controversial topics are present in drugs and driving, and their treatment in the popular literature deserves close inspection.

In summary, a general caveat included in the parent volume is repeated in this supplement. The reader should be careful to recognize that this selection does not represent an inclusive list of available literature, nor does it define the "state of the art" in drugs-and-driving research. It is believed, however, that the citations and accompanying abstracts present a useful and usable information base and form a valuable research collection.

2.4 Summary of Bibliographic Contents.

Thus far, this section has detailed the technical approach used to compile material for Supplement One. The scope and methods of literature search have been discussed with specific reference to topic areas in drugs and highway safety. This subsection focuses on what was found. A brief overview of the abstract collection presents information about the contents of this bibliography.

A total of 373 abstracts comprise five categories in Appendix D, Abstract Index. The two largest categories are the D and M series. The former collection deals with the general topic of "drugs and driving" and with related topics (e.g., drug usage patterns, drug effects research). Documents in the M series relate to the detection and measurement of drugs in body fluids. Although a detailed analysis of the available literature is not possible here, suggestive characteristics of the abstract collection are noted below.

The Topical Index in Appendix A indicates the relative representation of topical areas in the abstract collection. More experimental than epidemiological research is included. Reports of drug effects on human performance are most often included, but only three involve actual driving. The sheer volume of experimental research is deceptive, however, since the number of drugs and variety of methods are great. Papers that concern drug detection and measurement constitute another significant group of abstracts. Here, a bias toward gas chromatography

is quite noticeable. The large number of citations that concern drug concentrations in body fluids derives mainly from experimental and analytical reports. Relatively few abstracts are found in sections dealing with socio-legal and countermeasure topic areas.

The primary purpose of this report is not analytical, but presentative. Thus, readers desiring a review of literature and a discussion of research in drugs and highway safety are here referred to other reports produced under Contracts DOT-HS-5-01217 and DOT-HS-7-01530. The use of Supplement One, its appendices, and its collection of abstracts is covered in Section 3.0 and in Appendix A.

3.0 USE OF SUPPLEMENT ONE

This section presents in detail the format of the bibliography and the use of its indices.

This bibliography is intended for use as a resource document for research in the field of drugs and highway safety. Its primary aims are as follows:

- to adequately describe the information bases available to researchers in the field of drugs/highway safety;
- to provide a convenient means of access to the relevant literature in specific topic areas; and
- to give an accurate, informative indication of document contents to aid the user in selecting material for specific needs.

To facilitate use of this bibliography, the arrangement of bibliographic material is summarized in the next section. Subsequent sections deal separately with each appendix and the various indices are described.

3.1 Summary of Bibliography Contents

The bibliography consists of several indices in addition to the primary content material. The four sections which comprise the bibliography are presented in appendices as follows:

- Appendix A: Topical Index
- Appendix B: Title Index
- Appendix C: Author Index
- Appendix D: Abstract Index

Each document entered into the bibliography is identified by a unique accession number. The accession number consists of letter-number

combinations, and is used to order the documents presented in Appendix D. In addition, an accession number allows preliminary identification of the general type of subject area of a document as well as the year of its publication. A sample number appears below.

UM-75-D0606

The first two letters (UM) signify that the selection was placed in the file by University of Michigan researchers. A previous designator used in the Selected Bibliography, IU, indicated researchers at Indiana University. All selections in this bibliographic supplement are from the University of Michigan effort and are prefaced by UM.

Immediately following the research designator, a pair of numbers (75) indicates the year of publication (1975). If the selection was presented at a conference, the year of presentation is given. If a document was both presented at a meeting and subsequently published, the publication date is used in the accession number and the selection is cited as published.

The letter preceding the last number set classifies the selection by category. Categories used for this supplement are as follows:

- A Bibliographies
- B Books
- D Articles, papers, and other selections dealing with drugs and driving or closely related topics
- L Materials dealing with legal issues associated with drug research and countermeasures
- M Selections whose content relates directly to the determination and/or the interpretation of drug levels in body fluids (drug analytical methodology, pharmacokinetic studies, clinical studies involving drug concentration-effect relationships, etc.)

The last four digits simply represent the sequential assignment of documents to a given category. Appendix D lists the document abstracts alphabetically by category and sequentially by number within a category.

Other appendices list the accession number in whole or part to allow cross reference to Appendix D.

The following sections describe each index in more detail and provide suggestions for their use.

3.2 Topical Index (Appendix A)

A revised and expanded topical index has been developed to improve user access to document abstracts. To some extent, the changes reflect the reorganization of some topic areas under more general headings. However, the primary intent of the revision was to permit the inclusive citation of all selections in one or more topic areas or categories.

As in the parent volume, the index headings are not mutually exclusive. This has permitted multiple referencing for papers relevant to several topic areas. General categories have been included within the topical index. Used in combination with more specific headings (e.g., a drug name), selections more closely related to user needs may be quickly located. Detailed subheadings have been provided in those topical areas where a large number of selections have been included or where differentiation among closely related subtopics may be of value to the user.

Within the topical index are separate lists of drugs by name and by usage. The drug and chemical list contains two sub-indices. The first and main alphabetical grouping indexes drugs by common, non-proprietary nomenclature, generic or chemical. Chemical names were used to identify a compound only when necessary. A second, less extensive index lists drug substances by trade name or by an acronym in popular use (e.g., LSD). A drug classification scheme, also revised from the Selected Bibliography, arranges those drugs cited in the topical index by usage category. This supplement introduces a cross-referencing system to maximize the usefulness of these lists. Documents pertaining to specific drug substances are cited, for the most part, according to non-proprietary nomenclature.

In the Selected Bibliography, documents cited in the topical index were identified by an abbreviated form of the accession number (e.g., D0606). In this supplement, the date of document publication is also provided for most of the topical index. The drug list citations remain five-character identifiers.

The organization of the topical index is presented in outline form in the first pages of Appendix A. An explanation of each topical heading is provided. The type of documents which may be expected under each heading is described in a general and inclusive manner. Use of the drug and chemical lists is further detailed.

3.3 Title Index (Appendix B)

All selections are listed alphabetically by title in Appendix B. Titles as originally published have been used. Foreign language titles are followed by an English translation in square brackets. The document abstract itself may be consulted to identify the original language.

Associated with each title is the full accession number. If a document is a U.S. Government report, the selection is also identified by the assigned report number. The abstract of the document may be found by referring to Appendix D according to the accession number.

3.4 Author Index (Appendix C)

All names which appear as editors, authors, or compilers have been included in the Author Index. Editors and compilers have been identified by the abbreviations ed. and comp., respectively. The publications associated with each name are identified by accession number. All authors are listed regardless of their order of appearance on the original publication. The year of document publication is also included in this supplement to facilitate bibliography use.

3.5 Abstract Index (Appendix D)

The document abstracts are presented in Appendix D. The general approach followed for abstract preparation is that outlined in "NHTSA Document Analysis Manual," Rev. Ed. (HS-820 085). Within space limitations and constraints appropriate to a subsidiary contract objective, the bibliographic effort has been responsive to requests for increased information content. The following paragraphs describe the format and abbreviations used in preparing the abstracts.

Each document is identified by an accession number located immediately above and to the right of the abstract. (Government documents are further identified by report numbers placed opposite the accession number.) Accession numbers are continued serially from the Selected Bibliography. Headnotes identifying the number of the first and last abstract on each page are provided to facilitate use of Appendix D.

The importance of full, accurate referencing is reflected in document citation. Full titles of articles and other documents have been provided, along with the initials and last names of each author. The journal name has been given in full. Volume and issue numbers, full paging, and date of publication have been included. The corporate author or author affiliation is also given if the selection is other than journal-derived.

In accordance with the aims of the bibliography as a resource document, each abstract is intended to provide an accurate indication of document contents. The primary purpose of the abstract collection is to allow the user to make a preliminary selection of literature relevant to specific needs, eliminating from consideration selections whose main focus is not appropriate. The informative capacity of this abstract collection has been maximized within space and time constraints. Inherent limitations in the bibliographic effort have prevented the preparation of informative abstracts consistent with the length and quality of some abstract services, such as the Highway Safety Literature System.

As in the Selected Bibliography, author-prepared abstracts were used when consistent with the standards described above. Often a journal abstract was modified to include more information. Abstracts were prepared only for those selections without an appropriate synopsis. Abstracts prepared by indexing or bibliographic services were used when author abstracts were not available, or when their use allowed the efficient presentation of more complete information.

In order to inform the reader as to the source of abstracts included in Appendix D, letter combinations signifying the various sources utilized in this bibliography are included in parentheses at the end of each abstract. The following designations are used:

- JA; JAM--Journal Abstract; Journal Abstract Modified
- AA; AAM--Author Abstract; Author Abstract Modified
- AS; ASM--Author Summary; Author Summary Modified
- HSL--Highway Safety Literature
- HSRI--Abstract prepared by HSRI research staff

The designations JA, AA, and AS identify abstracts that were used verbatim. The designations JAM, AAM, and ASM indicate that some modification of the original abstract or summary was made. Most often, additional material was included to increase the information content without altering the main structure of the abstract. If the preparation of the abstract resulted in the significant alteration of an abstract, the designation HSRI was used. Newly prepared abstracts were also given this latter designation.

Additional information regarding each selection is presented below the abstract. If the selection represents a paper presented at a meeting, the author's affiliation is given in the line immediately below the abstract. The corporate author of a report is also given on this line. Another line is used to supply the date of document publication (or presentation), the number of references cited, and

full paging (if not given in the reference above the abstract). The language of the document is indicated and the page containing an English summary is referenced. The sponsoring agency and other information regarding report documents is presented in the final lines below the abstract. Book citations and conference descriptions are also provided below the abstract if not fully referenced above.

TOPICAL INDEX USAGE GUIDE

The organization of the topical index is presented below in outline form. Explanatory paragraphs are associated with each topical and subtopical heading. The purpose of this presentation is to define the scope of each heading in the topical index, and to facilitate the location of relevant documents.

1.0 REVIEWS AND RESEARCH COMPILATIONS

This section contains topic headings pertaining both to general and to specific research areas in drugs/highway safety. In addition, headings indicating certain types of documents are included. The selections for the most part do not report original research. Cited documents not strictly of a review nature do treat subject matter in a general and non-experimental fashion. Collections of research reports and other compilations are cited under the appropriate category. These documents may also be cited under specific research areas elsewhere in the topical index.

1.1 General Drugs/Driving Reviews

These selections deal directly with aspects of the drugs and driving problem. While not all treat the problem in a comprehensive fashion, most documents utilize findings from several research areas in discussing specific topics.

1.2 Drug Research Methodology

Reviews in this subsection deal with the development and/or evaluation of methodology useful in the study of drug effects or in the determination of drugs in body fluids.

1.2.1 Behavior Research Methodology. Documents under this heading pertain to the study of behavior related to driving, or to the methodology used in the assessment of drug effects on human performance.

1.2.2 Drug Analytical Methodology. Reviews related to the determination of drugs and their quantification in body fluids are divided into two categories:

1.2.2.1 Technology. Reviews of methodology not specifically concerned with drug analysis are referenced. "State of the art" assessments of techniques and analytical methods are included.

1.2.2.2 Drug Analysis. Reviews of methods as applied to the analysis of drugs are cited. Articles reviewing available methods for the determination of specific drugs or drug classes are among those included under this heading.

1.3 Drug Effects Research

The study and characterization of drug effects are topic areas included under this heading. Two subtopical divisions differentiate between selections:

1.3.1 Drugs and Drug Classes. Reviews of the biochemical, pharmacological, behavioral, and other effects of specific drugs or drug classes are included.

1.3.2 Drug Concentration-Effect Research. The interpretation of drug levels in body fluids and the characterization of drug concentration-effect relationships are subjects of referenced documents. Selections of a general nature as well as reviews of specific drugs or drug classes are included.

1.4 Epidemiological Research Methodology

Selections dealing with methodological and other research issues related to the epidemiology of drug-related problems are included.

1.5 Selected Reviews

Reviews not specifically related to the above subheadings are cited here. The primary subject matter of each selection is indicated in parentheses.

1.6 Research Compilations

Collections of research reports, monographs, and other unitary aggregations of material related to one or more research areas in drugs/highway safety are referenced. Conference proceedings are included under this heading.

1.7 Bibliographies

Selections include bibliographies which deal generally with drug/driving research and with more specific, but related topic areas.

2.0 EPIDEMIOLOGICAL RESEARCH

Under this general heading, studies related to drug use are cited. Documents are cited under three subheadings according to the following categories:

2.1 Drug/Driving Studies

Research studies directly pertaining to drug use in the driving population are included. The relevant studies are of three general types: direct, analytical assessment of drug use by drivers; questionnaire or other indirect means of investigation; and examination of the driving records of drug user groups.

2.2 Drug Usage Patterns

Documents dealing with drug use by the general population are included.

2.3 Selected Studies

Specific research reports dealing with drug use by special sub-

populations are referenced. The primary subject matter is indicated in parentheses. Most studies concern factors which indicate how and how often certain drugs are used, or by whom drugs are used.

3.0 EXPERIMENTAL RESEARCH

Under this general heading, all studies are included which involve the "laboratory approach" in investigating the effects of drug use. Two complementary subclassification schemes have been developed. First, drug studies are differentiated according to the number of drugs administered to experimental subjects. Second, the documents are cited under subheadings which specify the type of methodology or experimental test used to study drug effects. The drugs used in these studies are cited individually in Section 8.0, Drug and Chemical List.

The combined use of general and specific topic headings allows the user to locate directly those documents closely related to subjects of special concern. For example, psychological studies involving marijuana may be quickly identified by comparing accession numbers under the respective headings. Selections pertaining to this research area are indicated by matching accession numbers. Combined use of more general headings will locate certain types of experimental study, irrespective of the drugs employed.

Specific types of experimental study related to drug concentration-effect relationships as well as investigations involving animal research are also included in this section. Subheadings are described in greater detail below.

3.1 Single Drug Studies

Cited documents include those experiments involving the study of one drug, in addition to placebo. Reports which describe the effects of several drugs, but whose experimental design allowed the separate study of each differentiated as follows:

3.1.1 Analogue Studies. Studies that examine the effects of drugs which have similar chemical structures and are in the same therapeutic class are cited.

3.1.2 Acute Dosage Studies. Investigations of the effects of a drug administered once to experimental subjects are cited. Studies involving both acute and chronic dose regimens are cited under each appropriate subheading. Does-response studies, where single doses of increasing amounts of drugs are administered, are cross-referenced below (3.1.4).

3.1.3 Chronic Dosage Studies. Investigations in which the subjects are administered two or more serial doses of a drug are included. Chronic dosage studies involving the examination of drug effects following the first dose in a series are cited also as acute dosage studies (3.1.2).

3.1.4 Dose-Response Studies. Investigations which examine subject responses to two or more dosage levels of a drug (excluding placebo) are referenced.

3.2 Multiple Drug Studies

Investigations which examine the combined effects of two or more drugs are classified as following:

3.2.1 Drug Interaction Studies. Investigations are cited which deal specifically with the interactions of drugs administered in such a way as their separate effects overlap. Studies include those which attempt to describe the additive effects of drug combinations.

3.2.2 Other Multiple Drug Studies. Miscellaneous reports dealing with drug combinations are included in this section. The interaction of conditions resulting from drug use (e.g., tolerance, enzyme induction) and the effects of specific compounds is a topic cited under this heading.

3.3 Drug Effects Research

Experimental studies involving drug effects in man are cited according to the methodology or to the general test method(s) employed. Specific subheadings are described below.

3.3.1 Driving Task Studies. The evaluation of drug effects on driving performance may be made utilizing the actual driving task or laboratory simulation. Three main subheadings have been used to classify relevant studies:

3.3.1.1 Open Road Tests. Studies in which subjects administered drugs were observed in actual driving situations are included.

3.3.1.2 Closed Course Tests. Cited are studies in which experimental subjects drive a motor vehicle in a closed course or in an area devoid of actual traffic situations.

3.3.1.3 Simulator Tests. All studies are referenced which include a laboratory test, simple or complex, which is designed to replicate, at least in part, the actual driving task. Other tests related to driving skills are cited in Section 3.3.2 below.

3.3.2 Psychophysical Studies. Nearly all laboratory tests of human performance related to driving involve the participation of psychological (or mental) and physical (or somatic) functions. The relative significance of these various functions in a given test is often unclear. Therefore, a series of approximate classifications are used as described. Under this general heading, tests which involve perceptual elements in the measurement of motor or sensory performance specify the inclusion of a document. Those studies involving several different tests are cited under each appropriate subheading.

3.3.2.1 Psychomotor Testing. Investigations which employ tests of psychomotor behavior are cited. Simple and complex tests

of reaction time, tests of balance and steadiness, tracking tasks other than driving simulation, and eye-hand coordination tasks are examples of experimental methods considered to be psychomotor tests.

3.3.2.2 Sensory Function Tests. Studies which use methods which measure sensory functions are included. The critical flicker fusion frequency test and tests of visual and audio acuity are examples of such methods.

3.3.3 Psychological Studies. Investigations are cited which employ tests which measure the effects of drugs on psychological functions. Tests of memory, learning, perception, mood, and mental performance are among those which qualify a document for this classification.

3.3.4 Physiological Studies. Investigations which include the measurement of physiological parameters are cited under this subheading. Galvanic skin response, heart rate, and electroencephalographic effects are specific examples.

3.3.5 Clinical Studies. Investigations are cited which study the effects of drugs in patient groups or which attempt to determine the clinical efficacy of drugs in patients. Those studies employing similar tests to those described above are cross-referenced accordingly.

3.3.6 Self-Evaluation Studies. Investigations which include self-evaluation of drug effects by experimental subjects are included. Subject ratings of the intensity or nature of a drug's effect, or the degree of performance impairment, are examples of the self-evaluation approach which classify documents under this subheading.

3.4 Drug Concentration-Effect Correlation Studies

The need to quantify drug effects by means of objective, chemical measures, and the importance of data interpretation in field surveys of drugs in drivers led to the inclusion of this section

dealing with the topic of drug concentration-effect relationships. Documents are differentiated according to their relevance to drug effects on driving performance:

3.4.1 Investigations of Driving-Related Skills. Cited are studies which attempt to correlate behavioral measures related to the driving task and drug levels in body fluids.

3.4.2 Clinical Investigations. Studies are included which describe the efficacy of therapeutic drugs in terms of drug concentration in the blood or other body fluid.

3.5 Animal Studies

Generally, studies of drug effects in animals were excluded from this bibliography. Documents relevant to the nature of drug effects in man, or which report relevant research involving the incidental use of animals, are included under this subheading.

4.0 DRUG DETECTION AND MEASUREMENT

This general heading includes those topic areas directly or indirectly related to the detection, isolation, identification, or quantitative determination of drugs (and metabolites) in biological liquids. Studies involving the development, evaluation, and application of drug analysis methods are specifically cited.

Main divisions within this general research area reflect whether the methodology has been applied to the screening of one or more drugs in unknown samples, or to the determination of specific drugs known to be present in solution. Within each major subheading, reports are distinguished by the type of techniques used to determine drug presence. Investigations pertaining to the evaluation of analytical methods and to the evaluation of laboratories engaged in drug analysis are cited under separate subheadings as described below.

4.1 General Screening Methodology

Reports concerning the development or application of methodology designed to detect a wide range of drugs with diverse chemical structures are classified according to the following types of techniques:

4.1.1 Thin-Layer and Paper Chromatography. Methods which involve the separation of drugs by paper or thin-layer chromatographic techniques are referenced. Techniques used to confirm or quantitate results of the separation step may be other than paper or thin-layer chromatography.

4.1.2 Optical Techniques. Documents pertaining to methods primarily involving absorption spectrophotometry or spectrophotofluorometry are cited. Common techniques include ultraviolet, visible, and infrared absorption spectrometry, as well as fluorometric procedures.

4.1.3 Gas Chromatography. Methods involving vapor phase column chromatography are included under this heading. Almost without exception, the referenced methods utilize columns containing a high-boiling, inert liquid (stationary phase) coated on a solid support, a techniques specifically called gas-liquid chromatography. A variety of detectors may be used in these methods; however, the special instances in which a mass spectrometer is used as a gas-chromatographic detector are cited in the following section.

4.1.4 Other General Screening Techniques. Methods which involve the application of an analytical technique to general drug screening, and which are not included in the above sections, are cited under this heading. Reports dealing with general drug screening by gas chromatograph-mass spectrometric and high-pressure-liquid-chromatographic techniques are included.

4.1.5 Drug Screening Systems. Screening methods which employ two or more primary analytical techniques in general drug screening

are referenced.

4.2 Specific Screening Methodology

Articles describing methods developed for the specific analysis of individual drugs, small groups of drugs, therapeutic drug classes (e.g., anticonvulsive agents), or chemically-related drugs (e.g., barbiturates) are cited under this heading. The primary purpose of these methods is the detection and identification of specific drugs which may be present in body fluid samples. The differentiation of reports is similar to that used above for general screening methodology:

4.2.1 Thin-Layer and Paper Chromatography. See Section 4.1.1 for an explanation of the topic heading.

4.2.2 Optical Techniques. See Section 4.1.2 for an explanation of the topic heading.

4.2.3 Gas Chromatography. See Section 4.1.3 for an explanation of the topic heading.

4.2.4 Immunochemical Techniques. Analytical methods which are based on immunochemical principles are referenced. Approaches to the immunoassay of drugs include hemagglutination inhibition, radioimmunoassay, free radical, and enzyme techniques.

4.2.5 Other Specific Screening Techniques. Techniques not specifically included in the above sections are included under this heading. "Hybrid" methods, those involving a combination of techniques, are also referenced.

4.3 Methods for Confirmatory/Quantitative Drug Analysis

Included are articles describing analytical methods which are used to confirm the identity of drugs detected by other methods and/or which are used to quantitate specific drugs present in biological liquids. Documents are cited according to specific techniques, as follows:

4.3.1 Optical Techniques. See Section 4.1.2 for an explanation of the topic heading.

4.3.2 Gas Chromatography. See Section 4.1.3 for an explanation of the topic heading.

4.3.3 Gas Chromatography-Mass Spectrometry. Quantitative or confirmatory methods which utilize a gas chromatograph-mass spectrometer (GC-MS) are referenced. Several GC-MS ionization modes, including electron-impact and chemical ionization techniques, may be represented.

4.3.4 Immunochemical Techniques. See 4.2.4 for an explanation of the topic heading.

4.3.5 Other Techniques. Confirmatory/quantitative methods not specifically included in the above sections are included under this heading.

4.4 Analytical Method Evaluation

Articles which deal with the evaluation of drug analytical methodology are cited in one of the two following categories:

4.4.1 Single Method Studies. Included are reports which detail the development and evaluation of drug analysis methods, or which evaluate a method or technique currently available for use.

4.4.2 Intermethod Comparison Studies. Included are reports which describe the evaluation of newly developed methods by comparison with established methods, or which evaluate existing methods (in terms of cost, availability, analytical characteristics, etc.) for specific purposes, e.g., the analysis of morphine.

4.5 Laboratory Evaluation

Documents dealing with the evaluation of analytical performance are included under this heading. Articles are cited under two separate headings:

4.5.1 Quality Control. Intra-laboratory aspects of analytic capability are topics included under this heading. The accuracy and precision of an analytical procedure, as well as consistency of method application are examples of factors involved in quality control.

4.5.2 Proficiency Testing. Documents included under this heading pertain to the external evaluation of laboratories for proficiency in drug analysis. Studies include the multi-laboratory assessment of analytic capability as well as discussions of methodology appropriate for use in proficiency testing.

5.0 DRUG CONCENTRATION IN BODY FLUIDS

The importance of drug concentration data, for data interpretation as well as in the design of drug screening systems, is reflected in this general topic area. Reports which contain drug concentration data or which deal specifically with the determination of drug levels in body fluids are cited under three categories:

- Data compilations (5.1),
- Incidental reports of drug concentrations following drug administration (5.2), and
- Factors which influence the concentration of drugs in body fluids (5.3).

These categories are further broken down as described below:

5.1 Compilations

Reports which contain collections of drug concentration data are cited under two main subheadings as following:

5.1.1 Tabulated Summary Data. Documents which report general data pertaining to therapeutic, toxic, or fatal levels of drugs in body fluids are included.

5.1.2 Epidemiological Data. Collections of drug concentration data which result from original research are cited according

to the following populations:

5.1.2.1 Drugs in Drivers. Investigations of actual drug levels in the body fluids of drivers are cited.

5.1.2.2 Drugs in Patients. Drug concentration data obtained from patients, including drug-overdose victims, are contained in referenced documents.

5.1.2.3 Drugs in Others. Drug concentration data collections not specifically included above are cited. Reports primarily deal with the determination of drug blood levels in drug-involved deaths.

5.2 Specific Reports of Human Drug Concentration Data

Articles in which the determination of drug body fluid levels followed the administration of one or more dosage levels are here cross-referenced according to the mode of drug administration, and according to the type of study in which these determinations were made:

5.2.1 Acute Dosage Studies. Investigations in which drug concentration determinations were made following a single drug dose administration are cited. Studies which involve the one-time administration of a drug to experimental subjects described as a "chronic users" are included under this heading.

5.2.2 Chronic Dosage Studies. Investigations in which drug concentration determinations were made following two or more dose administrations are cited.

5.2.3 Pharmacokinetic Studies. More extensive investigations into the level of drugs in body fluids as a function of time after drug administration are included under this heading. Relevant reports are classified according to the mode of drug administration:

5.2.3.1 Acute Dosage Studies. See Section 5.2.1 for an explanation of the topic heading.

5.2.3.2 Chronic Dosage Studies. See Section 5.2.2 for an explanation of the topic heading.

5.2.4 Body Fluids Correlation Studies. Investigations which attempt to correlate human drug levels in two or more body fluids are referenced. Experiments usually involve the simultaneous collection of different body fluid samples following the administration of a single drug.

5.3 Factors Influencing Drug Levels in Body Fluids

Articles dealing with background variables which influence drug levels are included under this heading. Both experimental reports and review documents are cited according to the following subheadings:

5.3.1 Absorption and Distribution Factors. Reviews and studies of variables which operate during the pharmacokinetic phases of drug absorption and distribution are cited. The relationship of bioavailability in drug formulation and variability of patient response, and the influence of simultaneous food intake on resulting drug levels are examples of specific topics.

5.3.2 Metabolism Factors. Factors such as metabolic enzyme induction and inhibition and the first-pass metabolism of administered drugs are included under this heading.

5.3.3 Analytical Factors. Documents which discuss the influence of analytical methods on the objective determination of drug levels in body fluids are cited.

5.3.4 General. Articles which deal in a general way with this topic area, or which deal with factors not specified above, are included under this heading.

6.0 SOCIOLEGAL STUDIES

Documents which deal with specific or general sociolegal issues related to drugs and highway safety are referenced under this heading.

For example, research programs dealing with the drug/driving problem are subject to critical legal and ethical constraints. Topical headings such as

- Experimentation with Human Subjects,
- Informed Consent,
- Researcher Privilege, and
- Right of Privacy and Confidentiality

are included in this section.

7.0 COUNTERMEASURES IN DRUGS/HIGHWAY SAFETY

Articles which specifically discuss the development, evaluation, and implementation of drug countermeasures are referenced. Discussions of methodological issues related to these countermeasure topic areas are also included.

8.0 DRUG AND CHEMICAL SUBINDEX

The overall objective of this section is to provide a list of significant sources of information pertaining to individual drugs, their effects on driving behavior, and their determination in body fluids. Documents are cited according to each specific drugs involved in a study or discussed in an article. In general, studies have not been cited if a particular drug has been mentioned in an incidental or anecdotal manner. This exclusion also applies to analytical papers dealing with general drug screening. However, general methods applicable to specific drugs were cited under each appropriate drug name.

Separate lists of drugs comprise this subindex. In the following subsections, drugs are arranged alphabetically by chemical or generic name and by trade or other name, respectively. Some drugs are included in both lists to provide easier access. Primarily, citations are made using the generic or other common name (Section 8.1). Citation of relevant documents by the trade name

of certain pharmaceutical compounds was done only when necessary for a drug with no single generic or chemical name. Cross-indexing of drug names to a drug classification scheme is a special feature of this subindex.

The drug lists are discussed further in the following subsections.

8.1 Generic and Chemical Nomenclature List

Drugs identified in experimental, analytical, or other types of study have been placed in alphabetical order by generic or, if necessary, by chemical name. Other standardized equivalent names and trade names (R) follow in parentheses. Numbers which immediately follow the drug names refer to specific drug classes. To identify common therapeutic or other uses of each drug, user may refer to Section 9.0, Drug Classification, described below.

The documents containing information about the drug are listed by accession number. As indicated in Section 3.1, main categories of documents are identified by these letter-number combinations. The two most common letters classifying selections are the following:

- D, generally pertaining to drug effects research related to drugs and driving.
- M, generally pertaining to documents emphasizing either analytical methodology, or to articles dealing with methodological issues indirectly related to the determination or interpretation of drug levels in body fluids.

An asterisk (*) beside an accession number indicates that the cited document contains information regarding drug levels in body fluids or reports the experimental determination of drug levels following administration to human subjects.

8.2 Trade (R) or Other Identifying Name

This subsection lists drugs by trade name or by other common designators. Listed alphabetically, the trade names provide entry to the generic and chemical nomenclature list (Section 8.1) by

cross-referencing. Documents are only cited for those drugs or drug compounds without a single generic or chemical name. These latter drugs are cross-indexed to Section 9.0, Drug Classification.

9.0 DRUG CLASSIFICATION

The purpose of this section is to aid the user in identifying common therapeutic uses of a drug and to provide a succinct listing of identified drugs by type. A revised classification scheme was developed for this bibliographic supplement.

In general, drugs have been classified by main therapeutic actions (effects). Some classifications, such as that for marijuana, reflect the unique status of a drug substance. Some drugs with multiple effects and uses, such as atropine, have been classifiel under general pharmacological categories.

Drugs of interest may be located by name in either Section 8.1 or 8.2.

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8.0 DRUG AND CHEMICAL SUBINDEX

8.1 Generic and Chemical Nomenclature List

8.2 Trade(^{R}) or Other Identifying Name

9.0 DRUG CLASSIFICATION

9.1 Analgesics and Antipyretics

ACC (aspirin, caffeine, codeine compound)

acetylsalicylic acid (aspirin)

antipyrine

codeine

indomethacin (Indocin^{R})

pentazocine

phenylbutazone

propoxyphene (Darvon^{R})

9.2 Anesthetics

Althesin^{R}

bupivacaine

etidocaine

hexobarbital

lidocaine (Xylocaine^{R})

methohexital

propanidid

thiopental

9.3 Anorectics

amphetamine

dextroamphetamine sulfate (Dexedrine^{R})

methamphetamine

phentermine

9.4 Antacids

Maalox^{R}

9.5 Anticonvulsants

carbamazepine

clonazepam

ethosuximide

mephenytoin

mephobarbital

metharbital

methsuximide

phenobarbital

phensuximide

phenytoin (diphenylhydantoin) (Dilantin^{R})

primidone

9.6 Antidepressants

amitriptyline (Elavil^{R})

chlorimipramine

desipramine (Pertofrane^{R})

desmethylchlorimipramine

dothiepin

doxepin (Sinequan^{R})

imipramine (Tofranil^{R})

nortriptyline (Aventyl^{R})

trimipramine

viloxazine

9.7 Antihistamines

dexchlorpheniramine

diphenhydramine (Benadryl^{R})

meclastine

9.8 Antinauseants

benzquinamide

perphenazine

prochlorperazine (Compazine®)

9.9 Tranquilizers

9.9.1 Neuroleptic Agents

chlorpromazine (Thorazine®)

dipiperon

droperidol

flupenthixole

haloperidol (Haldol®)

methotrimeprazine

methylperone

perphenazine

prochlorperazine (Compazine®)

promazine

thioridazine (Mellaril®)

thiothixene

trifluoperazine (Stelazine®)

trifluperidol

triflupromazine

9.9.2 Ataractics

benzquinamide

bromazepam

chlorazepate (clorazepate)

chlordiazepoxide (Librium®)

clobazam

desmethylchlordiazepoxide

desmethyldiazepam

diazepam (Valium^{R})

doxepin

medazepam

meprobamate (Miltown^{R})

hydroxyzine

lorazepam

mebutamate

methyperone

oxazepam

prazepam

tybamate

Tranquil^{R}

9.10 Cannabis and Related Substances

cannabidiol

cannabis sativa

delta-9-tetrahydrocannabinol

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marijuana

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VISUAL SEARCH BEHAVIOR WHILE VIEWING DRIVING SCENES UNDER THE INFLUENCE OF ALCOHOL AND MARIHUANA, H. Moskowitz; K. Ziedman; S. Sharma, Human Factors v18 n5 p417-32 (Oct 1976)

UM-74-D0584

VOLATILE SOLVENT ADDICTION AND TRAFFIC SAFETY, M. Bauer; J. Molčan, Activitas Nervosa Superior (Praha) v16 n3 p178-9 (1974)

DHEW(ADM)76-311 UM-76-D0561

YOUNG MEN AND DRUGS - A NATIONWIDE SURVEY, J. A. O'Donnell; H. L. Voss; R. R. Clayton; G. T. Slatin; R. G. W. Room, NIDA Research Monography 5 (Feb 1976)

AUTHOR INDEX

Author Index Continued

Author Index Continued

Author Index Continued

UM-59-D0599

BEHAVIORAL EFFECTS OF CHRONIC ADMINISTRATION OF PSYCHOACTIVE DRUGS TO ANXIOUS PATIENTS, L. Uhr; J. C. Pollard; J. G. Miller, Psychopharmacologia v1 p150-68 (1959)

Experiments were performed to investigate chronic drug effects on a sample of patients psychiatrically diagnosed as anxiety neurotics. The effects of chronic administration of meprobamate (1600 mg), an over-the-counter bromide mixture (Tranquil), and placebo were examined in a counterbalanced partially blind design. Thirty-two subjects, including 23 anxious patients, employed as their own controls, were given behavioral tests, psychiatric interviews, and ratings after each of three twenty-one day periods. Among the behavioral evaluations were a driver test, vision tests, attention span, and muscular persistance.

Both meprobamate and Tranquil slowed reaction times in simulated driving at high speeds accompanied by decreased accuracy. Both compounds produced significant psychological reactions. While patients' self-ratings did not differentiate betweeen the compounds, ratings by observers indicated decreased anxiety under meprobamate and decreased symptoms under both treatments. (HSRI)

1959 23refs

UM-73-D0600

THE EFFECTS OF CERTAIN TRANQUILIZERS AND ALCOHOL UPON KINETIC VISUAL ACUITY, A. B. Clayton; G. M. Mackay; T. A. Betts, in Proceedings of Sixteenth Conference of the American Association for Automotive Medicine, New York: Society of Automotive Engineers, Inc., 1973, p199-215

This paper concerns the effects of four commonly prescribed tranquilizers (trifluoperazine, chlordiazepoxide, haloperidol, amylobarbitone sodium) and small amounts of alcohol on kinetic visual acuity (KVA)--the ability to perceive a moving object travelling towards the eye at a constant speed in a fully-randomized double-blind procedure; a fifth group received double-placebo treatment. Within each treatment, the subjects were also tested with and without alcohol (0.5 g/kg b. wt.). Five doses of drug were administered over two days before testing.

Amylobarbitone (30 mg/dose) and chlordiazepoxide (10 mg/dose) produced some improvement in KVA values. Trifluoperazine (2 mg/dose) produced significant impairment in KVA values for male subjects and for female subjects under alcohol. Haloperidol produced different effects: improvement in male subjects but significant deterioration in female KVA values. Alcohol did not produce a significant overall effect upon KVA. If significant changes in KVA values occur in the real driving situation then a potential danger may exist. It is suggested that physicians should warn patients of the possible danger in driving during the early stages of treatment. (AAM)

1972 25refs

UM-76-D0601

INCIDENCE OF DRUGS AND ALCOHOL IN FATALLY INJURED MOTOR VEHICLE DRIVERS, J. C. Garriott; V. J. M. DiMaio; R. E. Zumwalt; C. S. Petty, Journal of Forensic Sciences v22 n2 p383-9 (Apr 1977)

Analyses of blood samples obtained in connection with motor vehicle accident fatalities were reported and used to determine drug usage at the time of death. Of the drivers, 70% were positive for alcohol or drugs. Ethyl alcohol alone was detected in 52%; drugs in 9%, and both drugs and alcohol in another 9%. Seventy-six percent of the drivers determined to be at-fault in their respective accidents had alcohol or drugs compared to 41% for not-at-fault drivers. The minor tranquillizer diazepam accounted for over half of all positive drug findings.

UM-76-D0596

THE EFFECTS OF PSYCHOTROPIC DRUGS UPON DRIVING-RELATED SKILLS, A. B. Clayton, Human Factors v18 n3 p241-52 (Jun 1976)

The use of psychotropic drugs by drivers was considered to be on the increase although little accurate epidemiological data was available. To determine the effects of such drugs upon driving skills, reliance had to be placed upon laboratory investigations. This paper reviewed the results of studies of the effects of barbiturate and non-barbiturate hypnotics, tranquilizers, and antidepressants upon sensory functions and perceptual skills, cognitive skills, and motor skills. The relationship between such skills and actual driving performance, and some possible mechanisms whereby psychotropic drugs might contribute to the causation of accidents, were discussed. In view of the wide variety of drugs, dose levels and test situations used, few definite conclusions could be drawn regarding the effects of psychotropic drugs upon driving-related skills. (JA)

1976 54refs

UM-71-D0597

THE PRESCRIBING OF PSYCHOTROPIC DRUGS IN GENERAL PRACTICE, P. A. Parish, The Journal of the Royal College of General Practitioners v21 n92 Supplement No. 4 (Nov 1971)

The author examined national prescribing trends of psychotropic drugs and discussed the annual increase with particular reference to four drugs which contributed to the increase. Psychotropic drug prescribing patterns and habits of a group of general practitioners was analyzed. Influences which affect prescribing in general practice were delineated. An overview of the facts and opinions contained within the first three sections of the report developed further ideas about sales promotion and the role of education, especially in the areas of psychiatry and therapeutics. The report concluded by asking pertinent questions about prescribing in general practice and stressed the need for any future research to include sociological studies. (HSRI)

1971 77p 98refs

UM-75-D0598

THE INFLUENCE OF SEX AND PERSONALITY FACTORS UPON THE EFFECTS OF TRANQUILLIZERS ON DRIVING PERFORMANCE, A. B. Clayton; T. A. Betts; P. G. Harvey, in Proceedings of the 6th International Conference on Alcohol, Drugs, and Traffic Safety, S. Israelstam; S. Lambert, eds., Addiction Research Foundation of Ontario, Toronto, Canada, p415-22 (1975)

This paper described analysis of experimental data in an attempt to assess the influence of sex, certain personality factors and four psychotropic drugs on two actual driving tasks. In a double-blind cross-over design, four groups of twenty subjects, mainly student volunteers, were tested on two separate occasions after having taken five doses of an active drug or placebo in 36 hours. Chlordiazepoxide (10 mg), amylobarbitone (30 mg), trifluoperazine (2 mg), and haloperidol (0.5 mg) were used in the study.

A weaving task and a gap estimation task were performed in an off-highway situation using a small saloon car with a manual gearbox. The results clearly demonstrated that interactions did occur between the drug used, the skill measured, and the sex and personality of the drivers. The results were discussed in light of previous work and proposed models. (HSRI)

Dept. of Transportation and Environmental Planning, Univ. of Birmingham, Edgbaston, Birmingham 15, England.

1974 9refs

Presented at the 6th International Conference on Alcohol, Drugs and Traffic Safety, 8-13 September 1974, Toronto, Canada.

acuity" (KVA), the ability to see an object approaching from ahead, was reported. The newer model was tested for its suitability as an instrument to measure visual aptitude. In addition, KVA as a driver-related function was investigated.

Professional drivers (153 highway patrol officers) were found to have higher values for both "static visual acuity" (SVA), the basic ability to see, and KVA than a group of 540 nonprofessional male motorists aged 14 to 65, selected by a nondiscriminative sampling survey. Using a criterion based on SVA and KVA values and their difference, two subgroups were formed of the professional drivers, and their accident records were compared. Accident frequency was very much less in that group having the better visual aptitude rating. Eventual reduction in accident frequency was associated with improvement of eye conditions and correction of functional abnormalities which affected KVA but not SVA. A procedure for testing subjects was outlined, and criteria for licensing drivers were suggested. (HSRI)

1968 5refs

UM-58-D0594

PERSONALITY DIFFERENCES AND CONTINUED MEPROBAMATE AND PROCLORPERAZINE ADMINISTRATION, E. L. Kelly; J. G. Miller; D. G. Marquis; R. W. Gerard; L. Uhr, A. M. A. Archives of Neurology and Psychiatry v80 p241-6 (Aug 1958)

Individual personality differences among 51 normal subjects related to behavioral effects from continued administration of meprobamate or proclorperazine were investigated. Fifty-one behavioral scores were obtained for all subjects, and a representative group of forty of these scores was selected for the analysis presented in this paper. Twenty of the 69 personality scores obtained through objective personality tests were selected on the basis of a factor-analytic study.

The study demonstrated no adverse effects of continued administration of double the standard dose of meprobamate on driving skills, perception, or any of a wide range of objectively measured behaviors either for normal subjects as a whole or for such subjects characterized by any of personality variables studied. Similar results were obtained with proclorperazine. (HSRI)

1958 14refs

UM-61-D0595

A CONTROLLED CLINICAL STUDY OF CHLORDIAZEPOXIDE, A. Z. Schwartzberg; R. W. Van de Castle, American Journal of Psychiatry v117 p922-3 (Apr 1961)

A controlled clinical study of chlordiazepoxide ("Librium") was reported. Twenty-one patients with a diagnosis of psychoneurosis or personality disorder with significant anxiety and tension components were divided into three carefully matched groups. Each patient served as his own control. Chlordiazepoxide (10 mg), meprobamate (400 mg) and placebo were taken for two weeks, t.i.d. Tests were administered before the start of the medication schedule and re-administered at two week intervals to measure anxiety parameters.

It was found that 79% of patients reported improvement while receiving placebo, 89% with meprobamate, and 74% with Librium. It was considered possible that changes in anxiety indices might have occurred as a simple function of participating in a drug study. The need for control groups in drug studies was emphasized. (HSRI)

1961 5refs

UM-62-D0590

THE EFFECTS OF METHAMPHETAMINE AND PENTOBARBITAL ON TWO MEASURES OF ATTENTION, G. C. Quarton; G. A. Talland, Psychopharmacologia v3 p66-71 (1962)

The effects of methamphetamine (15 mg/150 lb, i.v.), pentobarbital (100 mg/150 lb, i.v.), and placebo on two measures of attention were studied in 36 male student volunteers. Each subject served as his own control and was tested under each treatment. The results suggested that barbiturate does interfere with the capacity of the human subject to attend maximally as measured by the running digit span test, but the effects of methamphetamine on this function and the effects of both drugs on the focus of attention (modified Stroop test) could not be demonstrated by the methods employed. Further experimental work was considered necessary to determine the effects of drugs on the different parameters of attention. (AAM)

1962 5refs

UM-71-D0591

THE EFFECTS OF DIAZEPAM OR DIPHENHYDRAMINE ON HEALTHY HUMAN SUBJECTS, A. Jäätelä; P. Männistö; H. Paatero; J. Tuomisto, Psychopharmacologia (Berlin) v21 n3 p202-11 (Sep 1971)

The immediate effects on the mood and some mental and physical functions of a single oral dose of diazepam (10 mg) and diphenhydramine (50 mg) compared with placebo were studied in healthy human subjects. The subjects, 270 students, were divided into three similar groups. The mood was tested by the Nowlis adjective checklist; the digit symbol test and number series were used to test mental condition.

Diazepam decreased activity both in men and women and sociability in women. It increased euphoria in men and depressivity and withdrawing in women. It impaired the results in the digit symbol test and the ability to repeat the number series in both men and women. Diphenhydramine also decreased activity in men and women. It caused some euphoria in men. It had a slighter depressing effect on mental function than diazepam. (JAM)

1971 16refs

UM-70-D0592

PERSISTENT BEHAVIOURAL AND ELECTROENCEPHALOGRAPHIC CHANGES AFTER SINGLE DOSES OF NITRAZEPAM AND AMYLOBARBITONE SODIUM, A. Malpas; A. J. Rowan; C. C. R. B. Joyce; D. F. Scott, British Medical Journal v2 n5712 p762-4 (27 Jun 1970)

In a double-blind cross-over trial the effects of nitrazepam (5 and 10 mg), amylobarbitone sodium (100 and 200 mg), and placebo were compared in normal healthy young people. Though they reported a good night's sleep and adjudged themselves to be alert after all four drug treatments, behavioral tests (card sorting) showed their performance to be significantly impaired 13 hours after treatment with nitrazepam or amylobarbitone. EEG records showed more drowsiness and light sleep 18 hours after treatment with nitrazepam than with amylobarbitone or placebo. EEG fast activity was more plentiful after drugs in either dosage than with placebo. (JAM)

1970 17refs

UM-68-D0593

THE TRIAL PRODUCTION OF A KINETIC VISION TESTER (TYPE AS-4A) AND ITS APPLICATION, A. Suzumura, Annual Report of the Research Institute of Environmental Medicine, Nagoya University v16 p77-88 (1968)

The development of an improved apparatus designed to assess "kinetic visual

UM-59-D0587

THE INFLUENCE OF AMOBARBITAL (AMYLOBARBITONE) AND METHAMPHETAMINE ON THE FOCUS OF ATTENTION, E. Callaway, III, Journal of Mental Science v105 n439 p382-92 (Apr 1959)

A combination of the Stroop color-word interference test and Witkin's colored Embedded Figures test was used to assess the influence of drugs on the focus of attention. In this study methamphetamine was found to narrow attention and amobarbital was found to broaden attention.

A theoretical basis for expecting a correlation between measures of narrowed attention and the Maudsley Inventory measure of introversion was presented. The data, however, failed to bear out such a supposition since the observed correlations between measures of narrowed attention and introversion were significantly negative. The significance of the results, as well as certain reservations, were discussed. (HSRI)

1959 25refs

UM-63-D0588

THE EFFECT OF BENZQUINAMIDE, IN COMPARISON WITH CHLORDIAZEPOXIDE AND PLACEBO, ON PERFORMANCE IN SOME PSYCHOLOGICAL TESTS, G. Holmberg; U. William-Olsson, Psychopharmacologia v4 p402-17 (1963)

Benzquinamide (200 mg, "Quantril") was compared with chlordiazepoxide (60 mg, "Librium") and placebo in a double-blind acute experiment. A battery of psychological tests were administered to 20 young, healthy women before and one and two hours after ingestion. Tests included auditory span, coordinator test, cancellation test, flicker fusion frequency, mental arithmetic, and standing steadiness. Verbalizations of the subjects' experience were collected immediately following the experiment and the next day.

Among the results, both drugs depressed the flicker fusion frequency, while benzquinamide exerted more of a depressant effect than chlordiazepoxide in other tests. In a direct comparison between the two active drugs, the outcome was in favor of chlordiazepoxide on all significant points. Chlordiazepoxide did not impair psychological performance to any great extent when given in a single dose. In several subjects, euphoria and a long-lasting tendency to fall asleep were observed. (HSRI)

1963 15refs

UM-63-D0589

CHLORDIAZEPOXIDE, DIPIPERON AND AMOBARBITAL. DOSE EFFECT STUDIES ON HUMAN BEINGS, C.-M. Ideström; B. Cadenius, Psychopharmacologia v4 p235-46 (1963)

The effects of amobarbital, chlordiazepoxide, and dipiperon on 21 healthy subjects were studied with a double-blind technique and experimental-psychological tests. Those tests employed were a choice reaction-time test, tapping-speed, flicker fusion (CFF), hand-coordination, standing steadiness, counting and discriminating tones (level of attention test). Dose-response results for each of the drugs were presented.

The experiments showed that the administration of chlordiazepoxide and dipiperon causes an impairment of certain psychological functions, and that the effects are in direct relation to dose. Psychomotor functions were less sensitive than perceptive functions to the effects of chlordiazepoxide and dipiperon. The functions in most tests were impaired by 150 mg of amobarbital, but improved by 300 mg, and definitely impaired by 450 mg; this was paralleled by the results of the CFF test. The significance of the latter results was discussed in terms of the addiction liability of psychopharmaca. (HSRI)

1963 14refs

UM-74-D0584

VOLATILE SOLVENT ADDICTION AND TRAFFIC SAFETY, M. Bauer; J. Molčan, Activitas Nervosa Superior (Praha) v16 n3 p178-9 (1974)

The inhalation of volatile solvents and their deleterious effects on the central nervous system were discussed. The relevant symptomology of solvent intoxication for traffic safety was presented, and included emotional and perceptual disturbances, alterations of consciousness, and behavioral toxicity. The metabolism and detection of toluene and trichloroethylene were briefly treated. The inhalation of volatile solvents is clearly detrimental to driving performance; reliable and rapid analytic methods are available to assess their presence in body fluids or the expired air. (HSRI)

1974

UM-73-D0585

BEITRAG ZUM NACHWEIS DER KOMBINIERTEN EINNAHME VON ALKOHOL UND ARZNEIMITTELN (DETERMINATION OF COMBINED INGESTION OF ALCOHOL AND DRUGS), M. R. Möller; K. H. Witzmann; D. Tausch, Beitrage zur Gerichtliche Medizin v31 p259-66 (1973)

By means of a new analytical procedure, the assertions made by drivers concerning the use of drugs were checked using the test blood remaining after the determination of blood alcohol concentrations. Extraction of blood by means of one-way extraction columns and the fully automatic gas chromatographic injections were followed by separation on one of several different columns and detection with a nitrogen-sensitive flame-ionization detector. It was found that in 10% of the cases, the drugs declared could be qualitatively and quantitatively specified. The procedure offered the possibility of detecting drugs at therapeutic levels, and required much less time than traditional analyses. (JAM)

1973 7refs [German]

UM-75-D0586

CHARACTERISTICS OF HEAVY USERS OF OUTPATIENT PRESCRIPTION DRUGS, S. V. Lech; G. D. Friedman; H. K. Ury, Clinical Toxicology v8 n6 p599-610 (Dec 1975)

Users of prescription drugs, both heavy (8 or more different drugs) and light (1 or 2 different drugs) in a three month period, were identified using computer-stored pharmacy data, and compared for medical and social characteristics. Drug dispensing data, collected by a drug reaction monitoring system in the Kaiser-Permanente Medical Center in San Francisco, was used to describe the drug usage patterns in outpatients.

Compared with 99 light users, 158 heavy users were more likely to be older, female, and white; and to have blue collar occupations, if male, or to be housewives, if female. Heavy drug use was associated with greater use of other medical care and was usually a persistent characteristic. Prepayment for drug prescriptions was not associated with heavy use; only a small percentage of patients had histories of frank drug abuse. Among heavy users were found some severely ill individuals, and some with emotional problems that appeared to contribute to symptoms and requests for drugs. In a 21-month period, adverse drug reactions were experienced by 28% of heavy users as compared with 8% of light users. The type of drug most often prescribed to heavy drug users were sedative-hypnotic agents. (AAM)

1975 10refs

case led to a fruitful dialogue from which emerged increased awareness and understanding of the complexity of the problem. Essential in this process was a recognition of the need for a treatment component, and a relaxing of the traditional antagonism between treatment and punishment advocates.

Characteristics and drinking practices of those persons participating in the study were presented. The necessity of introducing compulsion and close supervision into a treatment program was recognized, as well as the requirement for individualized design according to a person's needs. The results of the study were discussed and related to the apparent failure of the criminal justice system to deal effectively with the problem of drinking and driving. (HSRI)

1975 24refs

UM-76-D0582

TOXICOLOGICAL FINDINGS IN VICTIMS OF TRAUMATIC DEATHS, M. L. Bastos; L. Galante, Journal of Forensic Sciences v21 n1 p176-86 (Jan 1976)

Presented were the toxicological findings from 6037 analyses of viscera obtained from victims dying under established or suspected violent circumstances in New York City during a two year period, 1973-1974. The relative incidence of carbon monoxide, ethyl alcohol, narcotics, hypnotics, analgesics, and tranquillizers-antidepressants in deaths under a variety of traumatic circumstances was given, as were tissue concentrations of drugs found in the victims.

Ethanol alone and in combination with other drugs was present in 42.3% and 19.5% of driver and pedestrian victims, respectively, of vehicular accidents in the year 1974. New York City and Detroit data are comparatively analyzed for victims of homocide and the incidence of drugs. Tissue concentrations of drugs found in victims of traumatic death were also presented. Drugs found in normal therapeutic levels included diphenylhydantoin, diazepam, meperidine, and slow-acting barbiturates. Amitriptyline, chlorpromazine, propoxyphene, short-acting barbiturates, and methadone were present in higher concentrations. (AAM)

1976 44refs

(ADM)76-314 UM-76-D0583

MARIHUANA AND HEALTH. FIFTH ANNUAL REPORT TO CONGRESS FROM THE SECRETARY OF HEALTH, EDUCATION, AND WELFARE. 1975, National Institute on Drug Abuse, Washington, D. C.: U. S. Governement Printing Office, 1976

This volume represents the fifth in a series of annual reports to Congress concerning marihuana. The report was issued as a general overview accompanied by nine technical chapters which discuss research findings in the following areas: epidemiology of marihuana use, merihuana chemistry and metabolism, pharmacology, toxicology, and behavioral effects in animals and man. The purpose of the report was to provide a broader perspective than in past years for both the general reader and research specialists.

Evidence had been obtained that cannabis use had significantly increased among Americans during the last two years. Cannabinoid chemistry was increasingly appreciated as complex. Reliable and sensitive methods were still required for the detection and analysis of marihuana constituents in clinical areas and for roadside use. Some potentially useful methods were currently under development and testing. The effects of marihuana in man were discussed in terms of acute effects and the longer range consequences of regular or chronic use. The therapeutic aspects of marihuana, both historical and current, were reviewed. (HSRI)

1976 145p 639refs

DHEW/(ADM)76-314

Since all the hypnotics studied interacted with alcohol taken the next morning, it was concluded that any of these combinations was deleterious to driving. (JAM)

1973 16refs

UM-73-D0579

RAUSCHMITTELGENUSS UND LEISTUNGSFÄHIGKEIT (THE USE OF INTOXICANTS AND PERFORMANCE), J. G. Gostomzyk; P. Parade; H. Gewecke, Zeitschrift fur Rechtsmedizin v73 n2 p131-36 (1973)

Physiological and psychophysical tests were performed on habitual smokers of hashish. In different psychophysical tests of skills related to driving, hashish did not cause a significant delay of the responses but rather an increase of errors. The experience of intoxication and its intensity was found to depend strikingly on "set and setting." A high degree of compensation for the effects of hashish was observed when functional performance was required.

Factors of respiration and circulation were measured during rest and physical exercise under control and drug conditions. Pulse rate increased but blood pressure and oxygen consumption remained unchanged. Changes in respiration under the influence of hashish seemed to play a major role in the developing experience of intoxication. It was suggested that the regulation of hashish intoxication could be explained by the correction of respiratory acidosis under voluntary hyperventilation. (JAM)

1973 13refs [German]

English summary on p131.

UM-74-D0580

EFFECT OF TREATMENT WITH DIAZEPAM OR LITHIUM AND ALCOHOL ON PSYCHOMOTOR SKILLS RELATED TO DRIVING, M. Linnoila; I. Saario; M. Mäki, European Journal of Clinical Pharmacology v7 n5 p337-42 (Aug 1974)

The effects of diazepam (5 mg t.i.d.) or lithium administered for two weeks on psychomotor skills was examined in 20 healthy male volunteers. The drugs were administered either with alcohol (0.5 g/kg) or a placebo. Psychomotor skills were measured by a choice reaction test, two coordination tests and an attention test. Serum drug concentrations and blood alcohol levels were also measured.

Alcohol impaired all the psychomotor factors tested. Diazepam improved the choice reaction test performance and slightly enhanced eye-hand coordination. Lithium impaired the choice reaction performance. Alcohol and diazepam potentiated each other's harmful effects, while lithium tended to antagonize the effects of alcohol, except on coordination. The combination of alcohol in the dose administered and lithium was considered potentially dangerous in motor vehicle drivers. Alcohol and diazepam together also had a very deleterious effect on psychomotor skills related to driving. (JA)

1974 16refs

UM-75-D0581

UNDER THE INFLUENCE, E. W. Fine; P. Scoles; M. Mulligan, Public Health Reports v90 n5 p424-9 (Sep/Oct 1975)

The objective of this study was to investigate the incidence and severity of alcohol and drug use and abuse in a population of persons arrested in the City of Philadelphia for the first time for driving while intoxicated (DWI). The authors emphasized the pressing need for a collaborative effort by all concerned agencies and the criminal justice system in developing alternative mechanisms for managing the problems of DWI offenders. Cooperation in this

UM-75-D0576

FACTORS INFLUENCING THE INTERPRETATION OF DRUG CONCENTRATION IN ACUTE DRUG OVERDOSAGE, E. M. Sellers, in Clinical Pharmacology of Psychoactive Drugs, E. M. Sellers, ed., Addiction Research Foundation of Ontario, p73-86 (1975)

While the therapeutic effectiveness of some drug classes has been improved by studies which have defined their therapeutically effective or toxic range of serum concentration, for most psychoactive drugs this was not shown to be the case. Poorly designed, uncontrolled clinical studies were cited as the reason. Factors contributing to the large individual differences in the relationship between the dosage of a drug, serum concentration and intensity of its pharmacological action were then discussed.

The author offered guidelines for determining serum concentrations in acute drug overdose cases. He concluded that there was still need to further reduce the morbidity and mortality due to acute drug ingestion; to develop clinically useful measures of psychoactive drug effects; to define more exactly the relation of concentration and response in serious overdose; to quantitate the individual variations of elimination rates of psychoactive drugs; to determine the frequency and importance of multiple drug ingestion and drug interactions; and to study alternative forms of therapy. (AAM)

1975 12refs

Presented at the symposium "Clinical Pharmacology and Toxicology of Psychoactive drugs," held Oct. 22-24, 1973, at the Clinical Inst., Addiction Res. Foundation, Toronto.

UM-76-D0577

ALCOHOL AND OTHER DRUGS RELATED TO YOUNG DRIVERS' TRAFFIC ACCIDENT INVOLVEMENT, P. C. Whitehead; R. G. Ferrence, Journal of Safety Research v8 n2 p65-72 (Jun 1976)

Studies are cited which indicate more young people are driving under the influence of alcohol and drugs. Rising collision rates, especially in conjunction with lowered drinking age, offer evidence of the problem's extent. The paper examined patterns of driving, drinking, and drug-taking among young people and assessed hypotheses linking these behaviors to collision involvement. The implications for social policy of current knowledge about these problems were discussed in terms of approaches that stress primary prevention. Specific recommendations were offered for legal changes to reduce the incidence of alcohol- and drug-related damage among young people. (JAM)

1976 43refs

UM-73-D0578

DRUG INTERACTION ON PSYCHOMOTOR SKILLS RELATED TO DRIVING: HYPNOTICS AND ALCOHOL, M. Linnoila, Annales Medicinae Experimentalis et Biologiae Fenniae v51 n3 p118-24 (1973)

The effects of nitrazepam, diazepam, ethinamate, and bromvaletone administered the previous evening were studied the next morning on 260 volunteer students and policemen. Psychomotor skills were measured by a choice reaction test, two coordination tests, and an attention test. In addition, their interaction with alcohol was tested.

Nitrazepam impaired the psychomotor performance of middle-aged subjects. Diazepam alone showed minimal effects but interacted with alcohol in a different way from nitrazepam. Ethinamate slightly improved coordinative skills but impaired attention. Its interaction with alcohol was very mild. Bromvaletone alone showed minimal effects on psychomotor performance but a strong interaction with alcohol.

between the benzodiazepines account for the anxiolytic-hypnotic distinction. The cumulative effects of chlordiazepoxide, diazepam, and nitrazepam were thought to deserve special attention. Long-acting drugs with active metabolites are unsuitable as nighttime hypnotics, since central nervous system depression can persist well into the next day. (HSRI)

1975 102refs

Presented at the symposium "CLinical Pharmacology and Toxicology of Psychoactive Drugs," held Oct. 22-24, 1973, at the Clinical Inst., Addiction Res. Foundation, Toronto.

UM-75-D0574

FACTORS AFFECTING THE PHARMACOKINETICS OF SOME PSYCHOACTIVE DRUGS, W. J. Jusko, in Clinical Pharmacology of Psychoactive Drugs, E. M. Sellers, ed., Addiction Research Foundation of Ontario, p55-72 (1975)

In an overview of psychoactive drug pharmacokinetics, the author concluded that psychotherapeutic drugs have many common physicochemical and pharmacokinetic properties. Compounds classified as psychomotor stimulants and anorectic agents were exceptions. High lipid-solubility, extensive biotransformation, and lack of significant urinary excretion were common characteristics. These drugs were often bound appreciably to plasma proteins. Patients commonly exhibited a long half-life and large volume of distrubution of these agents and, related to the preceding factors, usually show a large degree of intrasubject variation in their distribution, metabolic clearance, and steady-state plasma drug levels.

A physiological pharmacokinetic model was used to simulate the temporal behavior of a hypothetical drug with the general characteristics of a psychoactive agent. This model showed the role of factors such as rate of hepatic metabolism, liver blood flow, protein binding, body fat mass, and perfusion rates of various tissues in explaining some of the pharmacokinetic characteristics of psychotherapeutic drugs. (AAM)

1975 58refs

Presented at the symposium "Clinical Pharmacology and Toxicology of Psychoactive Drugs," held Oct. 22-24, 1973, at the Clinical Inst., Addiction Res. Foundation, Toronto.

UM-72-D0575

EMERGENCY DRUG ANALYSIS, H. E. Sine; M. J. McKenna; M. R. Law; M. H. Murray, Journal of Chromatographic Science v10 n5 p297-302 (May 1972)

A drug screening procedure for a variety of drugs subject to abuse and accidental overdose was presented. Preparation involved simple serum extraction and aqueous dilution techniques which were followed by a gas-liquid chromatographic analysis. The assay techniques were reproducible at a level of less than 8%; all extractable drugs were detected at concentrations of less than or equal to 0.1 mg/100 ml.

Application of this method effectively established the presence of one or more drugs at serum levels greater than therapeutic in about 80% of suspected drug overdose cases. Therapeutic and toxic blood level data for considered drugs were tabulated. (JAM)

1972 23refs

administered to 587 controls. The driving populations of all groups were matched as to their age and living district.

Comparing those with driver licenses, subject characteristics were found to be similar among the various groups. Driving patterns varied more considerably. Characteristics of prescribed drug use and alcohol consumption patterns also differed significantly between patient and control groups. The use of alcohol was greatest in the control group. Of this group, 41% used some kind of medication.

The main finding of the study was that, as traffic exposure was controlled, nondrug-treated patients were not involved in accidents more often than the nondrug-using control group. In the psychiatric outpatient group, drug use was linked with an increased accident rate. Heavy use of alcohol was associated with increased traffic exposure in the study. In the control and rheumatoid arthritic groups, alcohol use was positively correlated with accident involvement. The combined use of drugs and alcohol also tended to increase involvement in accidents. (JAM)

1976 6refs

UM-75-D0572

SOME METHODOLOGICAL CONSIDERATIONS IN RESEARCH ON JOINT ACTION, J. A. Carpenter, in Clinical Pharmacology of Psychoactive Drugs, E. M. Sellers, ed., Addiction Research Foundation of Ontario, p147-64 (1975)

Drug interactions were considered ill-defined and beyond characterization by such terms as synergism, antagonism, etc. The author discussed the inadequacies of existing models and attempted to develop unambiguous mathematical statements to describe the results of combining chemical substances, based on significant pharmacological concepts.

Simultaneous with model development, data on two drugs, alcohol and meprobamate, were gathered in five experiments to establish the dose-response function for each drug alone, and to study combinations in which meprobamate was administered chronically and acutely. The data of the experiments did not provide an adequate test of the validity of the models, because the doses did not discriminate between the models that could fit the results of the drug combination. The behavior in response to the doses of the two drugs in combination could not be characterized by the existing terminology. The individual and combined functions were too complicated. Blood levels of meprobamate were found to be related to the presence of alcohol and the results suggest that the reverse may also be true. (AAM)

1975 18refs

Presented at the symposium "Clinical Pharmacology and Toxicology of Psychoactive Drugs," held Oct. 22-24, 1973, at the Clinical Inst., Addiction Res. Foundation, Toronto.

UM-75-D0573

BLOOD LEVELS OF BENZODIAZEPINES: APPLICATIONS IN MEDICINE AND TOXICOLOGY, D. J. Greenblatt; R. R. Shader, in Clinical Pharmacology of Psychoactive Drugs, E. M. Sellers, ed., Addiction Research Foundation of Ontario, p87-104 (1975)

The pharmacology, pharmacokinetics, metabolism, and assay methods for eight benzodiazepines classified as antianxiety and hypnotic agents were reviewed. The toxicology of the drug class was also summarized. The paucity of information concerning benzodiazepine pharmacokinetics and the relation of their blood concentrations to clinical effects was attributed to the difficult and expensive methodology necessary for blood analysis.

It was considered doubtful that intrinsic neuropharmacological differences

cation, diazepam and nordiazepam are found in approximately equal concentrations. Since the elimination rate is of the same order of magnitude for these drugs, the difference in clinical profile between chlorazepate and diazepam might be due to their different pharmacokinetic patterns. (JAM)

1975 11refs

UM-75-D0569

PSYCHOTROPIC DRUGS AND IMPAIRMENT OF PSYCHOMOTOR FUNCTIONS, A. Penttilä; H. Lehti; J. Lönnqvist, Psychopharmacologia (Berlin) v43 n1 p75-80 (23 Jul 1975)

The report dealt with the effects of psychotropic drug thereapy on the operation of psychomotor functions used in the clinical examination of suspected drunken drivers. A group of psychiatric mental patients using various types of medication and numbers of drugs was examined. In 71 of the 100 cases the mean degree of error in the clinical examination was higher, and, in several of these, markedly higher than the reference values obtained earlier from suspected drunken drivers when the blood contained very small amounts of alcohol or none at all.

The results indicated that application of the clinical examination method, which was originally developed for and related to the examination of alcohol cases, to subjects on psychotropes was adequate, and it was possible with such examination to obtain valuable medicolegal information on the impairment of physiological functions. The review of suspected drugged drivers examined in Helsinki in 1969-1972 also supported this view. (JAM)

1975 26refs

UM-75-D0570

INTERACTION OF DRUGS WITH ALCOHOL ON HUMAN PSYCHOMOTOR SKILLS RELATED TO DRIVING: EFFECT OF SLEEP DEPRIVATION OR TWO WEEKS' TREATMENT WITH HYPNOTICS, I. Saario; M. Linnoila; M. Mäki, Journal of Clinical Pharmacology v15 n1 ptl p52-9 (Jan 1975)

The authors investigated the effects of two hypnotic agents on psychomotor skills in repetitive tests performed during long-term treatment. Twenty healthy volunteers were treated in a double-blind crossover study with 6-(4-methyl-1-piperazinyl)- morphanthridine (PLP), nitrazepam, or placebo, administered orally every evening for two weeks. On the 7th and 14th mornings subjects received either ethyl alcohol or placebo, and psychomotor skills were measured 30, 90, and 150 minutes after the drink. Subjects were also tested after sleep deprivation. The psychomotor tests included choice reaction, two coordination tests, and an attention task.

Alcohol and PLP alone impaired eye-hand coordination, and nitrazepam impaired attention. Either hypnotic enhanced the alcohol-induced impairment of skills. Nitrazepam in combination with alcohol was especially deleterious on these skills. One night's deprivation of sleep did not impair psychomotor performance. The findings suggest consideration before using hypnotics when one has to get up early and carry out difficult psychomotor tasks such as driving. (AAM)

1975 13refs

UM-76-D0571

TRAFFIC ACCIDENT RATES AMONG FINNISH OUT-PATIENTS, M. Mäki; M. Linnoila, Accident Analysis and Prevention v8 n1 p39-44 (Feb 1976)

A questionnaire was administered to 765 rheumatoid arthritic, 715 tuberculous, and 1050 psychiatric outpatients concerning their use of alcohol and drugs, driving habits, and traffic accident involvement. The same questionnaire was

UM-74-D0566

FEASIBILITY OF ESTABLISHING PRESUMPTIVE LIMITS FOR DRUGS, California Highway Patrol, Sacramento (Jan 1974)

The purpose of this study was to determine the feasibility of establishing presumptive limits for drugs and to survey the "state of the art" in drug analysis. It was found that analytical resources were not adequate to meet the needs of a law requiring accurate and reliable quantitative and qualitative analyses of drugs in body fluids. No valid epidemiological studies for drugs other than alcohol were identified which showed that any drug had contributed disproportionately to accidents. The scarcity and inadequacy of drug-behavior studies was noted. Barbiturates appeared to be the class of drugs for which presumptive limits could be established at the earliest time. (AAM)

California Highway Patrol, Dept. of Justice, Dept. of Health, Sacramento, Calif.

1974 122p 130refs

Study resulted from California Assembly Concurrent Resolution 31.

UM-74-D0567

THE EFFECT OF CARBON MONOXIDE ON SEVERAL MEASURES OF VIGILANCE IN A SIMULATED DRIVING TASK, N. Rummo; K. Sarlanis, Journal of Safety Research v6 n3 p126-30 (Sep 1974)

This study investigated the effects of low levels of carbon monoxide (6 to 8% COHb) in seven volunteer subjects on several measures of vigilance. A two-hour car-following task was performed in an optical driving simulator. Subjects under CO were significantly slower in responding to lead car speed changes and non smokers made significantly fewer steering wheel corrections. There was no decrement under CO in responding to a dashboard warning light or in maintenance of lane position. The results indicate that low levels of CO produce performance decrements in a vigilance task. Further work is needed in the area of carbon monoxide effects on driving, and the investigation of the combined effect of CO and other agents (alcohol, drugs) on human performance may prove worthwhile. (HSRI)

1974 20refs

UM-75-D0568

CLINICAL AND EXPERIMENTAL COMPARISON OF DIAZEPAM, CHLORAZEPATE AND PLACEBO, I. Dureman; B. Norrman, Psychopharmacologia (Berlin) v40 n4 p279-84 (10 Mar 1975)

A double-blind clinical evaluation of chlorazepate, diazepam, and placebo on a psychiatric outpatient group of somatically healthy university students was reported. Both drugs were significantly better than placebo and according to global assessment chlorazepate was superior to diazepam. In patients' self-ratings, chlorazepate was also considered superior to diazepam in causing less drowsiness during the day time.

Performance tests in simulated car driving by 42 healthy young adult volunteers did not demonstrate any significant difference as compared with placebo. Psychophysical effects, as indicated by signs of compensatory effort by the subjects, were more pronounced after diazepam than after chlorazepate medication, however.

Results were discussed with reference to EEG studies and the pharmacokinetic properties of the drugs. Since chorazepate is immediately converted to nordiazepam at normal pH of the stomach and by decarboxylating enzymes in human serum, there is only one active compound, nordiazepam, circulating after a single dose or during continuous medication. During continuous diazepam medi-

patterns of use and abuse of 16 substances including alcohol, prescribed, nonprescribed, and illicit drugs. The percent of the population or a subgroup who used a substance during a stated period of time was determined for five geographic areas, and estimates for the total population of Michigan were given. Detailed data, sample population characteristics, and sampling error tables were presented in a separate volume. (HSRI)

Macro Systems, Inc., Silver Spring, Md.; Market Opinion Research, Detroit, Mich.

1975 40p

UM-75-D0564A

ALCOHOL AND OTHER DRUG USE AND ABUSE IN THE STATE OF MICHIGAN. DETAILED STATISTICAL DATA AND INFORMATION, Office of Substance Abuse Services, Michigan Department of Public Health (Mar 1975)

The presentation of detailed data; sample population characteristics; definitions of geographic areas and drugs considered; and statistical error tables complements the Summary Report (D0564). Thirty-one exhibits of detailed data are included, which present further data from the study and are organized by substance (alcohol; prescribed, nonprescribed, and illicit drugs; polydrug use) and category of information. The total sample of persons in the household survey and the subpopulations of interviewees by sex, race, age, level of education, geographic location, and income level are summarized. (HSRI)

Macro Systems, Inc., Silver Spring, Md.; Market Opinion Research, Detroit, Mich.

1975 52p

UM-74-D0565

DRUGS (OTHER THAN ALCOHOL) AND DRIVING, H. N. Colburn; B. H. Garland, in Scientific Conference on Traffic Safety. Proceedings p8-20A (1974)

The evaluation of the traffic safety problem engendered by the use of drugs other than alcohol was deemed difficult due to the lack of information. Related epidemiological studies were briefly surveyed, and an ecological model was described and used to deal with problems associated with the use of drugs or motor vehicles.

While the effects of drugs on traffic safety did not appear to challenge those of alcohol, the pressing need was emphasized for studies of the amounts of various drugs, prescribed and illicit, in body fluids and tissues of persons injured or killed in highway crashes compared to suitable control groups of drivers. The problem of multiple drug use and drug interactions with alcohol was also mentioned as facets of the problem. The elements of a comprehensive program were outlined, and the authors recommended several initial steps to be taken. (HSRI)

Department of National Health and Welfare, Ottawa, Canada.

1974 14p 13refs

Presented at the Scientific Conference on Traffic Safety, 23 and 24 May 1975 at Government Conference Center, Ottawa, Ontario, by H. N. Colburn.

Convened by the Traffic Injury Research Foundation of Canada, the Dept. of National Health and Welfare, and the Ministry of Transport.

UM-75-DO562

DRUGS AND DRIVING. AN EXPLORATORY-DESCRIPTIVE STUDY OF SUBSTANCE USE AND DRIVING AFTER SUBSTANCE USE AMONG LICENSED DRIVERS IN SOUTH CAROLINA, J. G. Jaeger; J. Fleming; G. W. Appenzeller, South Carolina Commission on Alcohol and Drug Abuse (1975)

The purpose of this research was to explore the incidence of drug use and driving by the population of South Carolina. The study was limited to licensed drivers and efforts were concentrated on the 16-49 age group. Since 81.6% of the population aged 16-49 were licensed drivers, the results were considered to be highly suggestive of the general population.

Of the sample of 488 drivers 16-49 years, 60% had used psychoactive drugs during the previous year, and 39% had driven afterwards. The figures for alcohol were 72% and 52%, respectively. Over-the-counter, prescription, and illicit drugs were used with alcohol by 9-18% of the sample. A majority of these persons reported that they had driven afterwards. Drug usage patterns varied with age, type of drug, geographical location, and urban development. Projections to the licensed driver population of South Carolina were made, based on the collected data. Recommendations for remedial actions and further research were made. (HSRI)

South Carolina Commission on Alcohol and Drug Abuse, Columbia, S. C.; Alcohol Safety Action Project--Columbia, S. C.

1975 126p 43refs

Sponsored by South Carolina Plan Interagency Committee on Alcohol and Drug Abuse, Columbia, S. C.

UM-75-DO563

MARIJUANA AND HUMAN PERFORMANCE, G. Salvendy; G. P. McCabe, Jr., Human Factors v17 n3 p229-35 (Jun 1975)

The purpose of this study was to explore the impact of marijuana smoking on human manipulative and coordination skills important in industrial and occupational tasks. Four groups of ten subjects each represented different levels of marijuana involvement: naive (control), ex-smokers, habitual users (placebo, marijuana groups). Consistent patterns of inferior performance on two psychomotor tasks (one-hole and rotary pursuit tests) were found for the marijuana users. For habitual smokers, smoking marijuana immediately prior to performance of manipulative and coordination tasks decreased performance.

The experiments indicate that the smoking of marijuana negatively affects both the acquisition and initial performance of manipulative and coordination skills. Furthermore, individuals who previously smoked marijuana are likely to perform less efficiently than those who have not smoked it. (HSRI)

1975 45refs

UM-75-DO564

ALCOHOL AND OTHER DRUG USE AND ABUSE IN THE STATE OF MICHIGAN. SUMMARY REPORT, Office of Substance Abuse Services, Michigan Department of Public Health (Mar 1975)

This epidemiological study was conducted by interviews in August 1974 of a representative sample of 2,539 persons, age 13 and over, selected in proportion to the population distribution across the State of Michigan. Prevalence estimates were based on self-reported usage of alcohol and other drugs. Other analyses were done to validate these data and to provide additional information.

The results of this study provide information describing the extent and nature of substance use and abuse in Michigan. The study focused on the

UM-75-D0560

THE APPLICATION OF HUMAN OPERATOR DESCRIBING FUNCTIONS TO STUDIES ON THE EFFECTS OF ALCOHOL AND MARIJUANA ON HUMAN PERFORMANCE, L. D. Reid; M. F. K. Ibrahim, IEEE Transactions on Systems, Man, and Cybernetics vSMC-5 n5 p506-19 (Sep 1975)

The application of human operator describing functions in the investigation of the influence of drugs (alcohol and marijuana) on subjects performing a compensatory visual-manual tracking task was studied. The describing functions were measured through the application of power spectral density techniques to the signals circulating in the control loop. A range of drug dosages was employed which included alcohol alone, marijuana alone, and a combined dose of marijuana and alcohol. Significant alterations in the describing functions were observed and interpreted as changes in amplitude, phase, and operator injected noise. Linear models fitted to the raw describing function data were used to summarize the observed trends in the human operator's dynamic characteristics.

The describing function measurements are capable of detecting the influence of drugs on the dynamic characteristics of the human operator. Subjects less skilled at the tracking task were more sensitive to alcohol than the more skilled trackers; care must therefore be taken in applying results obtained with highly skilled subjects to a broader population. Alcohol and marijuana alone both degraded tracking performance, but in ways distinguished by experimental parameters. The combined marijuana and alcohol dose tended to appear similar to the low alcohol dose in some instances and to the low marijuana dose in others. (HSRI)

1975 12refs

DHEW(ADM)76-311 UM-76-D0561

YOUNG MEN AND DRUGS - A NATIONWIDE SURVEY, J. A. O'Donnell; H. L. Voss; R. R. Clayton; G. T. Slatin; R. G. W. Room, NIDA Research Monography 5 (Feb 1976)

This preliminary report contains a wealth of data obtained in a major epidemiological study of nonmedical psychoactive drug use. Based on 2,510 completed interviews between October 1974 and May 1975, the report details lifetime and current use of nine drug classes among young men aged 20-30 years in 1974. Trends in drug use and associated factors are presented, although complete data analyses were not yet available.

Best estimates of lifetime and current use on the sample of men indicated that marijuana ranked third behind alcohol and cigarettes. For most other drugs, half or more of the users used the drug less than 10 times. Differences between blacks and whites in drug use seem to be diminishing. There is no indication of any recent decline in the annual prevalence of use of any drug, except perhaps psychedelics. Use of any of the nine drug classes is associated with both lifetime and current drug use, including size of city inhabited to age 18, employment status, degree of unconventionality, and education level attained. (HSRI)

1976 158p 11refs

DA-3AC678; DA-01121

UM-76-D0557

ALCOHOL, MARIJUANA, DRUGS....THE HIGHWAY KILLER-COMBINATION, W. L. Roper, California Highway Patrolman v40 n1 p4-5, 24-5 (March 1976)

This article is an anecdotal account of increased drug use and polydrug use among youth, and its implications for traffic safety. The hard line taken by law enforcement officials is espoused and defended. Increased awareness of alcohol and drug involvement in automobile accidents and crime is advocated. The dangers of polydrug mixtures should also be emphasized, according to the author. (HSRI)

1976 10p

UM-75-D0558

ANGABEN VON ALKOHOLTÄTERN ÜBER IHRE ARZNEIMITTELEINNAHMEN UND DETERN ÜBERPRÜFUNG (CLAIMS OF ALCOHOL USERS ABOUT THEIR DRUG INTAKE AND THEIR EXAMINATION), H. J. Mallach; J. Seitz, Blutalkohol v12 n6 p337-47 (Nov 1975)

This report described the results of drug analyses performed on blood samples taken by police order between May and December 1974. Of 28,552 persons, 4,943 (17.3%) claimed to have taken drugs before blood sampling. Most of the drugs were soft anodynes as claimed by the accused persons. The confirmation of claimed drug-use diminished with increasing blood-alcohol-concentration (BAC) of the accused.

Analgetics, opiates, sedatives, and hypnotic drugs were reported to influence the frequency of accidents when people showed a BAC between 0.08% and 0.10%. The need for direct and sure proof of the interaction between alcohol and drugs and their influence on the psychophysical efficiency was emphasized. (JAM)

1975 25refs [German]

English summary given on p346

HS-801 828 UM-76-D0559

MARIHUANA CONTACT TEST. EVALUATION AND DEVELOPMENT. FINAL REPORT, E. J. Woodhouse, National Highway Traffic Safety Administration (Feb 1976)

Methods for the detection of marihuana constituents on lips and skin areas of smokers were investigated. The study was designed to evaluate the previously used "colorimetric swab (CS) test" and to develop and evaluate a new swabbing method utilizing thin-layer chromatography (TLC). The CS test was found capable of detecting 2 mcg of tetrahydrocannabinol (THC) per swab, but was also demonstrated to be subject to a wide range of possible interferences. The test identified only 83% of marihuana smokers immediately after smoking.

An alternative swabbing method was developed. Using a TLC system, the optimized test has a sensitivity of 100 ng THC. Interferences, as documented for the CS test, were eliminated. The new test was also evaluated and validated using human subject smoking programs. Immediately after smoking, 86% of the smokers were detected, 74.4% being detected on the lips. Detection rates were dependent on elapsed time between smoking and testing. The test, having a false negative problem, should be used for survey data with great caution. Mass spectrometry and radioimmunoassay techniques were recommended for use in surveys of the incidence of marihuana contact. (HSRI)

Midwest Res. Inst., Kansas City, Mo. 64110

1976 121p. 4refs

DOT-HS-801 828; 3964C

UM-75-D0554

ALCOHOL, DRUGS, AND ACCIDENT RISK, R. K. C. Teo, comp., New South Wales Department of Motor Transport (Nov 1975)

An investigation of the effects of drugs, alone and in combination with alcohol, on the performance of subjects in a number of tests of sensory, cognitive and motor functions related to driving skills is reported. Drugs which are taken to counteract the inebriate effects of alcohol (fructose, dextrose, caffeine), and those for which there is clinical evidence of an interactive effect (antihistamines, benzodiazepines) were studied.

Among the results, the rate of alcohol metabolism and the detrimental effects induced by alcohol were not altered by either fructose or dextrose. Caffeine had no "sobering-up" effect, but did antagonize the alcohol-induced increase in reaction times. Two antihistamines differed in their interaction with alcohol and when taken alone, indicating that the investigation of the effects of antihistamines on human performance should be carried out on the individual drugs. Diazepam (10 mg) slightly depressed psychomotor performance and had a significant synergistic interaction with alcohol. Chlordiazepoxide (40 mg), although decreasing performance per se, antagonized some but not all of the depressant effects of alcohol. (HSRI)

New South Wales Dept. of Motor Transport, Traffic Accident Res. Unit, Sydney, Australia; Sydney Univ., Dept. of Pharmacology, Sydney, Australia.

1975 34p 28refs

Report No: 4-75.

UM-75-D0555

RAUSCHMITTEL ALS VERKEHRSSICHERHEITSPROBLEM (INTOXICANTS AS A TRAFFIC SAFETY PROBLEM), L. Moser, Zeitschrift fur Verkehrssicherheit 21 Quartal, Heft 3, p161-72 (Jahrgang 1975, III)

The special literature about the drug problem in road traffic and the results of standardized interviewing of habitual consumers of intoxicants are evaluated. The effect of hashish and marihuana in dosages up to 1 g or 60 to 80 mcg THC concentration per kg body weight is comparable to that of a blood alcohol concentration of about 0.8 per ml. LSD stimulants and "hard" drugs are, on principle, much more dangerous than cannabinol and alcohol in road traffic. The number of habitual, if not addicted, consumers of drugs holding a driving license in the Federal Republic of Germany is estimated to be 60,000. (JAM)

1975 41refs [German]

English summary on p172

UM-76-D0556

MARIJUANA AND THE DRIVER, D. Guthrie, Traffic Safety v76 n2 p14-5, 34 (Feb 1976)

The possible impact of the national trend to reform marijuana laws on traffic safety is discussed. Research findings concerning the effects of marijuana on driving skills are summarized and their implications for the actual driving situation are given. Techniques for the detection of marijuana in drivers are briefly described. (HSRI)

National Safety Council, Chicago, Ill.

1976 3p

HS-801 721 UM-75-D0552

THE DEVELOPMENT OF TECHNOLOGY FOR DETECTION OF MARIJUANA INTOXICATION BY ANALYSIS OF BODY FLUIDS. FINAL REPORT, P. J. Bryant, J. L. Valentine; P. L. Gutshall; O. H. M. Gan; P. Driscoll, National Highway Traffic Safety Administration (Sep 1975)

A method employing high pressure liquid chromatography-mass spectrometry (hplc-ms) was developed for detecting trace amounts of the principal biologically active constitutent (delta-9-THC) in marijuana. The method was successfully applied to detecting and quantitating delta-9-THC added to human plasma, and to determining nanogram levels of the compound in blood of young male volunteers after they smoked a marijuana cigarette of known composition up to 24 hours.

The detection of a marijuana metabolite in blood plasma up to 24 hours following smoking was accomplished using an ultra-violet spectrophotometer attached to the hplc. The usefulness of the hplc method for indicating prior marijuana use and for studying the correlation of driver impairment and blood levels of marijuana constitutents was pointed out. (AAM)

University of Missouri, School of Pharmacy, Kansas City, Mo. 64108

1975 33p 7refs

DOT-HS-4-00968

DOT-HS-801 721

UM-75-D0553

DRIVING RECORDS BEFORE AND DURING METHADONE MAINTENANCE, J. F. Maddux; T. R. Williamson; J. A. Ziegler, in Problems of Drug Dependence. 1975. Proceedings, Washington, D. C., National Academy of Sciences, 1975 p275-88

This study concerned the motor vehicle driving experience of 174 former heroin users who had been maintained on methadone for one year or longer in San Antonio. The subjects were predominantly male and nearly all were Mexican-American. Analysis of the self-reported driving experience, confirmed by study of official driver records, revealed that the annual rates of driving violation convictions and accidents decreased when the subjects began heroin use, but increased moderately when they entered methadone maintenance. The increase in convictions for speeding was found statistically significant.

While maintained on methadone, the subjects recorded accidents with significantly greater frequency than all Texas licensed drivers. The authors briefly analyzed the factors which may have contributed to the subjects' worsened driving records and stated that they did not advocate any restrictions of their driving privilege. (HSRI)

Texas University, San Antonio, Health Science Center; Southwest Research Institute, San Antonio, Tex.

1975 9refs

Presented at the 37th Annual Scientific Meeting of Committee on Problems of Drug Dependence, Division of Medical Sciences, Assembly of Life Sciences. National Research Council, 19-21 May 1975, Washington, D. C.

UM-75-D0550

EVALUATION OF EFFECTIVENSS OF PUBLIC EDUCATION AND INFORMATION PROGRAMMES RELATED TO ALCOHOL, DRUGS, AND TRAFFIC SAFETY, G. J. S. Wilde, in Alcohol, Drugs, and Traffic Safety, Proceedings, S. Israelstam; S. Lambert, eds., Toronto, Addiction Research Foundation, 1975, p813-23

The author discussed measures of publicity campaign effectiveness and presented factual findings and interpretations related to the promotion of road safety. Comparisons were made with alternative countermeasures, including legislative change and enforcement, and problems and consequences associated with each were discussed. Research in the 'academic' or 'experimental' literature was evaluated and considered of little value in learning to make communication procedures more effective. The author concluded that a truly scientific knowledge of how to influence behavior through mass communication can best be derived from operational research involving field experience and field studies. He advocated a comprehensive approach to the area of drinking and driving with the aim of increasing countermeasure effectiveness, and listed salient points for consideration in this regard. (HSRI)

Queen's University, Dept. of Psychology, Kingston, Ontario, Canada

1975 11p 37refs

Presented at the International Conference on Alcohol, Drugs, and Traffic Safety, 6th, 8-13 Sep 1974, Toronto, Canada.

UM-75-D0551

RECOVERY AND SIMULATED DRIVING AFTER INTRAVENOUS ANESTHESIA WITH THIOPENTAL, METHOHEXITAL, PROPANIDID, OR ALPHADIONE, K. Korttila; M. Linnoila; P. Ertama; S. Häkkinen, Anesthesiology v43 n3 p291-9 (Sep 1975)

Recovery from anesthesia was assessed in a double-blind manner in 40 healthy volunteer students pretreated with atropine after intravenous anesthesia with thiopental (6.0 mg/kg), methohexital (2.0 mg/kg), propanidid (6.6 mg/kg), or alphadione (Althesin, 85 mcl/kg), using a modified Sim-L-car driving simulator 2, 4, 6, and 8 hours after injection of the drugs. Clinical recovery was faster after propanidid and methohexital than after thiopental or alphadione.

It was found that driving performances remained significantly worse than in a control group for 6 hours after thiopental and for 8 hours after methohexital, and reaction times 8 hours after thiopental remained worse than in control subjects. After alphadione driving skills were impaired at 6 hours only. Propanidid produced no impairment in driving skills at any time during the experiment.

The pharmacology of the compounds was discussed in relationship to the experimental results and to other studies. It was concluded that after the doses used in this study patients should not drive or operate machinery for at least 2 hours after propanidid and for at least 8 hours after alphadione. After methohexital and thiopental patients should probably not drive for 24 hours because of the severity of the disturbances at 8 hours. (JAM)

1975 48refs

the lights and delayed response times to their appearance. The results were said to suggest that the prime locus of marihuana impairment of driving performance was in interference with perceptual processes involved in data acquisition necessary for safe control of the vehicle. (JAM)

1976 10refs

HS-801 721 UM-75-D0548

STUDY OF THE DETECTABILITY OF CONTROLLED SUBSTANCES ON BREATH. FINAL REPORT
P. J. Bryant; J. L. Valentine; P. L. Gutshall; O. H. M. Gan; P. Driscoll
National Highway Traffic Safety Administration (Jul 1975)

The development of a technique for the quantitative analysis of marihuana metabolites in blood and breath was reported. High pressure liquid chromatography-mass spectrometry was used in conjunction with a newly designed breath collector suitable for roadside sampling to detect and quantitate 1 nanogram delta-9-tetrahydrocannabinol (THC). The group also detected a previously unreported metabolite which is present in blood and breath for at least five days after smoking. Initial correlations between blood and breath levels of THC as well as the marihuana metabolite demonstrated that the lungs are acting as one excretory route for these compounds. The potential for the detection and quantitation of other drugs in breath and saliva using this technique was pointed out. (HSRI)

University of Missouri, School of Pharmacy, Kansas City, Mo. 64108

1975 49p 11refs

DOT-TSC-389

DOT-HS-801 660

Report covers the period 28 June 1974 to 28 June 1975

UM-76-D0549

DRUG DETECTION IN CASES OF "DRIVING UNDER THE INFLUENCE," J. C. Garriott; N. Latman, Journal of Forensic Sciences v21 n2 p398-415 (Apr 1976)

This study reported the analyses of blood samples of drivers arrested in Dallas County, Texas, for "driving under the influence of drugs" (DUID) for a 1-1/2 year period. Screening procedures were described for basic drugs (gas chromatography), for acidic, neutral, and basic drugs (ultraviolet spectrophotometry TLC), and for ethanol. The detailed presentation of each individual case included the type and number of drugs detected, the blood concentration of each drug, the personal characteristics of the driver and the behavioral observations of the arresting officer.

Tabulated data showed the frequency of appearance of detected drugs. Sedative-hypnotic drugs (including diazepam) accounted for almost all the drugs detected. Cannabis, not detected by drug analysis, was mentioned in 13% of the arrest reports. Although DUID arrests amounted to 1% of the "driving while intoxicated" (DWI) arrests, the authors believed that the incidence of drug use among drivers was higher. Infrequent detection was blamed on difficulties in implementing and enforcing a DUID program. (HSRI)

1976 13refs

UM-76-D0545

BARBITURATES AND DRIVING, S. Sharma, Accident Analysis and Prevention v8 n1 p27-31 (Feb 1976)

The author reviews the relationship between barbiturate use and traffic accidents as assessed by epidemiological studies. The lack of controlled studies comparing barbiturate involvement in traffic accidents and in the at-risk population has restricted any conclusive interpretations which can be made about the causal relationship between barbiturates and traffic accidents. Barbiturate incidence in traffic accident involvement varies from 2 to 9%. The variance in numbers represents different methods in data collection, different techniques in identifying barbiturates in body fluids and the differences in the populations samples.

Laboratory studies have found barbiturates at moderate doses to degrade driving skills. Motor skills performance, perceptual and tracking task performance and vehicle-handling test performance are impaired under barbiturates. This impairment is further degraded by the combined use of alcohol and barbiturates beyond that found under either drug along. It is clear that barbiturates are dangerous for driving and their effects are likely to produce impairment on those components of driving necessary for safe operation of a motor vehicle. (JAM)

1976 36refs

UM-76-D0546

DRUG USE AND DRIVING RISK AMONG HIGH SCHOOL STUDENTS, R. G. Smart; D. Fejer, Accident Analysis and Prevention v8 n1 p33-8 (Feb 1976)

This epidemiological study attempted to determine the frequency of accidents and the frequency of drug related accidents, with comparisons of driving exposure while under the various drug effects, in a high school drug user population. Anonymous questionnaires of known validity were used to collect information about drug use, accidents, violations, drug related accidents and violations, and numbers of drug-driving occasions.

Of the 1538 students, 710 had driven in the past year. About 15% reported an accident and 20% a driving offense. Users of all drugs more often reported accidents than non-users, but the results were statistically significant for tobacco, marihuana, opiates, speed, LSD and other hallucinogens. Only 2.7% had an alcohol-influenced accident and 2.0% a drug-influenced accident. Exposure to drinking and driving was far more common than drug use and driving (56% of students compared to 1 to 6%). When exposure to drug related driving occasions are considered, LSD, tranquilizers and stimulants are the most dangerous drugs, and they are more dangerous than alcohol. The infrequent use of drugs makes their total effect on accidents small compared to alcohol. (JAM)

1976 13refs

UM-76-D0547

MARIHUANA: EFFECTS ON SIMULATED DRIVING PERFORMANCE, H. Moskowitz; S. Hulbert; W. H. McGlothlin, Accident Analysis and Prevention v8 n1 p45-50 (Feb 1976)

This study made use of a complex driving simulator to test the performance of 23 male subjects who smoked marihuana. Doses employed were 0, 50, 100, and 200 micrograms delta-9-tetrahydrocannabinol per kilogram body weight. The authors found little evidence for a significant effect of marihuana upon car control and tracking. None of the 25 car control-tracking scores was significantly changed in either mean or variance by the treatments. However, there was a clear, statistically significant decrement in performance of the search-and-recognition task. Marihuana produced increased errors in recognition of

and some known amphetamine abusers have been found to be involved in disproportionate numbers of highway accidents. Available epidemiological statistics are inadequate to establish how often such excessive consumption is associated with driving, or in any other way to quantify the total contribution of amphetamine abuse to traffic accidents. (JAM)

1976 16refs

UM-76-D0543

TRANQUILIZERS AND DRIVING, M. Linnoila, Accident Analysis and Prevention v8 n1 p15-9 (Feb 1976)

Increased consumption of tranquilizers (neuroleptics, antidepressants, and benzodiazepines) was noted. In a Norwegian study, diazepam was found in the blood of 18% of people injured in traffic accidents. Other epidemiological studies have demonstrated an increased traffic accident risk to be associated with the use of tranquilizers. The combined use of tranquilizers and alcohol, which is common among patients, increases one's accident risk from that due to either agent alone.

Laboratory studies concerning the effects of tranquilizers on skills related to driving have demonstrated impaired information processing capacity and eye-hand coordination due to these agents. Neuroleptics impair information processing especially at the onset of the treatment whereas the hazards of benzodiazepines become evident during long term treatment. Most of the tranquilizers increase the deleterious effects of alcohol on skills related to driving. Particularly strong is the interaction between diazepam and alcohol.

At present the best countermeasure against accidents caused by tranquilizers seems to be easily available information about the effects of drugs on driving. At the onset of treatment with a neuroleptic or during long term treatment with a high dose of benzodiazepines, one should cease driving. (JAM)

1976 28refs

UM-76-D0544

MARIHUANA AND DRIVING, H. Moskowitz, Accident Analysis and Prevention v8 n1 p21-6 (Feb 1976)

Survey studies have found that marihuana use is increasing and that users frequently drive under its influence. But there is little direct epidemiological evidence to indicate if the presence of marihuana in drivers increases accident probability. However, there is a large body of experimental evidence indicating that marihuana impairs the performance of skills important for driving. Perceptual and attention functions show large decrements under marihuana with a less certain deficit for various tracking functions.

Marihuana studies in driving simulators have found the greatest deficit in perceiving and responding to potential dangers from the environment. Simulator studies of risk taking have found no evidence for impairment. Several studies of performance in actual cars have also demonstrated performance decrements but the behavior functions impaired have not been clarified. The author concludes that the experimental evidence suggests strongly that marihuana use while driving produces a performance impairment. (JAM)

1976 45refs

UM-76-B0007

CHEMICAL DERIVATIZATION IN LIQUID CHROMATOGRAPHY, J. F. Lawrence; R. W. Frei, Journal of Chromatographic Library v7 New York: Elsevier Scientific Publishing Co. (1976)

The purpose of derivatization through the use of chemical reactions and labeling procedures is to enhance the sensitivity, specificity, and separation properties of liquid chromatography. In this book, written for all investigators concerned with the use of physical separation techniques for solving complex analytical problems, a background chapter is provided for brief review of principles related to the various liquid chromatographic and detection techniques relevant to derivatization.

The chapter devoted to instrumentation covers both thin-layer and high pressure liquid chromatographic equipment, including chromatographs and detectors. The content of the application chapter is limited essentially to the new aspects of derivatization in liquid chromatography. Many of the practical examples are given with sufficient detail to permit an investigator to reproduce a method without the need to resort to the literature. (HSRI)

1976 213p 323refs

UM-76-D0541

INFLUENCE OF NARCOTIC DRUGS ON HIGHWAY SAFETY, N. B. Gordon, Accident Analysis and Prevention v8 n1 p3-7 (Feb 1976)

This is a review of available literature relevant to narcotic drug use and driver safety. It is estimated that there are currently (Feb 1976) about 100,000 individuals maintained on methadone in the U. S.; the additional number of individuals using heroin and other narcotics is estimated at over 250,000. Of the known legitimate and illegitimate users of narcotics, it is estimated that a minimum of 80,000 drive.

No studies were found that directly assessed driver capability either in driving simulators or actual driving conditions. There are some studies of illegal users' driving records, including interviews with methadone treated ex-heroin addicts, and laboratory studies of effects of narcotics on skills related to driving. The weight of evidence from available studies indicates that narcotic users do not have driving safety records that differ from age matched individuals in the general population. Furthermore maintenance on methadone (a synthetic narcotic used to treat heroin addicts) does not provide a risk for driving as indicated by laboratory studies (reaction-time, psychomotor skill, and sustained attention) and driving record studies. (JAM)

1976 23refs

UM-76-D0542

AMPHETAMINES AND DRIVING BEHAVIOR, P. M. Hurst, Accident Analysis and Prevention v8 n1 p9-13 (Feb 1976)

Direct evidence concerning the role of amphetamines in highway accidents is scant. Laboratory data indicate that most of the basic skills involved in driving are not adversely affected by amphetamine dosages within the normal clinical range, and may in fact be slightly enhanced. Such enhancement is generally greater in sleep-deprived subjects, but is not limited to states of sleep deprivation. Enhancement has also been reported in subjects whose skills have been degraded by alcohol, although results have not been consistent across performance measures.

Evidence that amphetamines induce overconfidence or increase risk acceptance is not such as would justify great concern. Abnormal psychological states resulting from excessive or "spree" use are incompatible with safe driving,

tion published by the same serial in May 1972. References were listed in alphabetical order according to the first author. (HSRI)

1974 246refs

UM-75-B0004

CLINICAL PHARMACOLOGY OF PSYCHOACTIVE DRUGS, E. M. Sellers, ed., Addiction Research Foundation of Ontario, Toronto (1975)

The papers in this volume comprise the proceedings of the symposium "Clinical Pharmacology and Toxicology of Psychoactive Drugs." The papers were presented in three sessions entitled, "Etiology and Epidemiology," "Factors Influencing Toxicity," and "Clinical and Molecular Drug Interactions." The wide range of topics included the epidemiology of suicidal drug intoxication, pharmacokinetics, and the molecular basis of psychoactive drug effects. (HSRI)

1975 226p

Symposium "Clinical Pharmacology and Toxicology of Psychoactive Drugs" was held Oct 22-24, 1973 at Clinical Inst. Addiction Res. Foundation, Toronto.

Available from: Marketing Services, Addiction Res. Foundation, 33 Russell St., Toronto, Ontario M5S 2S1.

UM-75-B0005

ALCOHOL, DRUGS, AND TRAFFIC SAFETY. PROCEEDINGS OF THE SIXTH INTERNATIONAL CONFERENCE ON ALCOHOL, DRUGS, AND TRAFFIC SAFETY, TORONTO, SEPTEMBER 8-13, 1974, S. Israelstam; S. Lambert, eds., Addiction Research Foundation of Ontario, Toronto, Canada (1975)

This collection of conference papers is arranged in five broad categories: the epidemiology of alcohol and drug related traffic accidents (21 papers); pharmacological, physiological, and psychological aspects relevant to driving impairment (22 papers); analytical aspects, concerning the measurement of drugs in breath and body fluids (19 papers); countermeasure development of evaluation (16 papers); and public education and information aspects (13 papers). (HSRI)

1975 939p 1082refs

UM-76-B0006

INSTRUMENTAL LIQUID CHROMATOGRAPHY. A PRACTICAL MANUAL ON HIGH-PERFORMANCE LIQUID CHROMATOGRAPHIC METHODS, N. A. Parris, Journal of Chromatography Library v5 New York: Elsevier Scientific Publishing Co. (1976)

This book briefly describes the historical background and basic principles of liquid chromatography, and emphasizes those aspects of the technique which are useful for practical application of the method. Information regarding the usefulness of available equipment and column packings is given, together with chapters devoted to the methodology of each separation method: liquid-solid (adsorption), liquid-liquid (partition), ion-exchange, and steric exclusion chromatography.

Applications of liquid chromatography are described with reference to the potential of the technique for qualitative, quantitative, and trace analysis as well as preparative liquid chromatography. Numerous applications from the literature are tabulated and cross-referenced to sections concerned with the optimization procedures of the particular method. (HSRI)

1976 329p 141refs

HS-801 658 UM-75-A0006

MARIJUANA AND HUMAN PERFORMANCE: AN ANNOTATED BIBLIOGRAPHY (1970-1975). FINAL REPORT, M. L. Pagel; M. G. Sanders, comps., U. S. Army Aeromedical Research Laboratory (Mar 1976)

The effects of marijuana upon human performance is currently an area of major concern. No place is this concern more acute than in complex man-machine systems, such as those found in aviation, where degradations in psychomotor and/or cognitive performance can result in catastrophic losses. This annotated bibliography consisting of 199 references was compiled to aid the reader in determining the impact of this drug on psychomotor, cognitive, and physiological factors considered pertinent to flight performance.

The references are arranged alphabetically by the name of the first author. The bibliography contains an index which categorizes the references into the following major areas: (1) reviews or overviews of issues, literature or research; (2) psychological effects of marijuana use; (3) physiological and pharmacological research; (4) medical comments and research critiques; and (5) additional reference sources. The basic period of coverage is 1970-1975, although selected studies from earlier years are also included. (AAM)

U. S. Army Aeromedical Research Laboratory, Fort Rucker, Alabama 36362

1976 89p 199refs

USAARL Report No. 76-17

UM-72-A0007

A CURRENT BIBLIOGRAPHY FOR DRUG ANALYSIS BY GC, UV, AND TLC, J. A. Miller; V. Spiehler; C. W. Keller, Beckman Instruments, Inc., Fullerton, California (1972)

This bibliography of drug research methodology references is indexed by first author and contains 461 entries. The analytical disciplines covered by these references were deliberately limited to gas chromatography, ultraviolet spectrophotometry, and thin-layer chromatography. Because of their limited application to clinical drug screening (1972), all other techniques such as mass spectrometry and infrared spectroscopy have been excluded, except for an occasional reference. A cross-index to the bibliography was provided, with all references indexed from their titles only. (HSRI)

1972 461refs

UM-72-A0008

A BIBLIOGRAPHY OF REFERENCES ON THE ANALYSIS OF DRUGS OF ABUSE, Anonymous, Journal of Chromatographic Science v10 n5 p352-68 (May 1972)

This extensive bibliography of drug analysis references was included in the Journal of Chromatographic Science's special drug analysis issue, May 1972. Over 400 listings are provided and are alphabetized according to first author. (HSRI)

1972 413refs

UM-74-A0009

A BIBLIOGRAPHY OF REFERENCES ON THE ANALYSIS OF DRUGS OF ABUSE--1972 TO 1974, Anonymous, Journal of Chromatographic Science v12 n5 p328-27A (May 1974)

Almost 250 references were collected on the analysis of drugs and included in the Journal of Chromatographic Science's second special drug analysis issue, May 1974. The bibliography was designed to supplement an extensive compila-

The results indicated that psychoactive drugs are a significant contributory factor to motor vehicle accidents. When found alone, the drug concentrations suggested abuse; when found along with alcohol, the majority of drivers had therapeutic levels of drugs. (AAM)

1976 14refs

UM-75-D0602

EFFECT OF TWO WEEKS' TREATMENT WITH CHLORDIAZEPOXIDE OR FLUPENTHIXOLE, ALONE OR IN COMBINATION WITH ALCOHOL, ON PSYCHOMOTOR SKILLS RELATED TO DRIVING, M. Linnoila; I. Saario; J. Olkoniemi; R. Liljequist; J. J. Himberg; M. Mäki, Arzneimittel-Forschung v25 n7 p1088-92 (Jul 1975)

The effects of two weeks' treatment with chlordiazepoxide (10 mg, t.i.d.) or flupenthixole (0.5 mg, t.i.d.) on human performance related to driving was examined on 20 healthy male students. The tests used were a choice reaction, two coordination tests, and an attention test having correlation with traffic behavior.

Neither chlordiazepoxide nor flupenthixole impaired psychomotor performance on the 7th or 14th days of the experiment. The combination of either drug with 0.5 g/kg of alcohol impaired coordination and attention to an extent which can be considered dangerous for traffic and occupational life. Their interaction with alcohol was less than that of diazepam. The combination of chlordiazepoxide with alcohol tended to increase the anxiety of normal subjects. (AAM)

1975 15refs

UM-65-D0603

COMPARATIVE EFFECT IN HUMAN SUBJECTS OF CHLORDIAZEPOXIDE, DIAZEPAM, AND PLACEBO ON MENTAL AND PHYSICAL PERFORMANCE, F. W. Hughes; R. B. Forney; A. B. Richards, Clinical Pharmacology and Therapeutics v6 n2 p139-45 (Mar-Apr 1965)

Two benzodiazepine tranquilizers, chlordiazepoxide (15 mg/day) and diazepam (6 mg/day), were studied for their effects on mental and motor performance with and without small amounts of ethanol (0.66 ml/kg b. wt.). Eighteen paid volunteer students (6 female, 12 male), aged 20-31 years, were tested on six occasions under the following conditions: placebo drug plus placebo alcohol; (2) drug plus placebo alcohol; (2) drug plus alcohol; placebo drug plus alcohol. The drugs were administered in three daily doses for 2 days prior to testing and at breakfast on the day of the test. Treatments were randomized with 48 hour intervals between schedules.

Attentive motor performance was measured with a pursuit meter developed by the authors. Ethanol was the only drug used alone that impaired motor performance. Overall drug-alcohol interaction was not significant with diazepam or chlordiazepoxide. However, in one test pattern, a synergistic effect of diazepam with alcohol was observed. Mental performance was measured with a delayed auditory feedback system. The subjects had nine verbal or arithmetic tests on six different occasions on a 6 X 6 random plan. By this procedure only alcohol effected a decrease in performance scores. No appreciable additive effect of chlordiazepoxide or diazepam with alcohol was evident. (JAM)

1965 9refs

UM-67-D0604

STRASSENVERKEHR, TRANQUILIZER UND ALKOHOL (ROAD TRAFFIC, TRANQUILLIZERS, AND ALCOHOL), P. Kielholz; L. Goldberg; J. Im Obersteg; W. Poeldinger; A. Ramseyer; P. Schmid, Deutsche Medizinische Wochenschrift v92 n35 p1525-31 (1 Sep 1967)

The impairment of driving ability by the tranquillizers chlordiazepoxide and

meprobamate was examined both in respect to direct effects and their possible interaction with alcohol. Under double-blind conditions, subjects selected from the Basle police corps were examined after receiving placebo, meprobamate (400 mg), or chlordiazepoxide (10 mg), with and without alcohol. A series of driving tests were administered on a special test site; at the same time, blood alcohol levels, drug concentrations in the blood, and subjective self-ratings were determined according to a fixed experimental design.

The statistical evaluation of the results of 120 subjects showed no direct effects of the psychoactive agents, nor were any drug interactions with alcohol indicated. On the other hand, the authors stated that the impairment of driver ability with a higher statistical significance could be shown in these experiments with a blood alcohol concentration of 0.8%. (HSRI)

1967 10refs [German]

UM-76-D0605

MINOR OUTPATIENT ANAESTHESIA AND DRIVING, K. Korttila, in "Alcohol, Drugs and Driving," M. Mattila, ed., Modern Problems in Pharmacopsychiatry, v11, Basel (Switzerland): S. Karger AG, 1976, p91-8

Increasing use of outpatient anesthesia and sedation raises concern about possible impairment of patients' psychomotor skills following treatment. This review presents data concerning the effects of drugs used as premedication and as anesthetics on psychomotor skills related to driving. Techniques used to assess recovery from anesthesia at various stages are outlined and briefly described. Driving skills were evaluated using a psychomotor test battery.

Analgesic drugs (phenylbutazone, and indomethacin, but not aspirin), and certain premedications (including atropine, diazepam, and pethidine) impaired performance. Local anesthetics not coadministered with adrenaline also impaired performance. Longer lasting residual effects were observed following psychotropic drugs such as diazepam, flunitrazepam, and droperidol. Intravenous and inhalation anesthetic agents also produced significant residual effects on driving-related skills. A table with 24 different treatments was included which listed minimum times recommended for hospital stay and length of time patients should be advised against driving. (HSRI)

1976 26refs

Conference: International Congress of Pharmacology on Alcohol, Drugs, and Driving, 6th, 26-27 Jul 1975, Helsinki, Finland.

UM-75-D0606

ROAD USER BEHAVIOUR AND TRAFFIC SAFETY: TOWARD A RATIONAL STRATEGY OF ACCIDENT PREVENTION, G. J. S. Wilde, presented at the Annual Convention of the Dutch Road Safety League, Amsterdam, (26 Apr 1975)

Tolerance for risk as a factor in the causation of accidents was emphasized in the development of a comprehensive model from existing theories of driver behavior. Theories and empirical findings were categorized. Social interaction with other drivers while on the road was given special attention and was illustrated by a number of experiments.

The proposed model viewed the causation of accidents as a homeostatically controlled process. Equilibrium was seen as a balance of perceived and tolerated risk. Driving skills as a function of these variables were discussed. The relation of countermeasures to the level of perceived risk was discussed. (HSRI)

Queen's Univ., Kingston, Ont. K7L 3N6 Canada.

1975 35p 32refs

Presented at the Annual Convention of the Dutch Road Safety League in the RAI Conference Centre, Amsterdam, 26 Apr 1975.

UM-74-D0607

STUDENT DRUG USE, RISK-TAKING, AND ALIENATION, B. A. Rouse; J. A. Ewing, College Health v22 n3 p226-30 (Feb 1974)

This questionnaire study of undergraduate university students focused on illicit drug use (marijuana), alienation, and the kinds and levels of risk which the students perceived to be associated with drug use. The rate of marijuana use had increased since previous studies by the authors. Users saw arrest and punishment as the primary risk, while nonusers perceived legal, emotional, physical, and social risks which deterred experimentation.

Driving after using drugs was examined in the men undergraduates as most women did not drive or own cars. Seventy per cent of the total sample drove after drinking alcohol; 26% after smoking marijuana; 20% after both drugs combined; and 5% combined alcohol and amphetamines.

Results of the study indicated that those students who experimented with marijuana were less alienated than either continued users or nonusers. (HSRI)

1974 18refs

UM-74-D0608

TRAFFIC SAFETY. PROCEEDINGS OF THE SCIENTIFIC CONFERENCE, OTTAWA, ONTARIO, CANADA, MAY 23 AND 24, 1974, Traffic Injury Research Foundation of Canada; Canadian Department of National Health and Welfare; Canada Ministry of Transport (1974)

Various factors in traffic safety were evaluated: the influence of alcohol and drugs on traffic safety; behavior, psychological, and social factors; seat belts; motorcycle safety; and emergency medical care. The following specific topics are discussed: an experimental evaluation of a community-based campaign for the prevention of drunk driving in Ontario; drugs and driving; alcohol involvement in fatal and non-fatal crashes; driver-road sign interaction; driver performance related to the vehicle; methods of measuring driver behavior; the seat belt wearing law in Australia.

Also discussed are: motorcycle accident injuries; the protective value of motorcycle helmets; motorcycle training; an evaluation methodology for emergency medical services; and quality measurement of emergency medical care. A panel discussion of the problems, progress, and goals of traffic safety is also provided. (HSL)

1974 212p 94refs

UM-74-D0609

PSYCHOMOTOR SKILLS RELATED TO DRIVING AFTER INTRAMUSCULAR LIDOCAINE, K. Korttila, Acta anaesthesiologica scandinavica v18 n4 p290-6 (1974)

Psychomotor skills related to driving and the ability to discriminate the fusion of flickering light were measured double-blind in 30 healthy volunteer students 25, 90, and 180 minutes after an intramuscular injection of either lidocaine (200 mg), lidocaine (500 mg) with adrenaline, or a saline placebo. The tests used were an attention test, two coordination tests, and a choice reaction test.

After plain lidocaine, the cumulative reaction times were significantly longer at 25 minutes than after saline or lidocaine with adrenaline. Lidocaine with adrenaline did not impair psychomotor performance or flicker fusion discrimination. Thus the results suggest that patients treated with high doses of plain lidocaine should not drive or operate machinery for 1 to 1-1/2 hours after the injection. (JA)

1974 27refs

DHEW/(ADM)76-292 UM-75-D0610

OPERATIONAL DEFINITIONS IN SOCIO-BEHAVIORAL DRUG USE RESEARCH 1975, J. Elinson; D. Nurco, eds., National Institute on Drug Abuse Research Monograph 2 (Oct 1975)

The monograph is a series of papers by prominent social research scientists appointed to consider the critical problem of introducing comparablility or uniformity in key terms and concepts used in social science research. These operational definitions are proposed using a base of over 65 research reports from which definitions-in-use were culled and abstracted in an extensive appendix. The appendix also includes excerpted survey questionnaire samples used to investigate drug abuse epidemiology. (AA)

1975 168p 21refs

DHEW/(ADM)76-292

National Inst. on Drug Abuse, Div. of Res.

UM-76-D0611

PROSECUTION OF DRIVERS IMPAIRED BY ALCOHOL OR OTHER CHEMICALS, R. B. Forney, Sr.; R. B. Forney, Jr., in Legal Medicine Annual: Nineteen Seventy-Five, C. H. Wecht, ed., New York: Appleton-Century-Crofts, 1976, 85-99

The legal and medical aspects of drug use and driving are discussed with an emphasis on ethanol. Prosecution of a driver accused of chemical misuse while operating a motor vehicle requires establishing that the chemical has potential for detrimental effects and that the effects had impaired the driver. In addition to its pharmacology, the absorption, distribution, metabolism, and excretion of ethanol is described. The relation of blood and tissue levels of alcohol to driving performance is reviewed. The laboratory and epidemiological studies cited demonstrate the usefulness of blood alcohol concentrations in assessing driver impairment. Sample collection and analysis for ethanol is discussed in the legal context, and the importance of procedural aspects is emphasized.

Legal limits of blood alcohol concentrations in drivers reflect dose-response relationships which, however, can not be used to predict the degree of impairment or per cent loss in driving skill. While this situation has worked for ethanol, drugs other than alcohol may present additional difficulty. For example, criteria relating blood concentrations of drugs to driving impairment are not available. Nevertheless, the goal of establishing drug concentrations beyond which it would be illegal to drive irrespective of driving impairment is deemed realistic. (HSRI)

1976 16refs

UM-75-D0612

SIDE EFFECTS AND SKILLS RELATED TO DRIVING AFTER INTRAMUSCULAR ADMINISTRATION OF BUPIVACAINE AND ETIDOCAINE, K. Korttila; S. Häkkinen; M. Linnoila, Acta anaethesiologica scandinavica v19 p384-91 (1975)

In a double-blind crossover study, eleven healthy subjects were injected intramuscularly with a saline placebo, 1.3 mg/kg of 0.5% plain bupivacaine, or 2.6 mg/kg of 1.0% plain etidocaine. Before and at 1/2, 2 and 4 hours after injection, side effects were recorded, and psychomotor skills related to driving were measured. A choice reaction test, two eye-hand coordination tests, and tests of visual function were employed.

Fatigue, dizziness, and sore thighs were significantly more common with etidocaine than with bupivacaine or the saline solution. Bupivacaine significantly impaired eye-hand coordination and flicker fusion discrimination during the whole observation period. Etidocaine impaired flicker fusion

discrimination only. The subjects' adaptation to darkness, sensitivity to brightness, and visual discrimination ability in bright counterlight remained unaltered after each treatment. The results suggested that such psychomotor performance as driving ability is impaired for at least 2 hours after a patient receives the doses of plain local anesthetics used in the study. (JAM)

1975 28refs

UM-75-D0613

SYNOPSIS OF ACCIDENT INVESTIGATION STUDIES OF THE ALCOHOL/DRUG PROBLEM IN FOUR ASAP CITIES, J. C. Fell, Office of Statistics and Analysis, National Highway Traffic Safety Administration (1975)

The results of studies performed by Multidisciplinary Accident Investigation Teams in Boston, Albuquerque, Oklahoma City, and Baltimore were summarized. Certain common data were collected and similar results were enumerated. Among the results presented were the following findings: single vehicle accidents are overrepresented in alcohol-related accidents; most of the alcohol-related accidents occur between 12 midnight and 4 a.m. on weekend nights; the typical alcohol-related driver is male, single, separated or divorced, and responsible for collisions (up to 90% of the time). In the Boston study, 9% of the collisions involved drugs other than alcohol. (HSRI)

1975 6p

UM-75-D0614

THE COMBINED EFFECTS OF ALCOHOL AND COMMON PSYCHOACTIVE DRUGS: I. STUDIES ON HUMAN PURSUIT TRACKING CAPABILITY, R. Burford; I. W. French; A. E. LeBlanc, in Proceedings of the 6th International Conference on Alcohol, Drugs, and Traffic Safety, S. Israelstam; S. Lambert, eds., Addiction Research Foundation of Ontario, Toronto, Canada, p423-31 (1975)

The drug interaction study examined those drug effects that might lead to automobile driving impairment, using a pursuit-tracking device (Stressalyzer) capable of measuring behavior relevant to driving. The interaction of alcohol and diazepam, phenobarbital, diphenhydramine, codeine, and marijuana was studied. Behavioral tests were supplemented by subjective impairment ratings and blood level analyses of drugs.

Results indicated that, at blood levels of ethanol below that taken by the law as presumptive evidence of impairment, meaningful additional impairment (equivalent to 0.08 g/100 ml) can be produced by the simultaneous use of moderate doses of the drugs used in the study. Impairments did not conform to subjective assessments of impairment and therefore presumably risk. The levels of impairment were considered clear threats to automotive safety. (HSRI)

Nucro-Technics Labs., 2000 Ellesmere Rd., Scarborough, Ont., Canada.

1974 11refs

Presented at the 6th International Conference on Alcohol, Drugs, and Traffic Safety, 8013 September 1974, Toronto, Canada.

UM-76-D0615

THE RISK COMPENSATION THEORY OF ACCIDENT CAUSATION AND ITS PRACTICAL CONSEQUENCES FOR ACCIDENT PREVENTION, G. J. S. Wilde, presented at the Annual Meeting of the Österreichische Gesellschaft für Unfallchirurgie, Salzburg (7-9 Oct 1976)

An acceptable theory of accident causation is necessary if a rational high-

way safety policy is to be developed. At present, the development of effective countermeasures is hindered by the lack of comprehensive models of driver behavior. Previous observations had demonstrated that drivers attempt to maintain a constant mental load and a constant level of experienced risk over time. In formulating a general theory of driver behavior, the author presents an integrated model based on the concept of "risk tolerance."

In the model, a driver's perceptions of risk are compared to the level of tolerated risk. On the basis of this comparison, decisions are made with respect to driving behavior. Cognitive and motivational states, as well as modulating factors (experience, personality, sex, drugs, etc.) influence the operational quality of driver functions and the amount of risk a driver is willing to accept. Risk tolerance is seen as the only independent variable which controls the number of accidents.

The author reviews the available literature in further support for the theory. Among its consequences, the temporal effects of countermeasure activity may be predicted. Means for lowering the existing level of tolerated risk in the driving population are discussed and two examples are presented. (HSRI)

Dept. of Psychology, Queen's Univ. Kingston, Ontario, Canada.

1976 38p 34refs

UM-75-D0616

EPIDEMIOLOGY OF DRUG-RELATED PROBLEMS IN CANADA, 1975. WORKSHOP PROCEEDINGS, I. Rootman; C. Billard, eds., Health and Welfare, Canada (1975)

The papers included in this volume were presented at a pilot orientation workshop on the epidemiology of drug-related problems in Canada. Participants, a group of Canadian epidemiologists and social scientists, were drawn mainly from the Non-Medical Use of Drugs Directorate. Two papers were devoted to epidemiology in general and the epidemiology of drug-related problems in particular. Substance-oriented papers featured two alcohol-related presentations, including one dealing with traffic accidents. A review of the epidemiology of tobacco-related problems was followed by two papers dealing with narcotic-related research and sources of information, respectively. Prescription drug use and multiple drug use formed the subject matter of two other presentations. (HSRI)

1975 183p 196refs

Sponsored by: Non-Medical Use of Drugs Directorate. English and French texts included.

UM-75-D0617

AUTOSCLEROSIS, L. Levi, World Health p10-3 (Oct 1975)

The factors of emotional and physiological stress in driving and health were discussed. Sex differences in the effect of accident provoking factors were described. The author related natural rhythms of the body and the occasional discrepancies between environmental demands and the human organism's abilities to the functional demands of driving. Recommendations were made which would promote the recovery of physiological and performance functions in fatiqued drivers. (HSRI)

1975

UM-76-D0618

EFFECTS OF HANGOVER ON PSYCHOMOTOR SKILLS RELATED TO DRIVING: MODIFICATION BY FRUCTOSE AND GLUCOSE, T. Seppälä; T. Leino; M. Linnoila; M. Huttunen; R. Ylikahri, Acta pharmacologia et toxicologia v38 n3 p209-18 (Mar 1976)

The intensity of the hangover produced by ethyl alcohol (1.75 g/kg) in thirty healthy male volunteers, twenty of whom also received glucose or fructose, was graded subjectively and objectively. In the hangover phase, psychomotor performance was recorded by a choice reaction test, two coordination tests and an attention test.

It was found that hangover decreased driving ability by reducing the accuracy of choice reactions and information retrieval on the "morning after." A dose of 1 g/kg of either glucose or fructose together with alcohol or 0.5 g/kg of either monosaccharide on the following morning was found to have a favorable effect on reactive skills, but a deleterious effect on coordinative skills during the hangover phase. There was no correlation between the subjective severity of hangover and the deterioration of psychomotor skills. (JAM)

1976 24refs

UM-76-D0619

ACUTE EFFECTS OF OXAZEPAM, DIAZEPAM AND METHYLPERONE, ALONE AND IN COMBINATION WITH ALCOHOL, ON SEDATION, COORDINATION AND MOOD, L. Molander; C. Duvhök; Acta pharmacologia et toxicologia v38 n2 p145-60 (Feb 1976)

Effects on critical flicker fusion frequency (CFFF), coordination, and mood were studied after single oral doses of placebo; alcohol (0.5 ml ethanol/kg b. wt.); and oxazepam (10, 20 and 40 mg), diazepam (5, 10, 20 and 40 mg) and methylperone (10, 25 and 50 mg), given alone, simultaneously with alcohol, or with delayed alcohol administration. Compared to the benzodiazepines, methylperone had equal or greater depressant effects. The correlation between sedative and anti-anxiety effects was discussed. The decrease in CFFF was paralleled by decreased coordination ability. Alcohol, while inactive on the test parameters when given alone, markedly increased the effect of diazepam, and to a much lesser extent, the other drugs. The effect of the drugs on psychomotor skills and the interaction between alcohol and the drugs have important implications when treating outpatients. However, the situation for patients on long-term treatment may be different because of adaptation to the side effects. (JAM)

1976 31refs

UM-73-D0620

A MARIHUANA DOSE RESPONSE STUDY OF PERFORMANCE IN A DRIVING SIMULATOR, H. Moskowitz; S. Hulbert; W. McGlothlin, presented at the International Conference on Driver Behaviour, 1st, Zurich (Oct 1973)

This investigation was a double-blind examination of the effects of three doses of marihuana (50, 100, and 200 mcg/kg b. wt.) and placebo upon performance in a driving simulator using a film projection system and containing a subsidiary task requirement. The results provided no evidence that marihuana significantly affects car control and tracking performance. However, a dose-related impairment of reaction times to the subsidiary task indicated the impairment of perceptual functions.

The comparison of studies from this simulator for alcohol and marihuana suggested that alcohol had a greater detrimental effect than marihuana with commonly used dose levels. To establish the degree of driving performance impairment was considered difficult because the mechanisms involved in the

marihuana induced perceptual deficits appeared to differ from those affected by alcohol. (HSRI)

Univ. of California at Los Angeles, Los Angeles, Calif.

1973 16p 15refs

Presented at the First International Conference on Driver Behaviour, 8-12 Oct 1973, Zurich, Switzerland.

UM-75-D0621

KINETIC VISUAL ACUITY AS A DRIVING RELATED FUNCTION, A. B. Clayton, presented at the First International Congress on Vision and Road Safety, Paris (Feb 1975)

The effects of various psychotropic drugs on kinetic visual acuity (KVA) were reported. Alcohol decreased KVA in males, an effect attributed to perceptual processes. Trifluoperazine decreased, but three other tranquilizers, amylobarbitone sodium, chlordiazepoxide, and haloperidol, increased this ability in males. Haloperidol decreased KVA in females, however. Research needs in the area of drugs and driving were more epidemiological data and experimental work elucidating the interaction of drugs with such factors as age, sex, personality, and alcohol, as relates to driving safety. (HSRI)

Dept. of Transportation and Environmental Planning, Univ. of Birmingham, England.

1975 4p 8refs

Presented at the First International Congress on Vision and Road Safety, 10-13 Feb 1975, Paris.

UM-76-D0622

A TEST OF STATE DEPENDENCY EFFECTS IN MARIHUANA INTOXICATION FOR THE LEARNING OF PSYCHOMOTOR TASKS, A. L. Beautrais; D. F. Marks, Psychopharmacologia (Berlin) v46 n1 p37-40 (1976)

Thirty-nine subjects (18 male, 21 female), aged 21-34 years, were selected. Four experimental groups were formed using marihuana users and nonusers matched for education level. Marihuana cigarettes prepared to deliver 7 mg delta-9-THC were used. A placebo control was not employed in the 2 X 2 design for studying state-dependency since subject recognition might influence test results. A nondrug-control condition was used instead. Psychomotor tests were used to assess eye-hand coordination, steadiness, and motor speed were Card Sorting, Minnesota Rate of Manipulation--Block Turning, and Pursuit Rotor.

Results indicated that the training state had no effect on the final test performance. There were no significant differences between experienced cannabis users and nonusers with respect to psychomotor performance. The results also indicated that for these tasks, performance was contingent upon the state in which the subjects were tested and was not conditional on the drug conditions in which the subjects were trained. The demonstration of psychomotor impairment by cannabis has general significance for the performance in real-life situations. (HSRI)

1976 22refs

UM-73-D0623

DÖDSFALL I SAMBAND MED MISSBRUK AV ORGANISKA LÖSNINGSMEDEL (DEATHS IN CONNECTION WITH ABUSE OF ORGANIC SOLUTIONS), M. Edh; A. Selerud; C. Sjöberg, Lakartidningen v70 n44 p3949-59 (31 Oct 1973)

This study reported 63 deaths in Sweden which occurred in association with

intoxication with organic solvents. In 58 cases, solvent sniffing was regarded as the sole cause of death or as a strong contributory factor. Poisoning (including Sudden Sniffing Deaths) was the major cause of death (50%), followed by suicides (20%) and car accidents (16%). Trichloroethylene was the predominant toxic substance identified, and thinner intoxication was implicated in other deaths.

Half of the deaths occurred in the 15-18 year age group. Social and demographic conditions were reported and discussed. According to the authors, this report provides very strong evidence of the danger of fatal poisoning with trichloroethylene and of the tendency to serious behavioral changes resulting from thinner intoxication which could lead to suicide and car accidents. (JAM)

1973 [Swedish]

English summary on p3959.

UM-73-D0624

ACCIDENT AND VIOLATION RATES AMONG CANNABIS USERS BEFORE AND AFTER THEIR CONVICTION FOR CANNABIS OFFENSES, R. G. Smart, presented at the International Conference on Driver Behaviour, 1st, Zurich, (Oct 1973)

The problem of cannabis use and driving risk was approached by studying the driving and accident experiences of marihuana users. The main purpose of the study was to determine how accidents and violations varied over the year prior to and subsequent to conviction.

The data for young people convicted of cannabis offenses indicated that a year prior to conviction their rates of collision and driving convictions were much higher than for experienced drivers of comparable age and sex in Ontario. For both collisions and driving convictions, rate reductions appeared to be associated with cannabis conviction. Alternative explanations were explored and previous study results were discussed. (HSRI)

Addiction Res. Foundation, Toronto, Canada

1973 11p 12refs

Presented at the First International Conference on Driver Behaviour, 8-12 Oct 1973, Zurich, Switzerland.

Report No.: SM9c

UM-74-D0625

HUMAN PERFORMANCE AFTER A BARBITURATE (HEPTABARBITONE), R. G. Borland; A. N. Nicholson, British Journal of Clinical Pharmacology v1 n3 p209-15 (Jun 1974)

The residual effects of heptabarbitone given overnight were studied in seven healthy males by an adaptive tracking technique. Decrements in performance were observed at the 10 h interval after 200 mg; at the 10 and 13 h intervals after 300 mg; and at the 10, 13, 16, and 19 h intervals after 400 mg of the drug. Decrements in performance at each interval and the persistence of the effects were dose related.

Subjective assessment of performance correlated with measured performance, but as a group the subjects overestimated performance after placebo and drug. Individual blood concentrations of heptabarbitone did not give a significant correlation with individual performance decrements, indicating blood levels of the drug would not provide a means of predicting performance decrements. However, blood concentrations and performance decrements at each dose were related. (JAM)

1974 12refs

UM-74-D0626

PHYSIOLOGICAL AND PSYCHOLOGICAL EFFECTS OF (±)-PROPRANOLOL, (+)-PROPRANOLOL AND DIAZEPAM IN INDUCED ANXIETY, P. J. Tyrer; M. H. Lader, British Journal of Clinical Pharmacology v1 n5 p379-85 (Oct 1974)

Four equal-sexed groups of eight normal subjects were given single doses of either (±)-propranolol (120 mg), (+)-propranolol (120 mg), diazepam (6 mg), or placebo using double-blind procedure. The drug effects were studied under three types of experimental stress and at rest. Finger tremor, EEG, averaged evoked response, skin conductance, heart rate, and respiratory rate were measured at each time of testing, and subjects also completed performance tests (reaction time, tapping speed and symbol copying) and subjective mood scales.

Diazepam reduced subjective anxiety, significantly lessened the main amplitude of the auditory evoked response and also reduced the proportion of the slower rhythms in the EEG. The results suggested that (+)- and (±)-propranolol had no psychotropic effects on induced anxiety and that their modes of action were fundamentally different than that of diazepam. Neither (+)- nor (±)-propranolol had any beneficial effects on mood and psysiological tests showed that, although adequate beta-adrenoceptor blockade was achieved, there was no evidence of sedation. (JAM)

1974 43refs

UM-74-D0627

THE CLINICAL PHARMACOLOGY OF VILOXAZINE HYDROCHLORIDE--A NEW ANTIDEPRESSANT OF NOVEL CHEMICAL STRUCTURE, P. F. C. Bayliss; S. M. Duncan, British Journal of Clinical Pharmacology v1 n5 p431-7 (Oct 1974)

Viloxazine (100 mg base) was compared to placebo and imipramine (50 mg salt) in a series of double-blind randomized studies. The effects of the compounds on flicker fusion frequency, salivary flow, pupil size and palpebral fissure size were determined. In addition, the possible interaction between viloxazine and alcohol was investigated using measurements of reaction time.

Among the experimental differences between the two antidepressants, viloxazine depressed critical flicker frequency whereas imipramine did not; imipramine prolonged reaction time while viloxazine did not; and imipramine reduced salivary flow and increased the size of the pupil and palpebral fissure, but viloxazine was inactive in these respects. Imipramine was shown to potentiate alcohol, whereas viloxazine appeared to have less anticholinergic and possibly less sympathomimetic properties than imipramine. (JAM)

1974 11refs

UM-75-D0628

IMMEDIATE EFFECTS ON HUMAN PERFORMANCE OF A 1,5-BENZODIAZEPINE (CLOBAZAM) COMPARED WITH THE 1,4-BENZODIAZEPINES, CHLORDIAZEPOXIDE HYDROCHLORIDE AND DIAZEPAM, R. G. Borland; A. N. Nicholson, British Journal of Clinical Pharmacology v2 n3 p215-21 (Jun 1975)

Measurements of adaptive track performance and reaction times after ingestion of clobazam (20 mg), chlordiazepoxide (20 mg), and diazepam (10 mg) were made at 0.5, 2.5, 5.5, and 9.5 hours. Performance decrements on adaptive tracking were observed after diazepam but not after clobazam and chlordiazepoxide. Reaction times were slowed by chlordiazepoxide and diazepam, but not by clobazam. Subjective assessments made by the subjects as a group differentiated correctly between performance decrements on adaptive tracking after diazepam and their absence after the other drugs. Differences in benzodiazepine properties led the authors to recommend that choice of drug be based on careful consideration of performance sequelae. (JAM)

1975 11refs

UM-75-D0629

COMPARISON OF THE RESIDUAL EFFECTS OF TWO BENZODIAZEPINES (NITRAZEPAM) AND FLURAZEPAM HYDROCHLORIDE) AND PENTOBARBITONE SODIUM ON HUMAN PERFORMANCE, R. G. Borland; A. N. Nicholson, British Journal of Clinical Pharmacology v1 n1 p9-17 (Feb 1975)

Measurements of adaptive tracking performance and reaction times were made 10, 13, 16, 19, and 34 hours after ingestion of nitrazepam (10 mg), flurazepam HCl (30 mg) and pentobarbitone sodium (200 mg). Impaired performance on adaptive tracking and increased reaction times were observed after each drug; the persistence of the effects varied according to the task and drug. During the morning after drug taking, the subjects could differentiate between drug and placebo, but could not correctly assess the persistence of the residual effects of nitrazepam and pentobarbitone sodium. Flurazepam appeared to be the most promising drug due to rapid recovery of performance and the ability of subjects to recognize impaired skills after taking the drug. (JAM)

1975 20refs

UM-75-D0630

BEHAVIOURAL SEQUELAE OF METHAQUALONE IN MAN AND IN THE MONKEY (MACACA MULATTA), R. G. Borland; A. N. Nicholson; C. M. Wright, British Journal of Clinical Pharmacology v2 n2 p131-41 (Apr 1975)

Residual effects of methaqualone hydrochloride (400 mg) were studied in six healthy male subjects. Measurements of adaptive tracking performance and reaction time were made 10, 13, 16, 19, and 34 hours after overnight ingestion of the drug. Subjective assessments of performance were obtained after each tracking task. Subjects were required to reach a plateau level of tracking performance before studies commenced, and practice sessions were permitted between experiments to maintain levels of performance reached after training. In the monkey, effects of methaqualone (20 and 30 mg/kg) were studied by a delayed matching task in which total response time was measured.

In the human subjects, there was no evidence of impaired performance on adaptive tracking from 10 to 19 hours, but enhanced performance was observed 34 hours after ingestion. An increase in reaction time was observed at 10 hours and a decrease was found at 19 hours. In the monkey, no consistent effects on matching behavior or on total response time were observed 2 hours after intraperitoneal injection. These studies suggest that methaqualone hydrochloride may be a valuable hypnotic for occasional use by persons involved in skilled activity. (HSRI)

1975 18refs

UM-76-D0631

PHARMACOLOGY AND TOXICOLOGY OF LITHIUM, M. Shou, Annual Review of Pharmacology and Toxicology v16 p231-43 (1976)

A selective review of the pharmacology and toxicology of lithium, this paper dealt with the element's pharmacokinetics, its effects on behavior and mental functions, and human and animal physiology. Specific topics included interaction with other drugs, lithium-induced thyroid dysfunction, and electrophysiological changes in human volunteers, patients, and experimental animals. The author concluded that the mode of action of lithium in manic-depressive disorder was still unknown, and that it was difficult to decide which, if any, of the many known lithium effects were relevant to the clinical action of the drug. (HSRI)

1976 150refs

HS-801 915 UM-76-D0632

PSYCHOSOCIAL IDENTIFICATION OF DRIVERS RESPONSIBLE FOR FATAL VEHICULAR ACCIDENTS IN BOSTON, R. S. Sterling-Smith, National Highway Traffic Safety Administration (May 1976)

This final report includes a total human factor data presentation, analysis, evaluation and interpretation of selected variables collected by the Boston University Traffic Accident Research Special Study Team during the 30 month period of the experimental sample field investigation. Throughout this research effort the primary focus of investigation has been with the historical and focal human factor variables associated with the operators of motor vehicles initially judged to have been "most responsible" operators for vehicular accidents involving a fatality.

The areas of primary interest presented in this report on 300 operators include: demographic and psychosocial variables, historical patterns of alcohol use and focal accident alcohol involvement, historical patterns of marihuana and street/entertainment drug use and focal accident involvement, the Risk Taking Behavior Scale, and the focal Human Factor Stress Scale. (AAM)

Traffic Accident Res. Proj., Boston Univ. School of Law, Boston, Mass. 02215.

1976 203p 20refs

DOT-HS-310-3-595

Final Report, Part 1; DOT-HS-801 915

HS-801 916 UM-76-D0633

AN ANALYSIS OF DRIVERS MOST RESPONSIBLE FOR FATAL ACCIDENTS VERSUS A CONTROL SAMPLE, Boston University Traffic Accident Research Project, National Highway Traffic Safety Administration (May 1976)

Following the field investigation in which data was collected on 267 motor vehicle operators "most responsible" for a highway fatality, the Boston University Traffic Accident Research Special Study Team collected a matched control sample of 801 operators "never responsible" for a fatal highway accident. The experimental sample was evaluated from two differing perspectives: accident typology and alcohol involvement.

Subsequent analysis established pre-identification and predictive variables to identify operators who might be potential candidates for a fatal highway accident. The variables most significant in the executed discriminant function analysis included: previous arrests for DWI and speeding, alcohol use patterns, levels of education and occupation. The results detailed a Boston Predictive Formula for identifying potentially high risk operators from the general population. (AAM)

Traffic Accident Res. Proj., Boston Univ. School of Law, Boston, Mass. 02215.

1976 177p 5refs

DOT-HS-310-3-595

Final Report, Part 2; DOT-HS-801 916

HS-801 917 UM-76-D0634

MARIJUANA AND DRIVER BEHAVIORS: HISTORIC AND SOCIAL OBSERVATIONS AMONG FATAL ACCIDENT OPERATORS AND A CONTROL SAMPLE, R. S. Sterling-Smith; D. D. Graham, National Highway Traffic Safety Administration (May 1976)

This analysis and evaluation of data from 1068 motor vehicle operators concentrated on marijuana use patterns and corresponding demographic, psychosocial, alcohol, and other drug and vehicular variables. A sample of operators "most responsible" for a fatal highway accident and a control group without any fatal accident histories were divided into subsamples of marijuana smokers and nonsmokers. Notable differences were observed between the four subsamples and between smokers and nonsmokers.

The control smokers were overachievers and the experimental ("most responsible") smokers underachievers. The control smokers were more successful with their education and occupation than were the experimental smokers. Other observations were collected from only the control smokers relative to subjective impressions of behavioral alterations when marijuana intoxicated as well as more objective variables associated with marijuana use patterns. The control operator smoking group presented opinions about levels of risk when marijuana influenced and when sober while operating a motor vehicle. The 43 (16%) of the experimental operators who were evaluated to have been marijuana influenced at the time of the focal accident were analyzed and the findings presented. (AAM)

Traffic Accident Res. Proj., Boston Univ. School of Law, Boston, Mass. 02215.

1976 196p 33refs

DOT-HS-310-3-595

Final Report, Part 3; DOT-HS-801 917

UM-74-D0635

ACUTE EFFECT OF ANTIPYRETIC ANALGESICS, ALONE OR IN COMBINATION WITH ALCOHOL, ON HUMAN PSYCHOMOTOR SKILLS RELATED TO DRIVING, M. Linnoila; T. Seppälä; M. J. Mattila, British Journal of Clinical Pharmacology v1 n6 p477-84 (Dec 1974)

Effects of acetylsalicylic acid (1 g), indomethacin (50 mg), and phenylbutazone (200 mg) on psychomotor skills were examined double-blind on 180 volunteer students. Ninety students received ethyl alcohol (0.5 g/kg) and 90 subjects an equal volume of placebo drink in combination with the drugs. Psychomotor skills were measured with a choice reaction test, two coordination tests, and a divided attention test having correlation with traffic behavior. Subjects assessed their feelings of performance by means of a rating scale. The tests were performed 30, 90, and 150 minutes after administration of the agents.

Acetylsalicylic acid proved inactive whereas both indomethacin and phenylbutazone impaired eye-hand coordination and divided attention. Acetylsalicylic acid did not interact with alcohol to a measurable extent whereas indomethacin in combination with alcohol proved less harmful than without it. The deleterious effects of phenylbutazone and alcohol were additive. It was concluded that an impairment of psychomotor skills related to driving by indomethacin and phenylbutazone should be considered when prescribing these drugs to active outpatients. (JAM)

1974 17refs

UM-74-D0636

EFFECTS OF LOW DOSES OF AMYLOBARBITONE AND DIAZEPAM ON HUMAN PERFORMANCE TESTS, C. Bye; J. Hart; A. M. Peck; R. T. Wilkinson, British Journal of Clinical Pharmacology v1 n2 p173P-4P (Apr 1974)

This communication reports a double-blind study designed to compare the effects of amylobarbitone (50 and 100 mg), diazepam (2.5 and 5.0 mg), and placebo on normal subjects. Forty-five minutes following administration, subjects began a 2 hour schedule which included tests of vigilance, short-term memory, auditory reaction time, visual search, tapping, digit symbol substitution, and subjective effects measurement. The tests were repeated after a 1 hour lunch.

Vigilance was impaired by each drug treatment; reaction time increased only after the higher doses, with the effect of amylobarbitone detectable more than 5 hour postdrug. Short-term memory was transiently affected by the drug treatments, as was digit symbol substitution. Impairment in performance following low doses of the drugs occurred in tests which were either long and tedious, or required efficient short-term memory. Diazepam (2.5 mg) gave no significant subjective effects, but impaired short-term memory and vigilance. (HSRI)

Wellcome Res. Labs., Beckenham; Medical Res. Council Applied Psychology Unit, Cambridge, England.

1974 5refs

Presented at a meeting of the British Pharmacological Society, Clinical Pharmacology Selection, 2-4 Jan 1974, King's College, Univ. of London.

UM-74-D0637

DRUG-ALCOHOL INTERACTION ON PSYCHOMOTOR SKILLS DURING SUBACUTE TREATMENT WITH BENZODIAZEPINES, FLUPENTHIXOLE, OR LITHIUM, M. Linnoila; I. Saario; M. J. Mattila, British Journal of Clinical Pharmacology v1 n2 p176P (Apr 1974)

Double-blind, crossover trials were performed in 40 healthy male volunteer students over three consecutive 2 week periods. Treatment with diazepam (5 mg t.i.d.), lithium (serum 0.75 mEq/l), chlordiazepoxide (10 mg t.i.d.), or flupenthixole (0.5 mg t.i.d.), and placebo was allocated according to a Latin square design. At the end of each week tests for choice reaction, coordination at two tracking speeds, and divided attention were done 30, 90, and 150 minutes after ingestion of placebo or an alcoholic drink (0.5 g/kg).

Among the findings, diazepam improved reactive skills and attention, slightly improved coordination at fixed speed, but provoked subjects to drive faster and make more mistakes at free speed. Alcohol and diazepam together impaired reactive skills. Neither chlordiazepoxide nor flupenthixole showed major interaction with alcohol on reactive skills, but both with alcohol contributed to deterioration of coordinative skills. Lithium alone impaired reactive but not coordinative skills or attention. (HSRI)

Dept. of Pharmacology, Univ. of Helsinki, SF-00170 Helsinki, Finland.

1974 1ref

Presented at a meeting of the British Pharmacological Society, Clinical Pharmacology Section, 2-4 Jan 1974, King's College, Univ. of London.

UM-75-D0638

A CLINICAL AND PSYCHOMETRIC EVALUATION OF FLURAZEPAM, M. R. Salkind; T. Silverstone, British Journal of Clinical Pharmacology v2 n3 p223-6 (Jun 1975)

The efficacy of flurazepam (15 and 30 mg) as a hypnotic, and the residual

effects of each dose were compared with placebo in a double-blind crossover trial involving 30 patients in a general practice setting. Patients received each medication for 1 week. Daily self-ratings of onset, duration and quality of sleep, together with reports of any untoward effects were made. At the end of each period of medication, psychomotor tests (reaction time, pursuit rotor, tapping speed) were administered.

Both doses were significantly more effective than placebo in inducing sleep, improving quality of sleep and extending its duration. "Hangover" effects were marked following 30 mg, but not after 15 mg. Thirty mg of drug significantly impaired performance on the pursuit rotor test and tapping speed. Flurazepam was considered to be an effective hypnotic drug with the optimum dose for use in general practice being 15 mg at night. (JAM)

1975 11refs

UM-61-D0639

THE EFFECT OF MEPROBAMATE ON THE PERFORMANCE OF NORMAL SUBJECTS ON SELECTED PSYCHOLOGICAL TASKS, L. Melikian, Journal of General Psychology v65 n1 p33-8 (Jul 1961)

This double-blind study compared the effects of meprobamate, placebo and water on the function and performance of seven psychological tasks of 30 normal subjects. Included in the study were the Maudsley Personality Inventory, Visual Threshold, Auditory Threshold, Digit Span, Draw-a-Person Test, Digit Symbol, and Speed of Speech. A daily dose of 800 mg meprobamate was given to the drug group subjects.

No significant differences in the effects of the variables on the tasks appeared during the initial testing, 30 min after administration of the drug, or one week later. The results indicated that the use of meprobamate at the dose used in the experiment does not impair performance on the selected tasks. (HSRI)

1961 6refs

UM-76-D0640

PHARMACOKINETICS OF DELTA-8-TETRAHYDROCANNABINOL (DELTA-6-TETRAHYDROCANNABINOL) IN MAN AFTER SMOKING--RELATIONS TO PHYSIOLOGICAL AND PSYCHOLOGICAL EFFECTS, S. Agurell; S. Levander; M. Binder; A. Bader-Bartfai; B. Gustafsson; K. Leander; J.-E. Lindgren; A. Ohlsson; B. Tobisson, in The Pharmacology of Marihuana, M. C. Braude; S. Szara, eds., Raven Press, New York (1967) p49-61

Using a highly sensitive, gas chromatography-mass fragmentographic assay, the authors correlated plasma levels of delta-8-tetrahydrocannabinol (THC) in six male casual smokers with the following measures of psychomotor performance; critical flicker fusion (CFF); two choice reaction time tests (RT); and vernier visual acuity (KVAT). In addition, physiological parameters (heart rate (HR), respiration, and electrocardiogram) were recorded.

Peak concentrations occurred immediately after the smoking of 8.3 mg THC, dropping from 100-200 ng/ml of plasma to 10-20 ng/ml in 30 minutes. A significant decrease in performance both for CFF and RT, and a slight trend in the same direction for KVAT, was observed. HR was positively correlated with plasma levels of THC, but CFF and RT results were not. The authors concluded that, if delta-8- and delta-9-THC have similar effects, then the plasma levels of THC are not an entirely relevant parameter for estimating the degree of impairment in performance. (HSRI)

1976 22refs

UM-66-D0641

THE STROOP COLOR-WORD TEST: A REVIEW, A. R. Jensen; W. D. Rohwer, Jr., Acta psychologia v25 n1 p36-93 (Jan 1966)

The history and development of the Stroop Color-Word Test was related, and the authors concluded that a standardization of the test form was required. Methods of administration and scoring of test results were discussed, and the effects of practice were analyzed. The phenomena of the test, why it takes one longer to name colors than to read color names, was explored, and theories were reviewed. The effects of such variables as age, sex, race, and the effects of drugs on the test were discussed. Psychological attributes and mental abilities were related to performance on the test.

The authors concluded that the Stroop measures certain highly stable characteristics of individuals, though the psychological nature of these characteristics are not known. The test yields highly reliable measures of individual differences on three "factors": speed or "personal tempo", color naming difficulty, and interference proneness. The test has been used in some seventy studies in such diverse fields as perception, learning, personality, psychiatric diagnosis, and psychopharmacology. (HSRI)

1966 83refs

UM-73-D0642

MENTAL AND PSYCHOMOTOR EFFECTS OF DIAZEPAM AND ETHANOL, J. F. W. Haffner; J. Mørland; J. Setekleiv; C. E. Strømsaether; A. Danielsen; P. T. Frivik; F. Dybing, Acta pharmacologica et toxicologia v32 n3-4 p161-78 (Mar 1973)

The perfomance of eight healthy young males was tested by means of eight psychological and psychomotor tests 1-3/4 and 4-1/2 hours after administration of either ethanol, diazepam (10 and 20 mg) or placebo. Mean plasma concentrations of diazepam and ethanol were estimated by gas chromatography and the ADH method, respectively, at the time of testing.

Both diazepam and ethanol reduced the scores in the following tests: memorizing, sorting (of colored tablets), complex coordination and critical flicker fusion frequency. Scores in letter cancellation and mirror tracing tests were also reduced by both drugs, but in different ways. Diazepam (20 mg) reduced subjects' time evaluation ability, while ethanol did not significantly affect it. Judged by clinical examination, diazepam had a less marked effect on proprioception, speech and balance than ethanol (0.05% - 0.09%). The effect of diazepam on the flicker fusion and mirror tracing tests could still be recognized 4-1/2 hours after administration of the drug. (JAM)

1973 9refs

UM-75-D0643

DRUGS AND DRIVING, B. M. Ashworth, British Journal of Hospital Medicine v13 n2 p201-4 (Feb 1975)

The author briefly reviews the methods of assessing the effects of drugs on driving and discusses the unsatisfactory nature of experimental work in this area. Literature concerning the effects of psychoactive drugs on driving related skills is cited for marihuana, barbiturates, ataractics, antidepressants, antihistamines and the interaction of drugs with alcohol. (HSRI)

1975 22refs

UM-74-D0644

THE EFFECTS OF TWO TRANQUILLIZERS ON DRIVING PERFORMANCE AS MEASURED IN THE NORMAL DRIVING TASK, B. Biehl, presented at the 18th Congress of the International Association of Applied Psychology, Montreal (Jul 1974)

The problems related to measuring the effects of psychoactive drugs on driving performance are briefly discussed. Subjects selected for high neuroticism were each tested under clobazam (20 mg), diazepam (10 mg) and placebo. A driving test using a car with dual controls and an instructor under actual driving conditions and a battery of four laboratory tests were used to assess the effects of the drugs on 37 variables.

Under the conditions of the tests, significant drug effects were registered for only three of the 37 variables. Under diazepam and clobazam, readiness to brake was lower and higher than placebo, respectively. None of the laboratory tests of performance, which have been shown to be sensitive as measures of drug influence, was significantly affected by the drugs. Subjective mood assessments indicated that diazepam induced more depressed feelings along with lower activity. (HSRI)

Univ. of Mannheim.

1974 16p

Conference: 18th Congress of International Association of Applied Psychology, Montreal, Canada, July 1974.

UM-76-D0645

DRUG INTERACTIONS, D. A. Hussar, Clinical Toxicology v9 n1 p107-18 (Feb 1976)

The incidence, cause and detection of drug interactions are the subjects of this editorial. The development of many new therapeutic agents has led to complex drug therapy and the greater possibility of drug-related problems. One solution is the keeping of a medication profile by the pharmacist. Studies of the incidence of drug interactions are reviewed.

Reasons discussed for the increased evidence of drug interactions are drug potency, use of several physicians by the same patient, concurrent use of prescription and nonprescription drugs, patient noncompliance with physician's instructions, and drug abuse. Reasons for the lack of detection and underreporting of drug interactions are cited. (HSRI)

1976 18refs

UM-76-D0646

THE CLINICAL TOXICOLOGY OF SOLVENT ABUSE, J. W. Hayden; E. G. Comstock, Clinical Toxicology v9 n2 p169-84 (Apr 1976)

Solvent abuse is defined as the intentional inhalation of volatile organic chemicals other than the conventional anesthetic gases. Pathologic changes in kidney and liver function, hematologic effects, and effects on neuromuscular function as a result of solvent inhalation are reviewed with 50 citations.

From the review of the literature and the authors' experience at the Houston Polydrug Abuse Project, it is apparent that gross pathologic changes in solvent abusers are rare. A problem is that possible metabolic or morphologic changes may not be detectable at an early stage by routine clinical laboratory tests. Further research may yield sensitive methods for the evaluation of solvent-induced physiologic damage before it reaches such gross proportions as diffuse cerebral atrophy. (HSRI)

1976 50refs

UM-75-D0647

THE ADVERSE EFFECTS OF AMPHETAMINES, J. B. Hart; J. Wallace, Clinical Toxicology v8 n2 p179-90 (Apr 1975)

An informal review of the major toxicological aspects of amphetamine use, both medical and nonmedical, includes discussions of addiction and tolerance, the hazards of intravenous use, cardiovascular effects, amphetamine-induced psychosis and its alteration of the user's life-style.

The authors see most of the adverse effects of amphetamine as indirect and psychosociologic. Indirect effects include hepatitis and infection; malnutrition; disrupted sleep patterns, interpersonal and occupational activities; and psychological addiction. Serious side effects are predominant with the repeated use of high doses of amphetamine. (HSRI)

1975 19refs

UM-75-D0648

COCAINE: HISTORY, EPIDEMIOLOGY, HUMAN PHARMACOLOGY, AND TREATMENT. A PERSPECTIVE ON A NEW DEBUT FOR AN OLD GIRL, G. R. Gay; D. S. Inaba; C. W. Sheppard; J. A. Newmeyer; R. T. Rappolt, Clinical Toxicology v8 n2 p149-78 (Apr 1975)

The authors contribute a well-rounded review of cocaine usage, including a detailed historical account and material drawn from the contemporary drug culture. The pharmacologic action of cocaine and its effects on the central nervous system and the cardiovascular system are briefly summarized. Toxic effects, in addition to euphoric excitement and the hallucinatory experience, are irrationality, paranoia, a proneness to violence, and a true toxic psychosis. Continued use leads to nervousness, depression and sleeplessness. The epidemiological aspects of recent cocaine use are discussed from the vantage point of the Haight-Ashbury Free Medical Clinic. (HSRI)

1975 61refs

UM-76-D0649

ETHANOL METABOLISM AND ETHANOL-DRUG INTERACTIONS, E. Mezey, Biochemical Pharmacology v25 n8 p869-75 (15 Apr 1976)

The metabolism of ethanol occurs principally by two routes: acetaldehyde formation by alcohol dehydrogenase and, to a lesser extent, by the microsomal enzyme system. Alcohol influences the microsomal metabolism of a number of drugs. Inhibition results from direct interference by ethanol while enhanced metabolism is due to enzyme induction. On the other hand, drugs may inhibit or accelerate the metabolism of ethanol. Since alcoholic patients are frequently given tranquilizing drugs, and since many people drink while taking drugs prescribed for other diseases, metabolic drug interactions have an obvious importance for further research. (HSRI)

1976 101refs

UM-74-D0650

COMBINED EFFECTS OF DIAZEPAM AND ETHANOL ON MENTAL AND PSYCHOMOTOR FUNCTIONS, J. Mørland; J. Setekleiv; J. F. W. Haffner; C. E. Strømsaether; A. Danielsen; G. H. Wethe, Acta pharmacologia et toxicologia v34 n1 p5-15 (Jan 1974)

The performances of eight healthy young males were tested 1-3 hrs after oral administration of placebo, 10 mg diazepam (mean serum levels 286-281 ng/ml, respectively), ethanol (mean serum levels 0.080-0.043), or the same amount of ethanol (mean serum levels 0.081-0.045) combined with 10 mg diazepam (mean serum levels 289-339 ng/ml).

Both ethanol and diazepam reduced concentration, efficiency and attention (Osgood Test). Combined administration augmented this subjective impression and also reduced motivation. Ethanol significantly reduced the score in the minor tracing test, and diazepam significantly reduced the score in the letter cancellation, flicker fusion frequency, and mirror tracing tests, and in the clinical examination. Combined administration of ethanol and diazepam increased the detrimental effects on the tests mentioned above, and also increased the effect on time evaluation, complex coordination, and sorting tests. (JAM)

Generally, diazepam slowed the subjects; ethanol speeded them up, but increased their errors; combined administration both slowed them and increased error making. Subjects tested were without medical need for diazepam, and psychomotor and mental functions might be changed differently in patients undergoing treatment with diazepam. However, it seems likely the effects are important for driving ability, and drivers should be warned against the use of alcohol while under diazepam treatment.

1974 6refs

UM-75-D0651

HUMAN AND ANIMAL STUDY ON ELIMINATION FROM PLASMA AND METABOLISM OF DIAZEPAM AFTER CHRONIC ALCOHOL INTAKE, R. Sellman; J. Kanto; E. Raijola; A. Pekkarinen, Acta pharmacologia et toxicologia v36 n1 p33-8 (Jan 1975)

Significantly lower concentrations of diazepam at 15 minutes and 1 hour after 10 mg intravenous diazepam injection was found in chronic alcoholic patients in comparison to healthy controls. In addition, a more rapid elimination of diazepam from plasma was observed in alcoholic patients during their alcohol free period. The alcoholics had a smaller concentration of the diazepam main metabolite, N-demethyldiazepam. Concentrations of free plasma oxazepam, a hydroxylated metabolite, were not observed after a single dose of diazepam in either group.

A more rapid elimination of diazepam after 5 mg/kg i. p. in the plasma of rats pretreated with ethanol (15% in drinking water for 3 weeks) was found than in control rats. Alcohol rats had higher plasma concentrations of oxazepam but not of the demethylated metabolite. Increased distribution of diazepam from plasma in man and in the rat was postulated to account for lower diazepam levels in plasma after ethanol pretreatment. (JAM)

1975 13refs

UM-75-D0652

EFFECTS OF DIAZEPAM AND ETHANOL ON HEART RATE AND GALVANIC SKIN RESPONSES, A. Danielsen; J. F. W. Haffner; J. Mørland; J. Setekleiv; P. T. Frivik; C. E. Strømsaether, Acta pharmacologia et toxicologia v36 n2 p113-22 (Feb 1975)

Heart rate (HR), heart rate variability (HRV), and the amplitude and frequency of galvanic skin responses (GSR) were studied in nine healthy young males 2-3 hours after oral administration of placebo, diazepam (10 or 20 mg/70 kg), ethanol (0.78 and 1.22 ml/kg), or combined administration of diazepam (10 mg) and ethanol (0.78 ml/kg). When examinations were performed in resting subjects, ethanol produced significant increases in HR, as did combined administration of the drugs. HRV, supposedly correlated with reaction time, was reduced by the combination. The frequency of GSR was reduced by both alcohol and 20 mg diazepam while complex patterns of the GSR amplitude were observed.

Stimulation of the subjects by mental arithmetic increased all parameters, and more so after drug treatment than after placebo. The results are discussed in relation to the possible effects of diazepam on the autonomic nervous system and in relation to a psychophysiological activation theory

which presupposes that increased activation is related to increased sympathetic activity. It is concluded that the parameters used are not reliable as indicators of whether a drug is deactivating or not. (JAM)

1975 17refs

UM-76-D0653

EFFECT OF SUBACUTE TREATMENT WITH HYPNOTICS, ALONE OR IN COMBINATION WITH ALCOHOL, ON PSYCHOMOTOR SKILLS RELATED TO DRIVING, I. Saario; M. Linnoila, Acta pharmacologia et toxicologia v38 n4 p382-92 (Apr 1976)

The effect of two weeks' treatment with amylobarbitone, flurazepam, a combination of methaqualone and diphenhydramine, or glutethimide, and their interaction with alcohol, was examined in 40 healthy volunteers in two double blind crossover trials. The drugs and placebo were given orally every night between 10 and 11 pm for two weeks; the treatment periods were alternated in random order. Psychomotor skills were tested on the 7th and 14th treatment mornings by a choice reaction test, two coordination tests and a divided attention task 30, 90 and 150 minutes after the previous administration of alcohol or placebo. In addition, serum levels of the drugs were determined. After both trials were over, the subjects of the final placebo trial were tested once more after one night's deprivation of sleep.

Amylobarbitone and flurazepam alone impaired eye-hand coordination whereas the residual effect after methaqualone-diphenhydramine or glutethimide on psychomotor performance was negligible. Amylobarbitone and flurazepam also enhanced the alcohol-induced impairment of coordinative skills. Deprivation of sleep did not impair psychomotor performance. The subjects regarded flurazepam and methaqualone-diphenhydramine as the most potent hypnotics, and these drugs caused most of the side effects reported. (JAM)

1976 15refs

UM-76-D0654

VISUAL SEARCH BEHAVIOR WHILE VIEWING DRIVING SCENES UNDER THE INFLUENCE OF ALCOHOL AND MARIHUANA, H. Moskowitz; K. Ziedman; S. Sharma, Human Factors v18 n5 p417-32 (Oct 1976)

Two experiments were performed to determine the effects of alcohol and marihuana on visual scanning patterns in a simulated driving situation equipped with an Eye Point of Regard system. Critical events (various events or objects on the film which an alert driver should notice since they might call for a safety reaction) were determined and the drivers' response to them analyzed.

In the first experiment 27 male heavy drinkers were divided into three groups of nine, defined by three blood alcohol levels produced by alcohol treatment: 0.0%, 0.075% and 0.15% BAC's. Significant changes in visual search behavior including increased dwell duration, decreased dwell frequency, and increased pursuit duration and frequency were found under alcohol. In addition, results for critical events indicated that alcohol caused reduced examination of events' internal details and reduced the attention paid to other events during that time.

In the second experiment 10 male social users of marihuana were tested under both 0 mcg and 200 mcg tetrahydrocannabinol per kilogram bodyweight. Marihuana was found to have no effect on visual search behavior. The results are related to previous studies of alcohol and marihuana effects on information processing. Other studies have shown that marihuana strongly affected visual autokinesis, vigilance and measures of concentrated attention in situations where alcohol has produced no impairment. It is concluded that the perceptual deficits in performance caused by alcohol or marihuana have a different character. (HSRI)

1976 22refs

UM-76-D0655

SMOKING POT AND DRIVIN', Anonymous, Driver v10 n3 p8-13 (Aug 1976)

This anecdotal summary of marihuana effects on driving performance contains personal accounts of driving experiences by users of the drug, and a description of the Department of Defense rehabilitation program for military personnel who are drug users. Those who make use of the service may volunteer, but most are mandatorily enrolled after being arrested, investigated for possessing or using drugs, or identified for rehabilitation following medical care or detection through urinalysis. (HSRI)

1976

UM-76-D0656

DRUG USE AND DRIVING BY A UNIVERSITY STUDENT SAMPLE, R. G. Mortimer, in Proceedings of 20th Conference of the American Association for Automotive Medicine, D. F. Huelke, ed., AAAM, 1976, p198-210

A survey was taken of the frequency and kind of drugs used at the University of Illinois in 1975, and compared with the same survey used to assess drug use by students at Eastern Michigan University (EMU) in 1971, at any time and shortly before driving. The survey provided biographical data of the respondents, their number of accidents, violations and miles driven in the previous 12 months. Alcohol, marihuana, caffeine and nicotine were most frequently used, but the use of narcotics, other sedatives, stimulants, hallucinogens, and chemicals was reported by the students.

Automatic Interaction Detector (AID) analyses were carried out on the EMU data to find those biographical and drug usage variables which were most associated with accident and violation rates. The results showed that those who had elevated violation rates had a different profile of drug use than those with higher rates of accidents. Alcohol users while driving had higher violation rates, while female marihuana and alcohol users and male alcohol users were identified as having higher accident rates. The use of caffeine or smoking tobacco (nicotine) appeared to reduce the effects of other drugs on both violation and accident rates. (AAM)

Illinois University, Champaign, Dept. of Health and Safety Education.

1976 13p 7refs

UM-76-D0657

EFFECTS OF MARIHUANA-DEXTROAMPHETAMINE COMBINATION, M. A. Evans; R. Martz; B. E. Rodda; L. Lemberger; R. B. Forney, Clinical Pharmacology and Therapeutics v20 n3 p350-58 (Sep 1976)

The purpose of this investigation was to evaluate the cardiovascular, psychologic and psychomotor effects of marihuana and amphetamine, alone and in combination, and to investigate the possibility and nature of an interaction between them. Under a double-blind, randomized, complete block design, subjects were given either placebo or 10 mg/70 kg dextroamphetamine sulphate (A) orally, followed 1-1/2 hr later by a marihuana cigarette (M) prepared to deliver 50 mcg/kg delta-9-tetrahydrocannabinol (THC).

Statistical analyses suggested that heart rate and blood pressure increased in an additive manner when both drugs were given. Electrocardiogram changes, when present, were nonspecific in character and appeared to be associated with marihuana. In a second experiment, psychomotor performance was evaluated by a similar design, using the Wobble Board, Pursuit Meter, and Delayed Auditory Feedback tests, and doses of 10 mg/70 kg of A and M prepared to deliver 25 mcg/kg THC. Impairment was related to smoking of marihuana, and no difference would be distinguished between M alone and M-A combination. Subjective evaluation, as measured by the modified Cornell Medical Index, demonstrated only additive effects for the combination.

The results suggested that the two drugs are additive in behavioral and neurophysical effects. There was no evidence of an interaction between them. Dextroamphetamine did not reduce the observed effects of marihuana. (JAM)

1976 22refs

UM-76-D0658

BLOOD LEVELS AND ELECTROENCEPHALOGRAPHIC EFFECTS OF DIAZEPAM AND BROMAZEPAM, M. Fink; P. Irwin; R. E. Weinfeld; M. A. Schwartz; A. H. Conney, Clinical Pharmacology and Therapeutics v20 n2 p184-91 (Aug 1976)

Blood levels and electroencephalographic (EEG) data were collected for 2 hours after single oral doses of bromazepam (9 mg), diazepam (10 mg), and placebo in 13 male adult volunteers. Both drugs caused an increase in beta activity (above 13 Hz) and a decrease in alpha activity (9-11 Hz) in the EEG. Blood levels of 100 ng/ml of diazepam or 50 ng/ml of bromazepam were associated with significant changes in EEG beta activity.

Temporal changes in the EEG after administration of the drugs paralleled development of plasma levels. Although a weakly significant correlation was found between measurable diazepam blood levels and amount of increased EEG beta activity, this was not the case for bromazepam. It was concluded that quantitative EEG is a sensitive continuous response measure, useful in defining cerebral activity, response latency, and relative potency of psychoactive benzodiazepines. (JA)

1976 20refs

UM-76-D0659

EFFECTS OF DEXTROAMPHETAMINE ON PSYCHOMOTOR SKILLS, M. A. Evans; R. Martz; L. Lemberger; B. E. Rodda; R. B. Forney, Clinical Pharmacology and Therapeutics v19 n6 p777-81 (Jun 1976)

The purpose of this investigation was to evaluate the effects of graded doses of dextroamphetamine on certain quantitative measures of psychomotor performance in a nonfatigue situation. Twelve healthy male volunteers were given 0, 5, 10 and 15 mg/70 kg dextroamphetamine orally in a randomized double-blind fashion in a series of four weekly sessions.

Blood pressure increased linearly with dose while heart rate was unchanged. Although selected individual tests of stance stability and motor function improved in a dose-related fashion, a generalized improvement in performance was not found in these nonfatigue situations. For example, in the Wobble Board test, stance stability improved when subjects' eyes were closed, but not when eyes were open. Pursuit Meter tests indicated that dextroamphetamine improved performance only with the fastest speed pattern. Delayed Auditory Feedback responses were unchanged with increasing doses and, therefore, did not permit inferences of a dextroamphetamine effect on mental performances. The drug was associated with improvement in tasks that rely on either rapid responses or increased alertness. (HSRI)

1976 18refs

UM-76-D0660

SOURCES OF INFORMATION OF DRUG USAGE IN SWEDEN, B. Westerholm, Clinical Pharmacology and Therapeutics v19 n5 pt2 p644-50 (May 1976)

Various aspects of drug usage in Sweden are examined, and the discussion is based on sales statistics, prescription habits and figures, interviews, and in certain instances on the determination of plasma levels of drugs. Sales data were considered the crudest source of information on drug use; by analysis one can acquire information on what preparations are used, changes in use over a period of time, and a rough estimate on the amount of drugs consumed

based on the "agreed daily dose" unit. Such data serve as indicators for further research.

Hospital and prescription data provided a more detailed pattern of drug use, and user characteristics could be defined. Analysis of repeat prescriptions for hypnotics and sedatives by the Department of Drugs in Sweden was accomplished by the use of prescription data combined with interviews. Plasma determinations were held to be the most objective method to measure consumption of drugs obtained over-the-counter or by prescription. Such analyses were performed for the most part in hospitals with a clinical pharmacology laboratory for inpatients receiving certain drugs.

Drug usage patterns remain ill-defined. Overconsumption of drugs has been studied while the problem of underconsumption has been more or less overlooked. Further efforts are needed to elucidate how optimal drug therapy can be reached. (HSRI)

1976 9refs

UM-76-D0661

THE BACKGROUND PATTERN OF DRUG USAGE IN AUSTRALIA, D. N. Wade, Clinical Pharmacology and Therapeutics v19 n5 pt2 p651-6 (May 1976)

The pattern of drug usage by urban populations has been studied in two typical Australian cities. Residents selected by random sampling and from pharmacists' records responded to questions related to state of health, recurrent or chronic disability, and drug exposures during 2 weeks preceding the interview. The incidence of drug taking by those who reported a current acute or chronic illness was no higher than in those who reported no current illness. Drug sales figures showed that Australians are near the top of the world's drug takers, with per capita consumption greater than in the United States.

Over-the-counter sales of drugs was also quite high; analgesics and cough suppressants were the two types of medication with the largest sales. The high consumption of analgesics was associated with the alarming increase in iatrogenic disease--analgesic nephropathy and gastrointestinal hemorrhage It was concluded that this level of drug usage must be symptomatic of underlying stresses and pressures of urban living in Australia, along with a cultural factor of ready acceptance of the social use of drugs. The attempt to identify the social and environmental factors that determine drug use patterns must be made, since failure to appreciate the cause must severely prejudice the chance of success of any educational or social program designed to alter the patterns of drug use in the community. (JAM)

1976 13refs

UM-76-D0662

PATTERNS AND PROBLEMS OF DRUG CONSUMPTION IN A DEVELOPING COUNTRY, A. Káldor, Clinical Pharmacology and Therapeutics v19 n5 pt2 p657-62 (May 1976)

The factors which influence drug consumption in developing countries affect procedures for introducing a new drug, its broad scale marketing, and its ultimate decline in acceptance. Physicians determine only partly the number of prescriptions and the choice of drug; government supplied medicaments, hard-sell marketing practices and other factors tend to set the pattern of drug usage. The practice of drug storing in "home pharmacies," a phenomenon surveyed by the author, is described and the reasons for it analyzed.

In general, the categories of drugs (e.g., antibiotics, cardiovascular, analgesics) consumed are the same as in the rest of Europe, the U. S., and Latin America. Among the minor tranquilizers, the consumption of meprobamate has risen about a third, chlordiazepoxide markedly, while phenobarbital has remained the same from 1969-1973. This is said to illustrate the pattern of

an upward curve in consumption of a new drug, and the displacement of an old one. The overall rise in drugs during this period was 72.1% in Hungary. (JAM)

1976 3refs

UM-76-D0663

INFLUENCE OF CANNABIDIOL ON DELTA-9-TETRAHYDROCANNABINOL EFFECTS, W. S. Dalton; R. Martz; L. Lemberger; B. E. Rodda; R. B. Forney, Clinical Pharmacology and Therapeutics v19 n3 p300-9 (Mar 1976)

Experiments utilizing healthy male medical students and investigating the possible interaction of tetrahydrocannabinol (THC) and cannabidiol (CBD), two major components of marihuana, were conducted under controlled laboratory conditions in a double-blind manner. Tests designed to assess psychomotor and mental performance were administered after volunteers were given placebo or 25 mcg/kg THC together with either placebo or 150 mcg/kg CBD by inhalation of the smoke of a single cigarette. All four treatments were assigned to each subject according to a series of Latin-square designs.

CBD significantly attenuated the subjective euphoria of THC. Psychomotor impairment due to THC was not significantly altered by the simultaneous administration of CBD, but a trend indicating a decrease in THC-like effects was observed. When administered alone, CBD was inactive in the standing steadiness test, Pursuit Meter, Delayed Auditory Feedback, and manual coordination tests. A 30 minute pretreatment with CBD in eight subjects did not alter the effects of THC on the parameters measured. (JAM)

1976 16refs

UM-75-D0664

FLURAZEPAM HYDROCHLORIDE, D. J. Greenblatt; R. I. Shader; J. Koch-Weser, Clinical Pharmacology and Therapeutics v17 n1 p1-14 (Jan 1975)

A review of the animal, human, and clinical pharmacology of flurazepam, a benzodiazepine hypnotic, is presented. The pharmacokinetics of flurazepam was investigated using both-radio tracer techniques and a chemical method to determine its concentrations in body fluids. In two human subjects, after a large single dose (90 mg), peak blood levels of flurazepam were less than 20 ng/ml, while metabolite levels were 4 times as large and reached about 1 hour after the dose.

Clinical evaluations of flurazepam as a hypnotic are reviewed, and its neurophysiological effects on sleep are described. Side effects have included psychomotor impairment, residual or "morning after" effects, and interaction with other depressant drugs. As with other benzodiazepine compounds, flurazepam has abuse potential and can produce habituation if large doses are taken over a long period of time. (HSRI)

1975 100refs

UM-75-D0665

PLASMA LEVELS AND SYMPTOM COMPLAINTS IN PATIENTS MAINTAINED ON DAILY DOSAGE OF METHADONE HYDROCHLORIDE, W. H. Horns; M. Rado; A. Goldstein, Clinical Pharmacology and Therapeutics v17 n6 p636-49 (Jun 1975)

Plasma methadone levels, symptom complaints and urine tests for illicit opiate use were followed weekly in 17 patients on a methadone maintenance program. A major finding of this investigation was that on constant or virtually constant dosage, there were very large differences in plasma methadone levels between patients, as well as very large and unexplained fluctuations in day-to-day and week-to-week levels in individual patients. Body weight was not a factor in determining the plasma level at a given dosage. Variations in plasma protein binding or in differential metabolism, or excretion

of either of the two enantiomers of methadone could not account for these differences.

With rare exceptions, there was no relationship between plasma methadone level and symptom complaints, or between weekly changes in plasma methadone and changes in symptom complaints. Except possibly to identify the occasional patient with unusually low plasma methadone levels, the determination of methadone levels is not likely to be of practical value in methadone programs. (JAM)

1975 25refs

UM-74-D0666

PLASMA CONCENTRATIONS OF DIAZEPAM AND OF ITS METABOLITE N-DESMETHYLDIAZEPAM IN RELATION TO ANXIOLYTIC EFFECT, H. H. Dasberg; E. van der Kleijn; P. J. R. Guelen; H. M. van Praag, Clinical Pharmacology and Therapeutics v15 n5 p473-83 (May 1974)

An investigation to establish the relationship between plasma levels and short-term clinical effects of oral diazepam; the minimal effective level of plasma diazepam and the optimal dosage required for the treatment of anxiety in crisis situations; and the therapeutic role of the active metabolite of diazepam, N-desmethyldiazepam, was reported. Fifteen non-psychiatric patients suffering from acute anxiety in a crisis situation, admitted for a short inpatient treatment, were treated orally with diazepam (20 mg daily) for at least 5 consecutive days. Psychometric measurements for improvement of anxiety symptoms, gas-liquid chromatographic determinations of plasma diazepam and N-desmethyldiazepam, clearance rates relative to body weight, and correlations between improvement ratings and drug concentrations and clearance ratings were presented. A control group of similar patients receiving a placebo was included in the double-blind, randomized study.

The results suggested that the degree of the diazepam effect is directly proportional to plasma concentrations and reciprocal clearance values for both compounds. The minimal effective plasma concentration in the steady state is 400 ng/ml. The metabolite has a slightly different action, exacerbating certain symptoms with plasma levels of 300 ng/ml or more. Monitoring plasma concentrations of diazepam during treatment seems to be advisable. (HSRI)

1974 33refs

UM-76-D0667

QUANTITATIVE RELATIONSHIP BETWEEN BLOOD ALCOHOL CONCENTRATION AND PSYCHOMOTOR PERFORMANCE, M. A. Evans; R. Martz; B. E. Rodda; G. F. Kiplinger; R. B. Forney, Clinical Pharmacology and Therapeutics v15 n3 p253-60 (Mar 1974)

In this study, psychomotor performance and psychological responses of apparently normal individuals were examined and related to various concentrations of blood alcohol in order to ascertain their association more closely. Following a series of doses of alcohol calculated to produce a BAC of 0, 25, 50, 75 and 100 mg%, 14 male medical and graduate students were evaluated for psychomotor impairment using a Wobble Board (WB) (standing steadiness) test, Pursuit Meter (PM), and Delayed Auditory Feedback (DAF). A modified Cornell Medical Index questionnaire was used to assess subjective impressions.

Covariance analysis indicated that performance deteriorated linearly with increasing BAC for both PM and WB tests. DAF also demonstrated increased impairment with an increase in BAC. Similar results were found for subjective evaluations. At a mean BAC of 61 mg%, 11 of 14 subjects indicated that their driving ability would be impaired; at a mean BAC of 89 mg%, all judged that their driving ability would be impaired. (JAM)

1974 10refs

UM-75-D0668

EFFECTS OF MARIHUANA COMBINED WITH SECOBARBITAL, W. S. Dalton; R. Martz; L. Lemberger; B. E. Rodda; R. B. Forney, Clinical Pharmacology and Therapeutics v18 n3 p298-304 (Sep 1975)

This investigation studied the psychomotor performance and psychological responses of humans receiving marihuana and secobarbital, alone and in combination. Male volunteers smoked a marihuana cigarette prepared to deliver 0 or 25 mcg/kg tetrahydrocannabinol (THC) 50 minutes after ingesting a capsule containing either placebo or 150 mg/70 kg sodium secobarbital. Drugs were administered in a double-blind manner, and all treatments were assigned to each subject in a randomized complete block design. Attentive motor performance, standing steadiness, mental performance and manual coordination were measured by Pursuit Meter (PM), Wobble Board (WB), Delayed Auditory Feedback (DAF) and the "suitcase test."

Objective and subjective assessments indicated that marihuana impaired stability, hand-eye coordination, and mental performance; secobarbital affected motor performance, manual coordination, and mental performance. In combination, the two drugs had an additive effect in subjective responses and impairment in the DAF, PM and "suitcase tests." (JAM)

1975 15refs

UM-75-D0669

N-DESMETHYLDIAZEPAM AND AMYLOBARBITONE SODIUM AS HYPNOTICS IN ANXIOUS PATIENTS. PLASMA LEVELS, CLINICAL EFFICACY, AND RESIDUAL EFFECTS, M. Tansella; O. Siciliani; L. Burti; M. Schiavon; C. Z. Tansella; M. Gerna; G. Tognoni; P. L. Morselli, Psychopharmacologia (Berlin) v41 n2 p81-5 (17 Apr 1975)

Estimates of hypnotic and residual effects were correlated with drug plasma levels of N-desmethyldiazepam (10 and 20 mg/day given at night) and amylobarbitone sodium (200 mg/day given at night) determined in 45 patients after 1 and 7 days of treatment. Gas-liquid chromatographic procedures were used to determine plasma levels of the drugs; clinical assessments were based on four self-rating scales while performance measures included the following tests: simple auditory reaction time, card sorting, digit symbol substitution test, Gibson Spiral Maze and tapping test.

N-desmethyldiazepam significantly accumulated during the experiment: from 270 to 1328 ng/ml and from 327 to 2850 ng/ml for the low and high dose, respectively. Significant interpatient variability in plasma levels was noted. No significant relationships were found between clinical ratings of hypnotic effect and drug plasma levels, while a clear relationship between drug concentrations and objective measures of hangover was observed for the barbiturate and high dose benzodiazepine groups. High levels of amylobarbitone sodium affected cognitive tasks, while N-desmethyldiazepam affected two motor tasks. The results underlined the difficulty of a rational therapeutic approach when standard doses and standard regimes are used. (HSRI)

1975 19refs

UM-75-D0670

DOSE EFFECTS OF SMOKED MARIHUANA ON HUMAN COGNITIVE AND MOTOR FUNCTIONS, J. Borg; S. Gershon; M. Alpert, Psychopharmacologia (Berlin) v42 n3 p211-8 (19 Jun 1975)

Graded doses (0 [placebo], 70, 130, 190 and 250 mcg/kg estimated delivered dose of delta-9-tetrahydrocannabinol) of marihuana were administered double-blind by smoking to five paid volunteers in a longitudinal, repeated measurements design. Speed of response of subjects trained to criteria was the basic parameter measured across tests of increasing cognitive involvement,

including simple and complex reaction time, temporal judgment, Digit Symbol Substitution Test, and Word Association Test. Estimations for magnitude of "placebo effect" were made by including a nonsmoking control condition.

The most significant linear dose-response effect was observed for mean pulse rate; all perfomance tests also demonstrated significant linear dose effects in terms of impaired response speed. Marihuana produced a more effective reduction on simple automatic and motor functions compared to those of greater cognitive involvement. Marihuana did not interfere with the subjects' ability to maintain a response set (sustained alertness, attention, or vigilance). While marihuana did not appear to induce defects in attention, the findings reported suggested the drug may have been responsible for a loss in short-term memory function.

A wide range of variability of placebo response was found. In addition, individuals performed differently during intoxication demonstrating the differential responsivity between subjects. However, the consistency of intra-subject drug effects on a range of behavioral measures suggested individuals may follow their own particular pattern of response. Evidence for tolerance development was presented. (HSRI)

1975 36refs

UM-76-D0671

EFFECTS OF PRACTICE ON MARIJUANA-INDUCED CHANGES IN REACTION TIME, S. C. Peeke; R. T. Jones; G. C. Stone, Psychopharmacology v48 n2 p159-63 (28 Jul 1976)

The effect of smoked marijuana on performance of complex reaction time (RT) task was studied in two groups receiving different amounts of practice. Group M-P had no undrugged practice before performing during marijuana intoxication for four consecutive daily sessions; on the fifth test day they performed while nonintoxicated. Group P-M performed the task on four consecutive test days while nonintoxicated, then smoked marijuana on session 5. Pulse rate and salivary flow were recorded several times per session in order to determine whether the magnitude of physiological effect changed over days; subjective responses were assessed by means of a drug effects questionnaire.

Results indicated that the opportunity for pre-intoxication practice was an important determinant of the magnitude of marijuana-induced impairment of perfomance. Significant RT slowing was found for session 1 for group M-P; performance of this group improved rapidly and by the end of session 2 was not different from undrugged performance. Group P-M showed no RT slowing while intoxicated. Although performance data indicated substantial decreases in marijuana effects after the first session, the physiological and subjective effects appeared quite constant over the days. Placebo responses were characterized.

Reaction time performance may involve two phases: an early, attention demanding phase which is sensitive to drug effects and a later, "automatic" phase which results from practice and is more resistant to drug effects. Behavioral tolerance and the role of attention in the effects of marijuana are briefly discussed. (JAM)

1976 13refs

UM-76-D0672

CRITICAL FLICKER FREQUENCY (CFF) AND PSYCHOTROPIC DRUGS IN NORMAL HUMAN SUBJECTS - A REVIEW, J. M. Smith; H. Misiak, Psychopharmacology v47 n2 p175-82 (28 May 1976)

This literature review presents summary methodological and statistical data on 33 studies in which critical flicker frequency (CFF) thresholds were used to evaluate the effects of acute oral doses of single psychotropic drugs in normal human subjects. In all, 96 drug-dose-study combinations are repre-

sented. CFF was found to be altered to a statistically significant degree in 51 (65%) of the 79 instances in which inferential statistical methods were used to evaluate the results. As expected, stimulants increased CFF while hypnotics decreased it.

There is also a discussion of important methodological considerations in the design of psychopharmacological studies employing CFF. While many studies have shown CFF to be sensitive to the effects of psychotropic drugs, there have not always been adequate controls for extraneous factors (especially, set and suggestion, changes in pupillary diameter, and the presence of other commonly used drugs). Finally, consideration is given to the attempts to increase the sensitivity of the CFF test to drug effects. (JA)

1976 69refs

UM-76-D0673

SENSORY, PERCEPTUAL, MOTOR AND COGNITIVE FUNCTIONING AND SUBJECTIVE REPORTS FOLLOWING ORAL ADMINISTRATION OF DELTA-9-TETRAHYDROCANNABINOL, B. A. Peters; E. G. Lewis; R. E. Dustman; R. C. Straight; D. C. Beck, Psychopharmacology v47 n2 p141-8 (28 May 1976)

This study was conducted to clarify the immediate effects of orally ingested delta-9-tetrahydrocannabinol (THC) on human functioning as assessed by a battery of ten tests. Three dose levels (0.2, 0.4 and 0.6 mg/kg) and a placebo were administered to 10 frequent and 10 occasional marijuana users. Following ingestion, objective tests routinely used to evaluate cerebral dysfunction in hospitalized patients were administered.

The influence of THC on proficiency and variability of performance was minimal. However, when individual test scores and variabilities were combined and converted to standard scores, allowing for analysis of overall performance, THC had a small but consistent effect on both proficiency and variability of performance. In contrast, THC exerted profound effects on the subjective experiences of the volunteers as assessed by the Subjective Drug Effects Questionnaire. It was proposed that the small impairment noted in objective test performance as contrasted to the large effects on subjective responses suggests that the principal effects of marijuana are on the autonomic nervous system rather than on higher cortical functions. (JAM)

1976 49refs

UM-74-D0674

DRUGS AND DRIVING, T. Silverstone, British Journal of Clinical Pharmacology v1 n6 p451-4 (Dec 1974)

This editorial briefly reviews the drugs and driving literature in discussing what effects drugs, particularly those used clinically, have on road traffic accidents. It is essential to know whether a patient taking a prescribed psychotropic drug actually drives better or worse with the drug. Unfortunately, most drugs and driving research has used normal, healthy volunteers. Most studies focused on psychomotor or attentional effects whose relevance to driving has been questioned.

Simulated driving studies, while being safe, lack certain extrapolation to driving performance. Most actual driving studies have been limited to closed course tests, probably due to the considerable medico-legal and ethical difficulties of conducting drug experiments in traffic. Epidemiological studies are needed to clarify the relationship of prescribed drugs to road traffic accidents involving their users. In the present state of knowledge, warnings should be issued to patients not to drive until the effects of the drug have been assessed, and not to ingest alcohol or other drugs while taking the drug as prescribed. (HSRI)

1974 38refs

UM-74-D0675

THE BIOCHEMICAL PHARMACOLOGY OF ABUSED DRUGS. I. AMPHETAMINES, COCAINE, AND LSD, J. Caldwell; P. S. Sever, Clinical Pharmacology and Therapeutics v16 n4 p625-38 (Oct 1974)

The chemistry, metabolism, and pharmacology of amphetamine, cocaine and lysergic acid diethylamide (LSD) are reviewed. Special topics include the manifestations of amphetamine abuse, the phenomenon of tolerance to these drugs, and their postulated mode of action. (HSRI)

1974 83refs

UM-74-D0676

THE BIOCHEMICAL PHARMACOLOGY OF ABUSED DRUGS. II. ALCOHOL AND BARBITURATES, J. Caldwell; P. S. Sever, Clinical Pharmacology and Therapeutics v16 n5 ptl p737-49 (Nov 1974)

The chemistry, metabolism, and pharmacology of ethyl alcohol (ethanol, alcohol) and the barbiturate drug class are discussed. Tolerance to these drugs, cross-tolerance between them, and the common aspects of central nervous system (CNS) tolerance to effects of depressant drugs are reviewed.

The literature indicates that alcohol tolerance is due principally to CNS adaptation, not metabolic alteration; that while tolerance to shorter acting barbiturates can be explained by induction of metabolizing enzymes, CNS adaptation becomes more important for the longer acting members of the drug class; that cross-tolerance between alcohol and the barbiturates is principally due to alteration of CNS sensitivity. The phenomenon of acute tolerance is introduced, and discussed in relation to chronic tolerance; an analogy to learning and memory is made. It is seen that the production of tolerance to CNS depressants may well be due to a basic cellular adaptation to the effects of the drug rather than to the drug itself. (HSRI)

1974 66refs

UM-74-D0677

THE BIOCHEMICAL PHARMACOLOGY OF ABUSED DRUGS. III. CANNABIS, OPIATES, AND SYNTHETIC NARCOTICS, J. Caldwell; P. S. Sever, Clinical Pharmacology and Therapeutics v16 n6 p989-1013 (Dec 1974)

The chemistry, metabolism and disposition, and pharmacology of the opiates, synthetic and naturally occurring, and the primary active constituent of cannabis, delta-9-tetrahydrocannabinol, are reviewed. Particular attention is given to three of the most important synthetic narcotics: meperidine, methadone and pentazocine. Tolerance both to cannabis and to narcotics is discussed in the light of recent research and theoretical constructs. (HSRI)

1974 131refs

UM-74-D0678

DIAZEPAM METABOLISM IN NORMAL MAN. I. SERUM CONCENTRATIONS AND CLINICAL EFFECTS AFTER INTRAVENOUS, INTRAMUSCULAR, AND ORAL ADMINISTRATION, L. Hillestad; T. Hansen; H. Melsom; A. Drivenes, Clinical Pharmacology and Therapeutics v16 n3 ptl p479-84 (Sep 1974)

The dependence of serum concentration on the mode of administration of diazepam to normal subjects was demonstrated. Serum levels were determined by the use of a gas-liquid chromatography-electron capture detector method. Subjects were examined for impairment of mental acuity, coordination and visual function.

Intravenous, intramuscular, and oral administration of 20 mg diazepam resulted in the following peak concentrations, respectively: 1600 ng/ml (15 min.);

290 ng/ml (60 min.); 490 ng/ml (30 min.). The clinical effects exhibited an accurate relationship to the serum concentration levels. At high levels of diazepam in the serum, the sedative effect was accompanied by marked deterioration of several mental functions and of coordination. The study revealed a conspicuous discrepancy between the judgment of the subjects and actual ability for adequate mental and physical function. This finding may be of practical importance. (HSRI)

1974 10refs

UM-74-D0679

DIAZEPAM METABOLISM IN NORMAL MAN. II. SERUM CONCENTRATION AND CLINICAL EFFECT AFTER ORAL ADMINISTRATION AND CUMULATION, L. Hillestad; T. Hansen; H. Melsom, Clinical Pharmacology and Therapeutics v16 n3 ptl p485-9 (Sep 1974)

Serum concentrations of diazepam and its principal metabolite, N-desmethyldiazepam, and clinical effects were measured daily following oral administration of 15 and 30 mg diazepam daily for one week. Experimental findings demonstrated that continuous oral administration of diazepam in ordinary doses causes conspicuous cumulation mainly during the first week. Tolerance develops, since clinical effects were less marked at serum levels causing deterioration of mental and physical functions on acute administration. The biologic half-life of diazepam was found to be 54 hours, and the apparent biologic half-life of its metabolite, which reached greater concentrations than its parent compound, was 92 hours. Clinical effects appeared to be related solely to serum levels of diazepam however. (HSRI)

1974 5refs

UM-74-D0680

CONCENTRATION-EFFECT RELATIONSHIPS WITH MAJOR AND MINOR TRANQUILIZERS, S. H. Curry, Clinical Pharmacology and Therapeutics v16 n1 pt2 p192-7 (Jul 1974)

Relationships between the effects of centrally acting drugs and concentrations of the pharmacologically active molecules in plasma are influenced by features of the drug, e.g., its metabolism and disposition; by features of the effect under study, e.g., the possible frequency of its measure and sensitivity of recording small changes; and by features of the relevant disease state, in clinical studies. Such relationships take a wide variety of forms, ranging from simple direct relationships, for instance, those involving effects on reaction time; to extremely complex relationships, for instance, those involving clinical rating of psychopathology.

Additional factors concerning experimental design and clinical pharmacology which influence the relationships between drug effects and drug concentrations in plasma are briefly summarized. A number of forms of relationships have been revealed with glutethimide, nordiazepam, and chlorpromazine, and a brief review is presented of the current status of studies of the relationship between concentration and effect for these compounds. (JAM)

1974 15refs

UM-74-D0681

PLASMA LEVELS AND TRICYCLIC ANTIDEPRESSANTS, A. H. Glassman; J. M. Perel, Clinical Pharmacology and Therapeutics v16 n1 pt2 p198-200 (Jul 1974)

This report reviews studies in which attempts were made to examine the relationships between the plasma levels of tricyclic antidepressants and clinical outcome. In each of four separate studies, a different relationship was found. Two major underlying problems, the heterogeneity of the depressive population and individual variability in plasma protein binding, have contributed to these apparent discrepancies.

The usefulness of plasma level measurements in depressive disease, a complex of behavioral patterns, remains to be seen. However, the monitoring of

plasma levels is a means to reducing the variability in a complex biologic system, and to allow a better examination of the disease process itself. (HSRI)

1974 15refs

UM-74-D0682

PLASMA NORTRIPTYLINE LEVELS--RELATIONSHIP TO CLINICAL EFFECTS, M. Åsberg, Clinical Pharmacology and Therapeutics v16 n1 pt2 p215-29 (Jul 1974)

The relationship between nortriptyline (NT) levels and therapeutic effects was studied in patients diagnosed with endogenous depression. After a washout period with patients on placebo for 4-7 days, 50 mg NT t.i.d. was given for 4 weeks. Different ratings for side effects and severity of depression were performed at the end of the washout period and once weekly during treatment, with NT concentrations determined twice weekly.

The best classification between "responders" and "nonresponders" to NT, based on psychiatrists' ratings with a modified Cronhelm-Ottosson scale, was obtained at 175 ng/ml of plasma. Although the general tendency is for patients to do less well on high plasma levels, some benefit while others do not recover even on moderate levels. On any standard dosage, a certain number of patients will have plasma levels that are too low to be effective, and some will develop toxic levels even on very low dosages. Monitoring NT levels may be a way to increase the efficacy of treatment in patients not responding to standard therapy and in those with disturbing side effects. (JAM)

1974 107refs

UM-74-D0683

INSTRUCTIONAL GOALS FOR PHYSICIANS IN THE USE OF BLOOD LEVEL DATA--AND THE CONTRIBUTION OF COMPUTERS, L. B. Sheiner; K. L. Melmon; B. Rosenberg, Clinical Pharmacology and Therapeutics v16 n1 pt2 p260-71 (Jul 1974)

The importance of a knowledge of pharmacokinetics in the physician's therapeutic decision-making is emphasized. Based on available studies of adverse drug reactions and serum drug levels (SDL), it is possible to optimize efficacy while preventing toxicity. A physician needs to understand the basic concepts of pharmacokinetics and how to apply SDL data selectively and more precisely to the individual patient. This is particularly important for drugs with narrow therapeutic indices.

A syllabus is outlined for the teaching of the qualitative aspects of pharmacokinetics to physicians, house staff, and medical students. The use of a feedback responsive computer system as an aid to making dosage decisions for the individual patient under therapy is defended as a means of personalizing and improving medical care. Results of such a system using the drug digoxin are presented. (JAM)

1974 25refs

UM-74-D0684

THE NATURE OF STORAGE DEFICITS AND STATE-DEPENDENT RETRIEVAL UNDER MARIHUANA, C. F. Darley; J. R. Tinklenberg; W. T. Roth; R. C. Atkinson, Psychopharmacologia (Berlin) v37 n2 p139-49 (21 Jun 1974)

To explore the nature of the storage deficit produced by marihuana intoxication and to determine if retrieval is state dependent for this drug, 48 subjects were presented ten 20-word lists before receiving an oral dose of marihuana (20 mg tetrahydrocannabinol estimated), and another ten lists following drug administration. Study of the lists was divided between an overt fixed rehearsal procedure and the subjects' normal covert free rehearsal procedure.

On Day 1 of the experiment, an immediate recall test followed each of the lists presented. The marihuana-induced deficit in immediate recall performance on Day 1 for free rehearsal lists was not eliminated when the fixed rehearsal procedure was used. Thus, marihuana intoxication impaired the storage of information even when overt rehearsal in the drug and no-drug states were equated.

Three days later (Day 4) subjects returned, half receiving marihuana (Drug Group) and half receiving placebo (Placebo Group). All subjects were then administered delayed recall, recognition, and order tests on the words presented on Day 1. Delayed recall was asymmetrically state dependent, whereas delayed recognition performance was not state dependent. (JA)

1974 18refs

UM-74-D0685

PERFORMANCE ON A VERBAL LEARNING TASK BY SUBJECTS OF HEAVY PAST MARIJUANA USAGE, M. J. Cohen; W. H. Rickles, Jr., Psychopharmacologia (Berlin) v37 n4 p323-30 (23 Jul 1974)

Male subjects categorized as heavy marijuana users were given paired associate learning tasks in a 2 X 2 state dependent learning design. Galvanic skin resistance, electrocardiogram, respiration, and finger pulse volume were recorded continuously. Total training trials for each subject was twice the number needed to reach criterion learning, i.e. 100% overlearning. Seven days later, subjects were tested for recall. A second list of paired associates was then learned.

No significant effects were found between marijuana and placebo groups on trials to criterion, and recall of the task seven days later was not found to be state dependent. The results were compared to a previous study using light users that reported a state dependent effect. The effects of the subjects' past marijuana usage history and the drug's acute effects on learning and recall were discussed. It was argued that attempting to explain behavioral effects of drugs in terms of psychological models of learning and cognition is a more fruitful approach than employing the concept of behavioral tolerance. (HSRI)

1974 14refs

UM-74-D0686

BLOOD AND URINE LEVELS OF N,N-DIMETHYLTRYPTAMINE FOLLOWING ADMINISTRATION OF PSYCHOACTIVE DOSAGES TO HUMAN SUBJECTS, J. Kaplan; L. R. Mandel; R. Stillman; R. W. Walker; W. J. A. VandenHeuvel; J. C. Gillin; R. J. Wyatt, Psychopharmacologia (Berlin) v38 n3 p239-45 (20 Sep 1974)

Psychoactive doses (0.7 mg/kg) of the hallucinogen N,N-dimethyltryptamine (DMT) were administered intramuscularly to 11 male subjects, all of whom were experienced hallucinogen users. Blood and urine samples were collected and assayed for DMT using a gas chromatographic-mass spectrometric isotope dilution method. Subjective "high" was assessed with the use of a simple rating scale.

Blood DMT levels and the subjective high followed a similar time course, and indicated that DMT's psychological effects are mediated by a mechanism requiring little or no metabolism of DMT. The absolute amounts of DMT in blood and urine were quite small despite the extremely intense subjective effects. Any small amount of endogenous DMT produced in the brain probably would not be detectable in the blood. Urine levels of the drug were even less indicative of DMT levels. These data may explain why it is not feasible to demonstrate marked differences in DMT concentrations between patients and normals. Searching for differences in DMT metabolites may have more utility. (HSRI)

1974 21refs

UM-74-D0687

MARIHUANA EFFECTS ON LEARNING, ATTENTION AND TIME ESTIMATION, L. Vachon; A. Sulkowski; E. Rich, Psychopharmacologia (Berlin) v39 n1 p1-11 (17 Oct 1974)

Ten healthy male volunteers smoked a marihuana cigarette with 2.5% delta-9-tetrahydrocannabinol (THC) and a THC-exhausted placebo cigarette according to a crossover design, three days apart. Subjects were asked to rate the quality of the cigarette and the "high" and its "pleasantness," each on a scale of 0-100 points. Physiological, psychological, and psychomotor tests were administered.

The marihuana administration was associated with an increase in heart rate, elevation of systolic blood pressure, conjuntival reddening, and specific airway conductance increase. Time perception and Automated Digit Symbol Substitution Test performance were impaired. Diastolic blood pressure and attention measured by the continuous performance task were not affected. The placebo preparation produced a subjective pleasant high but not physiologic effects or performance change. The high induced by the active preparation was often rated as unpleasant. The data suggested that the acute marihuana intoxication impairs learning, probably by disrupting the memory acquisition processes. (JAM)

1974 32refs

UM-74-D0688

EFFECT OF TWO WEEKS' TREATMENT WITH CHLORIMIPRAMINE AND NORTRIPTYLINE, ALONE OR IN COMBINATION WITH ALCOHOL, ON LEARNING AND MEMORY, R. Liljequist; M. Linnoila; M. J. Mattila, Psychopharmacologia (Berlin) v39 n2 p181-6 (29 Oct 1974)

Twenty male students were treated double-blind with nortriptyline, chlorimipramine, or placebo for two weeks in a crossover design. For the first 7 days the dose of nortriptyline hydrochloride or chlorimipramine hydrochloride was 10 mg t.i.d., and for the next 7 days the respective doses were 20 and 25 mg t.i.d. On the 14th day of treatment, the effects of drugs and their interactions with alcohol were tested in two kinds of learning situations. The presence of the antidepressants in plasma was checked by means of the tyramine pressor test.

Alcohol alone significantly increased the number of mistakes in the paired associated learning test. Nortriptyline alone slightly increased the number of mistakes in paired associated learning test and impaired the backward recall of digits. Chlorimipramine alone had no measurable effect on learning or memory. Nortriptyline enhanced the deleterious effect of alcohol on the ability to learn new material, whereas chlorimipramine antagonized alcohol in this respect. Both antidepressants significantly shifted the dose-response graph for the tyramine effect on systolic blood pressure to the right. The finding that results from the pressor test and the memory tests did not correlate with each other suggests that at these dosage levels, pharmacodynamics at central receptors did not correlate with pharmacokinetics in the periphery. (JAM)

1974 20refs

UM-74-D0689

EFFECT OF DELTA-8-THC ON ALCOHOL-INDUCED SLEEPING TIME IN THE RAT, E. Friedman; S. Gershon, Psychopharmacologia (Berlin) v39 n3 p193-8 (5 Nov 1974)

The effect of acute and repeated delta-9-tetrahydrocannabinol (THC) on alcohol-induced sleeping time was studied in male albino rats. Acute pretreatments with 1, 3, 5, and 7 mg/kg THC markedly potentiated sleeping time in a dose-related manner. The potentiation of the alcohol sleeping time is shortened significantly after repeated prior treatment with THC and can be observed

72 hours post-chronic treatment. The effects of THC on alcohol-induced sleeping time do not involve altered metabolic rates of alcohol, and may be due to action on the central nervous system. (JAM)

1974 17refs

UM-74-D0690

DISCRIMINATIVE RESPONSE CONTROL PRODUCED WITH HASHISH, TETRAHYDROCANNABINOLS (DELTA-8-THC AND DELTA-9-THC), AND OTHER DRUGS, T. U. C. Järbe; B. G. Henriksson, Psychopharmacologia (Berlin) v40 n1 p1-16 (2 Dec 1974)

In a series of experiments, the discriminative properties of hashish and its derivatives and other, noncannabinoid drugs have been examined. To determine the specificity of the drug induced response control, a variety of psychoactive drugs were tested for their possible generalization to the training drugs. It is concluded that tetrahydrocannabinols (delta-8- and delta-9-tetrahydrocannabinol) (THC) are interchangeable with respect to cue function and that hashish, inhaled as smoke, produces cue effects similar to synthetic THC in rats. Neither cannabidiol nor cannabinol evidenced transfer to hashish or its derivatives.

Lack of generalization to THC was also apparent for CNS depressants, anticholinergics, tacrine, sernylan, psilocybin, morphine, CNS stimulants, yohimbine, and phenitrone. Some drugs were tested for antagonistic effects, but all were found ineffective in preventing THC discrimination. The results from this and previous studies support an earlier suggestion about a unique mode of action for the cannabinoids. (JAM)

1974 58refs

UM-74-D0691

THE EFFECTS OF HYPNOTICS ON IMIPRAMINE TREATMENT, B. R. Ballinger; A. Presly; A. H. Reid; I. H. Stevenson, Psychopharmacologia (Berlin) v39 n3 p267-74 (5 Nov 1974)

Plasma imipramine and desmethylimipramine concentrations and depression ratings were measured over a 3 week period in 3 groups of hospitalized depressed patients given standard doses of imipramine (25 mg t.i.d. for three days, then 50 mg t.i.d. for 18 days). The first group received imipramine alone, the others either amylobarbitone (200 mg) or nitrazepam (10 mg) in a double-blind fashion.

Plasma antidepressant levels were consistently higher in the group receiving no hypnotic but only significantly so in the case of "total" IMI in the imipramine alone group compared to the group receiving imipramine plus amylobarbitone. The interindividual differences in plasma levels were large. There was no difference between the groups with regard to changes in depression, sleep, or side effects.

From a clinical point of view, there is, therefore, no evidence from this study of adverse effects of these drugs given in combination nor any evidence to suggest that the dosage of IMI given should be adjusted when administered along with either of the hypnotics studied. (JAM)

1974 14refs

UM-74-D0692

ALCOHOL AND INFORMATION PROCESSING, V. K. Tharp, Jr.; O. H. Rundell, Jr.; B. K. Lester; H. L. Williams, Psychopharmacologia (Berlin) v40 n1 p33-52 (2 Dec 1974)

Three experiments which investigate the effects of acute alcohol intoxication (average blood alcohol concentration of 100 mg-%) employed auditory or visual stimuli in character recognition tasks. Both error rates and reaction time were used to measure performance in sober and moderately intoxicated male

university students. The results are interpreted within the framework of a general information processing model, using the Sternberg additive factor method of analysis.

The three experiments strongly support the notion that, in character recognition tasks, one important source of impairment with moderate alcohol intoxication is a difficulty in selecting and organizing the correct response. The deficit may be manifested either by an increase in reaction time or in errors or both, depending on such conditions of the experiment as differential response probabilities and the payoffs for speed and accuracy.

There was no evidence that alcohol (100 mg-%) altered perceptual operations such as stimulus preprocessing or encoding. It is assumed on the basis of results that the drug did not cause qualitative alterations in the way information was processed. (HSRI)

1974 14refs

UM-74-D0693

EFFECTS OF MARIHUANA ON AUDITORY SIGNAL DETECTION, H. Moskowitz; W. McGlothlin, Psychopharmacologia (Berlin) v40 n2 p137-45 (18 Dec 1974)

Twenty-three male subjects were tested for auditory signal detection under a no treatment condition, and after smoking marihuana cigarettes designed to deliver 0, 50, 100, and 200 mcg delta-9-tetrahydrocannabinol (THC) per kg body weight. Signal detection was measured under conditions of concentrated attension, in which the subjects reported the presence or absence of a tone in a 3-second noise burst; and divided attention, where the subjects also repeated a series of six digits which were presented simultaneously with the noise burst.

No differences were found between the no treatment and placebo conditions. Significant dose-dependent impairment of signal detection resulted for the marihuana conditions under both concentrated and divided attention. Application of signal detection theory indicated that impaired performance was due to a decline in sensitivity, independent of changes of subject criteria. There was also some indication of change in criteria, i.e., a greater tendency for erroneous reporting of a signal when it was not present. (JA)

1974 13refs

UM-74-D0694

ANALYSIS OF EYE MOVEMENTS AND BLINKS DURING READING: EFFECTS OF VALIUM, J. A. Stern; D. A. Bremer; J. McClure, Psychopharmacologia (Berlin) v40 n2 p171-5 (18 Dec 1974)

Reading was discussed as a continuous performance task sensitive to sedative induced attentional deficits. Visual search activity was monitored during reading in 18 college undergraduates before and after a week long regimen of Valium (5 mg t.i.d.) or placebo. Horizontal eye movements and eye blinks were monitored by electrodes. Electrooculograms were recorded on magnetic tape, and the recorded data were processed on a PDP-12 computer.

Although Valium had little or no subjectively recognizable effect on participants in the study, computer analyses of electrooculograms did indicate significant changes in the Valium group. An increase in frequency of long fixation pauses, a general increase in duration of fixations following a line shift, and a decrease in velocity of saccadic eye movements during line shifts resulted from drug administration. The specific changes identified were consistent with an overall decrease in material read in the second session in the Valium group. (JAM)

1974 5refs

UM-76-D0695

DRUGS, DRIVERS, AND HIGHWAY SAFETY, K. B. Joscelyn; R. P. Maickel, HSRI Research v7 n2 p7-16 (Sep/Oct 1976)

A study conducted for the Department of Transportation focused on the use and effects of drugs (other than alcohol alone) and highway safety. A review of the literature preceded the evaluating of epidemiological and experimental studies, existing methods of measuring drug presence and behavioral effects, legal constraints on drug/driving research, and priorities for future research. As a part of the study, an international symposium was held to examine and evaluate the "state of the art" of drug and driving research. This article briefly describes some of its major findings and the recommendations made to the National Highway Traffic Safety Administration. (HSRI)

1976

Extract from final report on Contract DOT-HS-4-00994.

UM-76-D0696

A FATAL MOTOR-CAR ACCIDENT AND CANNABIS USE. INVESTIGATION BY RADIOIMMUNOASSAY, D. Teale; V. Marks, The Lancet v1 n7965 p884-5 (24 Apr 1976)

The case report of an automobile accident is presented in which the fatally injured driver was found with marijuana and pipe in the car. A post-mortem examination revealed no evidence of organic disease, and no alcohol was found in either urine or blood. Both fluids were examined for the presence of tetrahydrocannabinol-cross-reacting cannabinoids (THC-CRC) using a radioimmunoassay known to be specific for this group of drugs. The plasma contained THC-CRC at a concentration of 315 ng/ml, and urine at a concentration of 1210 ng/ml.

Since the levels of THC-CRC found were extremely high, the contribution of marijuana to the accident was held certain by the authors. The availability of a radioimmunoassay provides an objective method for measuring blood levels of THC-CRC, and hopefully information will accumulate about the contribution made by marijuana to road-traffic accidents. (HSRI)

1976 7refs

UM-76-D0697

KNOWLEDGE AND EXPERIENCE OF YOUNG PEOPLE REGARDING DRUG ABUSE BETWEEN 1969 AND 1974, J. D. Wright, Medicine, Science, and the Law v16 n4 p252-63 (Oct 1976)

A trend survey was carried out by anonymous questionnaire, with an additional 10% interview sample, of the knowledge and experience of drug abuse among fourth year pupils in three Wolverhampton secondary schools in 1969 and 1974, with additional reference to a smaller survey in 1968. The survey shows the range of drugs known to the groups, their contact with drugs and drug takers, their sources of information about drugs, and the reasons given for taking drugs. Changes between the earlier and later surveys are discussed.

The author found a decrease in interest in, and a continued ignorance of drugs. An increasing minority was in contact with drugs. Amphetamines and LSD (lysergic acid diethylamide) were less, and sedatives more, available. The young people, who were predominantly not drug takers and not in contact with drugs, considered that social and situational pressures were more important than mental or personality stress as the reasons for drug taking. The implications of the findings are discussed. (JAM)

1976 10refs

UM-76-D0698

A NATIONAL ASSESSMENT OF PROPOXYPHENE IN POSTMORTEM MEDICOLEGAL INVESTIGATION, 1972-1975, B. S. Finkle; K. L. McCloskey; G. F. Kiplinger; I. F. Bennett, Journal of Forensic Sciences v21 n4 p706-42 (Oct 1976)

Eighteen medical examiners, coroners, and forensic science laboratories and offices, representing a total jurisdictional population of 52.6 million, were visited during November 1975; and more than 1200 cases occurring in the four years from 1972 through 31 July 1975 were evaluated for inclusion in the study. Scientific data and circumstantial information was gathered consistently for each case and site by means of five questionnaires. Finally, 1022 cases were compiled and examined.

The authors found that the number of deaths involving propoxyphene is increasing each year and at a faster rate than total drug deaths. The deceased were mainly middle class, Caucasion, urban dwellers, with male and female evenly distributed. The deceased were not part of the illegal drug abuse population, but were a particular medical population of those who misuse prescription drugs and alcohol. Most individuals died at home or other residence and succumbed to a mixture of propoxyphene, other drugs or alcohol, or a combination.

The forensic toxicology and pharmacology of propoxyphene, and the analytical methods used to detect its presence were discussed. Fatal propoxyphene concentrations in blood and liver were presented and compared to therapeutic levels. The widespread use of propoxyphene would indicate that notice of caution be issued, particularly in regard to its use in conjunction with other depressant substances. The authors conclude that the drug appears no more dangerous, however, than the countless other drugs available to the public. (ASM)

1976 23refs

HS-801 658 UM-75-D0699

ETHANOL, OTHER CHEMICALS AND THEIR POTENTIAL COMBINATION WHICH MAY INFLUENCE AUTOMOBILE DRIVING PERFORMANCE. ALCOHOL COUNTERMEASURES LITERATURE REVIEW. FINAL REPORT, R. B. Forney; A. B. Richards, National Highway Traffic Safety Administration (Jul 1975)

The authors have reviewed the July 1973-June 1974 literature dealing with the effects of drugs, ethanol or their combination on ability to drive a motor vehicle. Although more data are now available relative to the impact of chemical ingestion on safe motor vehicle driving, they are not precise regarding effects. Information is more precise on the effects of ethanol than on other drugs or the combination of ethanol and other drugs.

Studies continue to verify that alcohol induces impairment of driver abilities and they reaffirm the dominant role of alcohol in crashes. But, no effect has been reported which would separate alcohol from other factors to indicate whether the accident would not have occurred had ethanol not been present. Although extensive studies have been made of the effects of drugs and drug-alcohol combinations, the pharmacology may be better understood than can be practically demonstrated in the driver of a motor vehicle. There is a need to formulate a consensus opinion as to the acceptable amounts of drugs and alcohol, individually and in combination, which can be allowed in the body fluids of drivers. When this is done, legislation can be developed that can be used to control the problem. (AA)

National Safety Council, Chicago, Ill. 60611

1975 18p 40refs

DOT-HS-4-00965
DOT-HS-801 658

HS-801 656 UM-75-L0078

LEGAL ASPECTS OF ALCOHOL AND DRUG INVOLVEMENT IN HIGHWAY SAFETY - ALCOHOL COUNTERMEASURES LITERATURE REVIEW, J. W. Little; M. Cooper, National Highway Traffic Safety Administration (Jul 1975)

This review of legal literature relevant to alcohol and drug involvement in highway safety included information published in scientific and other non-legal journals which had some relevance to legal issues. Although both alcohol and drug related publications were included, very few concerning legal aspects of drugs were available. In addition to references, a bibliography was compiled and provided. (AAM)

National Safety Council, Chicago, Ill. 60611

1975 27p 137refs

DOT-HS-4-00965

DOT-HS-801 656

UM-74-L0079

CHEMICAL TESTING OF IMPAIRED DRIVERS, D. Sohn; J. Simon; S. Sohn, Legal Medicine Annual: Nineteen Seventy-Four, C. H. Wecht, ed., New York: Appleton-Century-Crofts, 1974, p149-57

Epidemiological evidence for the impact of alcohol- and drug-impaired drivers on traffic safety was briefly surveyed. Lack of information was attributed to the small number of studies performed and the deficiencies in drug detection procedures. Methods of analysis for alcohol and drugs were described. The importance of drug screening in the identification and classification of impaired drivers was stressed. (HSRI)

1974 33refs

UM-75-L0080

SUBMISSION TO THE BLENNERHASSETT COMMITTEE ON DRINKING AND DRIVING, British Academy of Forensic Sciences, Medicine, Science, and the Law v15 n3 p218-23 (Jul 1975)

The British Academy of Forensic Sciences recommended that existing legislation be changed to reflect current problems in the area of alcohol/drugs and traffic safety. They described an Act in which one offence would be specified, that of "being unfit to drive through drink and/or drugs." The importance of sophisticated breath analysis for alcohol with supplemental evaluations of driver impairment was related to the proposed severing of procedural aspects from drug analysis resulting from the new legislation. Specifics of arrest procedure and biological sample handling were presented. Appropriate penalties for those convicted under the law were discussed. (HSRI)

1975 1ref

UM-74-L0081

CANNABIS AND THE CRITERIA FOR LEGALISATION OF A CURRENTLY PROHIBITED RECREATIONAL DRUG: GROUNDWORK FOR A DEBATE, G. Edwards, Acta psychiatrica scandinavica Supplementum 251 (1974)

Emergence of the British cannabis problem with subsequent polarization of views led to the author's attempt to analyze the legalization of a substance as a recreational drug. The definition of criteria applicable to the debate and the legal, social, and scientific context of the debate itself was held to be essential to continued discussion.

Recent advances in the pharmacological and toxicological evaluation of drug safety were presented. Relevant findings formed the basis for the development of some provisional criteria for debate on ending recreational prohibition. The author then applied the criteria to the cannabis debate, and reviewed the available scientific knowledge concerning cannabis and its constituents. He analyzed the post-prohibition situation and weighed the relative benefits to society of continued prohibition or legalization. (HSRI)

1974 62p 144refs

UM-75-L0082

DRINK, DRUGS AND DRIVING - A SURVEY, A. Brownlie, The Medico-Legal Journal v43 pt4 p143-65 (1975)

A history and analysis of law concerning drinking and driving in the United Kingdom was recounted. Special emphasis was given to the impact of the prescribed level offense statute with its attendant arrest procedures. Cases relevant to the Road Safety Act 1967 and Road Traffic Act 1972 illustrated legal points. (HSRI)

1975 99refs

Presented at a meeting of the Royal Society of Medicine, 8 May 1975, London, England.

UM-74-L0083

BEURTEILUNG DER ZURECHNUNGSFÄHIGKEIT UNTER DROGENEINFLUSS NACH DEM ÖSTERREICHISCHEN STRAFGESETZ (ASSESSMENT OF RESPONSIBILITY UNDER THE INFLUENCE OF DRUGS, ACCORDING TO THE AUSTRIAN PENAL CODE), K. Jarosch; G. Kaiser, Beitrage zur Gerichtliche Medizin v32 p11-5 (1974)

How the medical opinions about the problems of drug dependence and abuse stand in relation to the Austrian penal code is discussed. There is considerable flexibility for the interpretation of the irresponsibility of sick persons, as well as for controlling the drugs and the application of withdrawal therapy. (JAM)

1974 20refs [German]

UM-76-L0084

PRIVACY, PRIVILEGE, AND TRANSPORTATION RESEARCH, K. B. Joscelyn, Human Factors v18 n5 p507-16 (Oct 1976)

The increasing danger of legal entanglement for researchers who disregard the rights of human subjects used in research, in particular their right of privacy, is examined. The broad definition of a human subject and the equally broad definition of injury are discussed. The implications of the Privacy Act of 1974 are noted, and the critical need for a researcher privilege statute set forth. (JA)

1976 14refs

UM-75-M0001

CRC METHODOLOGY FOR ANALYTICAL TOXICOLOGY, I. Sunshine, ed., CRC Press, Inc., Cleveland, Ohio (1975)

This book is an updated compilation of methods in analytical toxicology. Acceptable methods for the analysis of therapeutic agents in biological fluids are provided and only experience-tested procedures are included. In addition, this volume presents several approaches to the systematic analysis of a biological fluid. Choice of a method is a function of local facilities. However, methods utilizing the more common laboratory techniques such as thin-layer chromatography, spectrophotometry, and gas chromatography have

been selected for this revision. Updated assessments of the interpretation of laboratory values, recent data reports, and literature citations supplement the drug methods. (HSRI)

1975 478p

Rev. from CRC Handbook of Analytical Toxicology, The Chemical Rubber Co. 1969.

UM-76-M0002

RELATIVE MERITS OF SOME METHODS FOR AMPHETAMINE ASSAY IN BIOLOGICAL FLUIDS, R. O. Bost; C. A. Sutheimer; I. Sunshine, Clinical Chemistry v22 n6 p789-801 (Jun 1976)

Principles and details concerning amphetamine determination in blood and urine by photometric, thin-layer chromatographic, gas chromatographic, and immunologic (EMIT and radioimmunoassay) procedures are described. Aqueous solutions (100 mcg/ml) of 31 substances were examined for possible interference with the methods. The stability of amphetamine in urine samples was studied. The results and economic considerations of the various methods are compared and recommendations for their use are made. (HSRI)

1976 14refs

UM-71-M0003

DIRECT BLOOD-INJECTION METHOD FOR GAS CHROMATOGRAPHIC DETERMINATION OF ALCOHOLS AND OTHER VOLATILE COMPOUNDS, N. C. Jain, Clinical Chemistry v17 n2 p82-5 (Feb 1971)

A simple method is described for the qualitative and quantitative screening of blood for methanol, ethanol, acetone, isopropanol, and low boiling hydrocarbons associated with glue sniffing. A small volume of blood containing an internal standard is injected directly into a low cost gas chromatograph equipped with a flame ionization detector. Sensitivity of the method is less than 10 mcg of alcohol per ml of blood. (HSRI)

1971 13refs

UM-74-M0004

MARIJUANA METABOLITES MEASURED BY A RADIOIMMUNE TECHNIQUE, S. J. Gross; J. R. Soares; S.-L. R. Wong; R. E. Schuster, Nature v252 n5483 p581-2 (13 Dec 1974)

A radioimmunoassay for delta-9-tetrahydrocannabinol (THC) utilizing goat antiserum and tritiated delta-8-THC was reported. Cross-reactivity with 11-OH-THC was high (50%) compared to cannabidiol (0.5%). Plasma of chronic marijuana smokers before smoking a marijuana cigarette (18.9 mg THC) contained 60-100 ng/ml. THC equivalents; 15 minutes after smoking, plasma levels increased to 200-250 ng/ml. Sensitivity of the method (25-50 ng/ml) was sufficient to estimate cannabinoids in chronic marijuana users. (HSRI)

1974 6refs

UM-75-M0005

THE DEVELOPMENT OF A RADIOIMMUNOASSAY FOR CANNABINOIDS IN BLOOD AND URINE, J. D. Teale; E. J. Forman; L. J. King; E. M. Piall; V. Marks, Journal of Pharmacy and Pharmacology v27 n7 p465-72 (Jul 1975)

This report outlines the development of a radioimmunoassay for cannabinoids. Antibodies were raised in sheep by immunization with a conjugate of delta-9-tetrahydrocannabinol (THC) hemisuccinate and bovine serum albumin. Antiserum titre and avidity were increased by booster doses of the conjugate. The high degree of nonspecific binding encountered in the radioimmunoassay of cannabinoids was reduced by the use of a solubilizing detergent and by restricting protein concentration in the assay medium. Plasma was deproteinized with ethanol; urine was directly assayed.

High avidity antibodies and high specific activity labled THC permitted the detection of 50 pg of cross-reacting cannabinoids--a sensitivity of 7.5 ng/ml of plasma and 10 ng/ml of urine. Specificity of the assay antiserum for the cannabinoid three-ring nucleus and cross-reactivity within the cannabinoid class are discussed. Partial identification of cross-reacting cannabinoids was achieved by the use of pure compounds and by the assay of plasma and urine samples collected from rabbits given pure cannabinoids intravenously. (JAM)

1975 8refs

UM-74-M0006

MASS FRAGMENTOGRAPHIC ASSAY FOR DELTA-9-TETRAHYDROCANNABINOL IN PLASMA, J. J. Rosenfeld; B. Bowins; J. Roberts; J. Perkins; A. S. Macpherson, Analytical Chemistry v46 n14 p2232-4 (Dec 1974)

The mass fragmentographic technique for the measurement of plasma delta-9-tetrahydrocannabinol (THC) was based on the chemistry of the phenolic group common to cannabinoids and their metabolites. Plasma extracts were purified by extraction with Claisen's alkali. Following addition of the conveniently synthesized internal standard, the perdeuteriomethyl ether of THC, cannabinoids were derivatized by on-column methylation. The administration by smoking of 88 mcg THC per kilogram body weight of subjects resulted in plasma levels of 10-30 ng/ml after 20-30 minutes. (HSRI)

1974 20refs

UM-73-M0007

QUANTITATION OF DELTA-1-TETRAHYDROCANNABINOL IN PLASMA FROM CANNABIS SMOKERS, S. Agurell; B. Gustafsson; B. Holmstedt; K. Leander; J.-E. Lindgren; I. Nilsson; F. Sandberg; M. Asberg, Journal of Pharmacy and Pharmacology v25 n7 p554-8 (Jul 1973)

A gas chromatography-mass fragmentographic assay for plasma delta-1-tetrahydrocannabinol (THC) is described. This method featured the use of stable isotope labeled THC (delta-1-THC-d2, synthesis described) as internal standard and prior sample purification by liquid chromatography. Extraction and purification efficiency was 70%; sensitivity of the assay was 1 ng/ml. Peak plasma levels of THC in three cannabis smokers who each smoked one cigarette containing 10 mg THC were 19-26 ng/ml in 10 minutes. In the opinion of the authors, the method is applicable to pharmacokinetic studies in man and may form the basis for the forensic identification of cannabis. (HSRI)

1973 16refs

UM-74-M0008

METHODS FOR THE ANALYSIS OF MORPHINE AND RELATED SURROGATES: CURRENT STATUS, S. J. Mulé, Journal of Chromatographic Science v12 n5 p245-53 (May 1974)

The author reviewed recent (1971-73) advances in analytical methodology for the detection of morphine and related drugs. Extraction techniques, new applications of thin-layer chromatography, gas-liquid chromatography, gas chromatography-mass spectrometry, spectrofluorometry and immunoassays were discussed. He described the essential features of the various immunoassay techniques and evaluated their usefulness for drug detection. Finally, the author presented a table comparing the analytical methods for cost, equipment requirements and maintenance, sensitivity and specificity. (HSRI)

1974 79refs

UM-75-M0009

COMPARISON OF RESULTS FOR QUANTITATIVE DETERMINATION OF MORPHINE BY RADIOIMMUNOASSAY, ENZYME IMMUNOASSAY, AND SPECTROFLUOROMETRY, V. R. Speihler; D. Reed; R. H. Cravey; W. P. Wilcox; R. F. Shaw; S. Holland, Journal of Forensic Sciences v20 n4 p647-55 (Oct 1975)

The quantitative aspects of two immunological assays, radioimmunoassay (RIA) and enzyme immunoassay (EMIT), and two spectrofluorometric methods were compared for the determination of morphine in urine, blood, bile, brain and lung tissue. In the absence of interfering substances, including codeine, the immunoassay methods were in good agreement. Immunoassay and fluorometric procedures agreed more often in blood (80%) than in urine (55%).

The non-optical method, the iodinated radioimmunoassay, was free from quenching to which the other methods were subject and was described as simplest and easiest to use. The immunological methods were deemed superior to fluorometry for quantitation of morphine in urine samples due to quenching interferences in fluorometry from urine. They were comparable to fluorometry for quantitation of morphine in blood samples. (HSRI)

1975 15refs

UM-75-M0010

A SIMPLE, RAPID ^{125}I RADIOIMMUNOASSAY FOR THE DETECTION OF BARBITURATES IN BIOLOGICAL FLUIDS, R. Cleeland; R. Davis; J. Heveran; E. Grunberg, Journal of Forensic Sciences v20 n1 p45-57 (Jan 1975)

The detailed evaluation of a barbiturate radioimmunoassay is presented. An ^{125}I-labeled secobarbital derivative (52 mCi/mg) served as the radioactive antigen for the reagent prepared from goat antibarbiturate serum. The stability of the ^{125}I reagent was directly related to its radioactive decay at 4°C and ambient temperature, while antigen degradation was apparent at higher temperatures.

Common barbiturates had 10-45% of the relative reactivity of secobarbital in the assay, which was applicable to blood or urine. Following administration of therapeutic doses to a group of volunteers, plasma and urine levels of pentabarbital, butabarbital, amobarbital, phenobarbital, secobarbital, and aprobarbital could be determined for at least 72 hours. The urine of volunteers given oral therapeutic doses of nonbarbiturate substances contained no cross-reacting material. The authors point out that the sensitivity, specificity, simplicity of operation and time of assay (1 hour), makes this method suitable for large scale testing of urine or serum specimens. (HSRI)

1975 5refs

UM-74-M0011

CORRELATION OF THE "EMIT" URINE BARBITURATE ASSAY WITH A SPECTROPHOTOMETRIC SERUM BARBITURATE ASSAY IN SUSPECTED OVERDOSE, C. B. Walberg, Clinical Chemistry v20 n2 p305-6 (Feb 1974)

An evaluation of the "Enzyme Multiplied Immunoassay Technique" (EMIT) for possible use in clinical screening for barbiturate overdose was made. The purpose of the study was to determine whether a negative result would be obtained with the EMIT assay in nonbarbiturate cases, and to determine whether a positive EMIT result in urine would be obtained when a significant quantity of barbiturate was present in the serum as determined spectrophotometrically.

A direct relationship in 190 of 203 patients was found for the two assays. The author concludes that the EMIT assay suffices to indicate whether or not barbiturates are present in toxic concentrations. A negative result obtained by the EMIT assay rules out further analysis of the serum for presence of barbiturates whereas a positive result may be quantified by the more lengthy ultraviolet assay. (HSRI)

1974 5refs

UM-75-M0012

PHARMACY-BASED ANALYTICAL TOXICOLOGY SERVICE, E. G. Curtis; J. A. Patel, American Journal of Hospital Pharmacy v32 n7 p685-93 (Jul 1975)

An analytical toxicololgy service, which primarily tests specimens for drugs of abuse but also determines blood levels of therapeutic drugs, is described. Immunoassay, chromatographic, and spectrophotometric techniques are discussed. The methods are compared for sensitivity, cost, and time requirements. A drug analysis scheme for urine, blood, and solid substances is also presented. (HSRI)

1975 13refs

UM-70-M0013

RAPID DETERMINATION OF DIPHENYLHYDANTOIN IN BLOOD PLASMA BY GAS-LIQUID CHROMATOGRAPHY, J. MacGee, Analytical Chemistry v42 n3 p421-2 (Mar 1970)

Plasma diphenylhydentoin was measured by a gas-liquid chromatography (GLC) method featuring on-column derivatization with trimethylammonium hydroxide. Buffered plasma was extracted with toluene containing the internal standard. The organic phase was then extracted with a small volume of methylation reagent, an aliquot of which was injected into the gas chromatograph. There was good agreement between the sensitive (1 ng/ml) GLC procedure and a more complicated spectrophotometric method. (HSRI)

1970 7refs

UM-75-M0014

THE SCREENING OF BLOOD BY GAS CHROMATOGRAPHY FOR BASIC AND NEUTRAL DRUGS, J. Wells; G. Cimbura; E. Koves, Journal of Forensic Sciences v20 n2 p382-90 (Apr 1975)

A screening procedure for basic and neutral drugs is described. Based on gas chromatography, the two-column system is designed so that a wide range of drugs can be detected, including amphetamines (routinely derivatized), tricyclic compounds, benzodiazepines, methadone, diphenhydramine, and methaqualone. A majority of the drugs is readily detectable in blood in concentrations of 1 mcg/ml. Practical application of the method is illustrated by case histories and "spiked" blood samples. (HSRI)

1975 9refs

UM-75-M0015

DETERMINATION OF MORPHINE AND CODEINE IN POST-MORTEM SPECIMENS, G. R. Nakamura; E. L. Way, Analytical Chemistry v47 n4 p775-8 (Apr 1975)

A gas-liquid chromatography (GLC) method utilizing published extraction and derivatization techniques was applied to the simultaneous determination of submicrogram amounts of morphine and codeine in post-mortem specimens. Extraction procedures and recovery data for blood, bile, urine, and tissue samples were presented. Acid hydrolysis of blood samples increased yields of morphine and codeine, but destroyed acid-labile drugs for which the method screened. A spectrofluorometric procedure was used for confirmation purposes. (HSRI)

1975 4refs

UM-74-M0016

MASS FRAGMENTOGRAPHY OF MORPHINE AND 6-MONOACETYLMORPHINE IN BLOOD WITH A STABLE ISOTOPE INTERNAL STANDARD, W. O. R. Ebbighausen; J. H. Mowat; H. Stearns; P. Vestergaard, Biomedical Mass Spectrometry v1 n5 p305-11 (Oct 1974)

A mass fragmentographic method for the estimation of free and bound morphine, and free 6-monoacetylmorphine (6-MAM) in blood, was described. The sensitive (1 ng/ml) method required the use of stable isotope internal standards, which allowed correction for sample preparation losses. Prior derivatization with trifluoroacetic anhydride contributed to the specificity of the assay.

Plasma levels of morphine and 6-MAM were determined following intraperitoneal administration of 3 mg/kg heroin to male rabbits. 6-MAM appeared to be a specific metabolite of heroin as it was not detected following similar injections of morphine or codeine. (HSRI)

1974 17refs

UM-72-M0017

GAS CHROMATOGRAPHIC DETERMINATION OF THERAPEUTIC LEVELS OF AMOBARBITAL AND PENTOBARBITAL IN PLASMA, M. Ehrnebo; S. Agurell; L. O. Boréus, European Journal of Clinical Pharmacology v4 n4 p191-5 (Aug 1972)

Gas chromatographic (GC) methods are described for the assay of amobarbital and pentobarbital in 0.5 ml plasma, in concentrations down to 250 ng/ml. After ether extraction of buffered plasma (pH 5.5), the barbiturates are re-extracted into an alkaline solution of trimethylanilinium hydroxide. The barbiturates are analyzed quantitatively by GC as their dimethylated derivatives. Plasma concentrations of amobarbital and pentobarbital were found to be 1-2 mcg/ml, two to six hours following oral administration of 100 mg to young healthy male volunteers. (HSRI)

1972 12refs

UM-74-M0018

PHARMACOKINETICS AND DISTRIBUTION PROPERTIES OF PENTOBARBITAL IN HUMANS FOLLOWING ORAL AND INTRAVENOUS ADMINISTRATION, M. Ehrnebo, Journal of Pharmaceutical Sciences v63 n7 p1114-8 (Jul 1974)

The pharmacokinetics of intravenously (i.v.) and orally administered pentobarbital (100 mg) was studied in seven healthy subjects. Plasma concentrations were determined by gas chromatographic analysis using an on-column methylation procedure developed by the author. Formulas are presented which allow the calculation of drug distribution to plasma water, plasma protein, and associated fluid in the central compartment.

Following i.v. administration, peak levels (3 mcg/ml) of pentobarbital in plasma were reached in 6 min., and a mean value of 1.6 mcg/ml was found after 1 hour. Apparent disposition half-life was slightly over 20 hours for both routes of administration. Plasma concentrations showed good agreement with those predicted by a two-compartment open model. Analysis of the distribution volumes referenced to plasma water concentration gave volumes that considerably exceeded the total body water. It was concluded from these results that pentobarbital exhibits extensive tissue binding. (HSRI)

1974 14refs

UM-69-M0019

GAS CHROMATOGRAPHY OF BARBITURATES, PHENOLIC ALKALOIDS, AND XANTHINE BASES: FLASH-HEATER METHYLATION BY MEANS OF TRIMETHYLANILINIUM HYDROXIDE, E. Brochmann-Hanssen; T. O. Oke, Journal of Pharmaceutical Sciences v58 n3 p370-1 (Mar 1969)

Improved gas chromatographic behavior of barbiturates, phenolic alkoloids, and xanthines was achieved by flash-heater methylation with trimethylanilinium hydroxide. Injection of methanol solutions of trimethylanilinium salts of the compounds produced thermal decomposition in the injection port to give methyl derivatives. A gas chromatogram showing the successful separation of twelve derivatized barbiturates was illustrated. In a similar fashion, morphine was derivatized to codeine, and theobromine and theophylline to caffeine. The method was deemed suitable for quantitative analysis. (HSRI)

1969 11refs

UM-73-M0020

RAPID DETERMINATION OF BARBITURATES BY GAS CHROMATOGRAPHY-MASS SPECTROMETRY, R. F. Skinner; E. G. Gallaher; D. B. Predmore, Analytical Chemistry v45 n3 p574-6 (Mar 1973)

The application of gas chromatography-mass spectrometry to the identification of barbiturates in body fluids is described. In the modification of a published method, whole blood, serum, or plasma (1 ml) is buffered, then extracted with ether-toluene. Barbiturates, glutethimide, and diphenylahydantoin are quantitatively extracted from the organic phase by the derivatizing agent, a methanolic trimethylanilinium hydroxide solution.

With the use of temperature programming, the gas chromatographic separation of a large number of barbiturates, derivatized by on-column methylation, is achieved with a maximum elution time of under 10 minutes. Positive identification was effected by mass spectrometry. Greater sensitivity than the limit of 2 mcg/ml could be obtained by extracting larger volumes of blood. (HSRI)

1973 10refs

UM-73-M0021

USE OF STABLE ISOTOPES IN MEASURING LOW CONCENTRATIONS OF DRUGS AND DRUG METABOLITES BY GC-MS-COM PROCEDURES, M. G. Horning; J. Nowlin; K. Lertratanangkoon; R. N. Stillwell; W. G. Stillwell; R. M. Hill, Clinical Chemistry v19 n8 p845-52 (Aug 1973)

The applicability of stable isotope labeled compounds in gas chromatography-mass spectometry-computer (GC-MS-COM) analyses of drugs in biological fluids was discussed. Use of such compounds with multiple ion detection obviated the need for checking calibration curves during daily operation of these systems.

Illustrations of drug analyses in plasma, urine, and breast milk were presented. The authors suggested additional clinical and toxicological applications of selected ion monitoring. For example, GC-MS-COM chemical ionization analyses of samples may be recorded, and, with appropriate computer programs, the data may be searched for ions characteristic of drugs such as barbiturates and narcotics. (HSRI)

1973 9refs

UM-74-M0022

PRELIMINARY STUDIES ON THE USE OF N-BUTYLCHLORIDE AS AN EXTRACTANT IN A DRUG SCREENING PROCEDURE, E. H. Foerster; M. F. Mason, Journal of Forensic Sciences v19 n1 p155-62 (Jan 1974)

A screening procedure for the detection and quantitation of nonvolatile drugs in blood specimens was described. The procedure employed n-butylchloride as an extractant and required gas chromatographic, ultraviolet photometry and thin-layer chromatographic instrumentation. Recovery data was presented for 18 drugs in aqueous reference solutions. The procedure was applicable to specific drug analyses (1 hour) as well as to general screening (4 hours). (HSRI)

1974 8refs

UM-74-M0023

THE IDENTIFICATION OF NON-BARBITURATE HYPNOTICS FROM BIOLOGICAL SPECIMENS, R. H. Cravey; N. C. Jain, Journal of Chromatographic Science v12 n5 p237-45 (May 1974)

Selected methods were presented for the extraction, identification and estimation of a wide variety of non-barbiturate hypnotics. While emphasis was placed on chemical, chromatographic and spectrophotometric methods adaptable to laboratories with limited instrumentation, it was concluded that the combination of gas chromatography and mass spectrometry was the most satisfactory method for the determination of any of these compounds. (HSRI)

1974 60refs

UM-73-M0024

DIAZEPAM METABOLISM DURING CHRONIC MEDICATION. UNBOUND FRACTION IN PLASMA, ERYTHROCYTES AND URINE, I. A. Zingales, Journal of Chromatography v75 n1 p55-78 (3 Jan 1973)

The metabolism of diazepam was studied in a group of patients receiving 4-60 mg/day for periods ranging from 2 days to 106 weeks. Quantitative extraction of diazepam and three metabolites from plasma was accomplished with a toluene-heptane-isoamyl alcohol mixture (80:20:1.6). The gas chromatographic-electron capture method was sensitive to 0.1 mcg% for the four compounds.

Chronic administration led to accumulation of diazepam and its major metabolite in the blood. Ninety minutes after doses of 2 to 20 mg plasma levels of diazepam ranged from 9 to 194 mcg%. The effect of dose and dose interval on average plasma concentrations of diazepam and demethyldiazepam was presented. The importance of evaluating plasma levels as a guide to chronic or high dose administration of diazepam was emphasized. (HSRI)

1973 33refs

UM-71-M0025

DETERMINATION OF CHLORDIAZEPOXIDE PLASMA CONCENTRATIONS BY ELECTRON CAPTURE GAS-LIQUID CHROMATOGRAPHY, I. A. Zingales, Journal of Chromatography v61 n2 p237-52 (14 Oct 1971)

A gas chromatographic method involving the use of an electron capture detector (e.c.d.) was employed in determining chlordiazepoxide plasma concentrations in a group of eleven subjects. The drug was extracted from 1 ml of alkalinized plasma in n-heptane/1.5% isoamyl alcohol. Re-extractions from heptane into small volumes of aqueous and organic solvents was required only at doses less than 20 mg.

The response of the e.c.d to amounts of chlordiazepoxide as low as 0.5 ng permits the determination of the drug in 1 ml plasma samples after a single

oral dose of 5 mg. Chlordiazepoxide plasma concentrations ranged from 17 mcg% (one 5 mg dose) to 689 mcg% (multiple 50 mg doses). (HSRI)

1971 19refs

UM-71-M0026

GAS-LIQUID CHROMATOGRAPHY AND MASS SPECTROMETRY OF VARIOUS BENZODIAZEPINES, A. Forgione; P. Martelli; F. Marcucci; R. Fanelli; E. Mussini; G. C. Jommi, Journal of Chromatography v59 n1 p163-8 (8 Jul 1971)

The gas chromatographic separation of a mixture of five benzodiazepines and their identification by mass spectrometry was reported. Of the benzodiazepines (nitrazepam, N-methyloxazepam, N-demethyldiazepam, diazepam, and oxazepam), only oxazepam was structurally modified by the experimental conditions. The latter compound, as a result of heating, is rearranged to form 6-chloro-4-phenylquinazoline-2-carboxaldehyde with the loss of a water molecule. (HSRI)

1971 9refs

UM-70-M0027

DETERMINATION OF AMPHETAMINE, METHAMPHETAMINE, AND RELATED AMINES IN BLOOD AND URINE BY GAS CHROMATOGRAPHY WITH HYDROGEN-FLAME IONIZATION DETECTOR, P. Lebish; B. S. Finkle; J. W. Brackett, Jr., Clinical Chemistry v16 n3 p195-200 (Mar 1970)

A sensitive gas chromatographic (GC) method suitable for clinical and forensic purposes is presented for measuring methamphetamine, amphetamine, and other phenethylamines in blood and urine. Analytical procedures for extraction and derivatization of the amines are detailed. Retention data obtained from polar and nonpolar GC-column packings are tabulated for over 50 compounds related to phenethylamine. Suitable tests are described for the more stringent confirmation of amphetamine and methamphetamine required for court testimony. (JAM)

1970 4refs

UM-72-M0028

DETERMINATION OF AMPHETAMINE AND PHENTERMINE IN BIOLOGICAL FLUIDS, J. E. O'Brien; W. Zazulak; V. Abbey; O. Hinsvark, Journal of Chromatographic Science v10 n5 p336-41 (May 1972)

Techniques are described for the gas chromatographic measurement of amphetamine and phentermine at the concentration levels found in blood and urine following the administration of therapeutic doses. Lower levels in blood requires the using of coated glassware; co-precipitating with a scavenger amine; forming a hydrochloride salt; and utilizing an internal standard to counteract irreversible absorption, volatility, and incomplete derivatization.

Adequate sensitivity of the method (10 ng/ml) was demonstrated by determining blood and urine concentrations of amphetamine (12.5 and 20 mg) and phentermine (15 and 30 mg) in four subjects throughout a twenty-four hour period. Urine concentrations of amphetamine were much higher than blood levels. The higher drug level permits direct derivatization on the benzene extract without an intervening concentration step. (HSRI)

1972 9refs

UM-73-M0029

APPLICATION OF QUANTITATIVE GC-MASS SPECTROMETRY TO STUDY OF PHARMACOKINETICS OF AMPHETAMINE AND PHENTERMINE, A. K. Cho; B. J. Hodshon; B. Lindeke; G. T. Miwa, Journal of Pharmaceutical Sciences v62 n9 p1491-4 (Sep 1973)

Quantitative gas chromatographic-mass spectrometric (GC-MS) assays were used

to determine plasma and brain levels of amphetamine and phentermine in rats. The assays involved extraction of the amines from biological fluid, formation of N-trifluoroacetyl derivatives, and multiple ion detection GC-MS. Deuterium-substituted variants of the two amines were used as internal standards in the sensitive (10 pmoles/ml) procedures. (HSRI)

1973 18refs

UM-73-M0030

DEUTERIUM SUBSTITUTED AMPHETAMINE AS AN INTERNAL STANDARD IN A GAS CHROMATOGRAPHIC/MASS SPECTROMETRIC (GS/MS) ASSAY FOR AMPHETAMINE, A. K. Cho; B. Lindeke; B. J. Hodshon; D. J. Jenden, Analytical Chemistry v45 n3 p570-4 (Mar 1973)

The development of a mass fragmentographic assay for amphetamine was described. Three deuterium substituted amphetamines were synthesized and evaluated as internal standards; higher isotope content and greater isotopic purity made amphetamine-d_3 preferable in the determination of plasma amphetamine.

Extraction and purification steps were followed by formation of the trifluoroacetamide derivative of amphetamine. Plasma concentrations as low as 5-10 pmoles/2 ml could be accurately measured with this method. (HSRI)

1973 12refs

UM-72-M0031

QUANTITATIVE DETERMINATION OF METHADONE CONCENTRATIONS IN HUMAN BLOOD, PLASMA AND URINE BY GAS CHROMATOGRAPHY, H. R. Sullivan; D. A. Blake, Research Communications in Chemical Pathology and Pharmacology v3 n3 p467-78 (May 1972)

A sensitive (15 ng/ml) gas chromatographic method for the detection and quantitative estimation of methadone in human body fluids was reported. Buffered samples were extracted twice with n-butylchloride, and the combined organic phase was evaporated to dryness. The residue was reconstituted in n-butylchloride containing an internal standard for gas chromatography (GC) injection. Clinical applicability was demonstrated by monitoring blood and plasma levels of patients receiving maintenance doses of methadone. Analysis of human urine using this method has allowed the quantitation not only of methadone but also of two of its metabolites. (JAM)

1972 2refs

UM-74-M0032

QUANTITATION OF PLASMA LEVELS OF PROPOXYPHENE AND NORPROPOXYPHENE BY COMBINED USE OF STABLE ISOTOPE LABELING AND SELECTED ION MONITORING, H. R. Sullivan; J. L. Emmerson; F. J. Marshall; P. G. Wood; R. E. McMahon, Drug Metabolism and Disposition v2 n6 p526-32 (Nov/Dec 1974)

Specific and sensitive (1 ng/ml) assay methods for propoxyphene (Darvon) and its principal metabolite were reported. The methods involved the use of propoxyphene-d_7 and norpropoxyphene-d_3 as internal standards and gas chromatography-mass spectrometry selective ion monitoring. Plasma levels of norpropoxyphene were considerably greater than its parent in the rat and dog following a single 20 mg/kg dose. (JAM)

1974 18refs

UM-59-M0033

STUDIES ON THE METABOLIC DEGRADATION OF PROPOXYPHENE, H. M. Lee; E. G. Scott; A. Pohland, Journal of Pharmacology and Experimental Therapeutics v125 n1 p14-8 (Jan 1959)

The metabolic fate of propoxyphene was studied using radiolabeled, as well as unlabeled, drug. N-demethylation was established as the principle pathway of

degradation. Only a small fraction of the amount of drug administered to human subjects appeared unchanged in the urine. (HSRI)

1959 16refs

UM-73-M0034

THE SIMULTANEOUS DETERMINATION OF PROPOXYPHENE AND NORPROPOXYPHENE IN HUMAN BIOFLUIDS USING GAS-LIQUID CHROMATOGRAPHY, K. Verebely; C. E. Inturrisi, Journal of Chromatography v75 n2 p195-205 (17 Jan 1973)

A gas-liquid chromatographic (GLC) method for the simultaneous determination of propoxyphene and its major metabolite, norpropoxyphene, was developed. Optimal conditions for their extraction from plasma and urine were determined, and the conversion of norpropoxyphene to norpropoxyphene amide prior to GLC analysis was described.

Plasma levels and urinary excretion of both drug and metabolite were reported after the administration of a single oral dose to a normal volunteer. Plasma propoxyphene declined rapidly after one hour, while norpropoxyphene levels remained elevated at 6 hours. Propoxyphene was excreted mainly as its N-demethylated metabolite. Multiple oral doses of propoxyphene led to significant plasma accumulation in cancer patients and normal volunteers. (HSRI)

1973 8refs

UM-67-M0035

GAS CHROMATOGRAPHIC DETERMINATION OF MEPROBAMATE, 2-METHYL-2-PROPYL-1,3-PROPANEDIOL DICARBAMATE, IN PLASMA AND URINE, J. F. Douglas; T. F. Kelley; N. B. Smith; J. A. Stockage, Analytical Chemistry v39 n8 p956-8 (Jul 1967)

A simple gas chromatographic (GC) method for the quantitative determination of meprobamate was described. The extraction procedure separated meprobamate from constituents of normal plasma and urine, and from three other commonly used carbamates. The technique was reproducible and accurate in the therapeutic range of 1 to 10 mcg/ml of plasma, and had a detectability limit of 0.2 mcg/ml using 1 ml samples. A less sensitive, more rapid procedure for routine use was also described. (JAM)

1967 8refs

UM-69-M0036

GAS CHROMATOGRAPHIC DETERMINATION OF MEBUTAMATE, CARISOPRODOL, AND TYBAMATE IN PLASMA AND URINE, J. F. Douglas; N. B. Smith; J. A. Stockage, Journal of Pharmaceutical Sciences v58 n1 p145-6 (Jan 1969)

The gas chromatographic (GC) procedure described permits the measurement of the carbamates individually or in combination with meprobamate. A simple chloroform extraction of the biological fluid is followed by GC analysis. A number of drugs were investigated as possible interfering substances. The simultaneous determination of four carbamates was demonstrated. (HSRI)

1969 3refs

UM-74-M0037

A COMPREHENSIVE GC-MS REFERENCE DATA SYSTEM FOR TOXICOLOGICAL AND BIOMEDICAL PURPOSES, B. S. Finkle; R. L. Foltz; D. M. Taylor, Journal of Chromatographic Sciences v12 n5 p304-28 (May 1974)

A gas chromatography-mass spectrometric (GC-MS) reference data collection is presented which embodies chemical ionization (CI) and electron impact (EI) spectral information for 450 drugs and metabolites. The experimental detail and rationale in generating the data by a GC-quadrupole mass spectrometer system is discussed. The practical routine of identification is described

through case examples, along with a description of the interactive computer capability. The choice of library compounds was dictated by the needs of toxicologists and pharmacologists faced with the demanding problem of specific identification and characterization of sub-microgram amounts of drugs, metabolites, and biochemicals. (JAM)

1974 21refs

UM-75-M0038

DETERMINATION OF PICOMOLE QUANTITIES OF METHAQUALONE AND 6-HYDROXYMETHAQUALONE IN URINE, J. H. McReynolds; H. d'A. Heck; M. Anbar, Biomedical Mass Spectrometry v2 n6 p299-303 (Dec 1975)

An ultrasensitive analytical method involving isotope dilution analysis with multilabeled standards and using field ionization mass spectrometry was developed for the determination of methaqualone and its metabolite, 6-hydroxymethaqualone, in urine. The limit of sensitivity was 200 pg/ml for the two compounds. Analysis of urines collected over 11 days following ingestion of a single 250 mg tablet of Mandrax by a human subject indicated that the slow phase of excretion of both compounds has a half-life approximately 50 hours long. (JAM)

1975 29refs

UM-74-M0039

IDENTIFICATION OF FREE AND CONJUGATED METABOLITES OF METHAQUALONE BY GAS CHROMATOGRAPHY-MASS SPECTROMETRY, R. Bonnichsen; Y. Marde; R. Ryhage, Clinical Chemistry v20 n2 p230-5 (Feb 1974)

Gas chromatography-mass spectrometry (GC-MS) was used to identify and measure methaqualone metabolites as their trimethylsilyl derivatives. As methaqualone is known to be metabolized and excreted mainly as the glucuronate in the urine, free metabolites were obtained by enzymatic hydrolysis with B-glucuronidase and characterized by mass spectrometry. Concentrations of uncharged and metabolized methaqualone in blood, urine, and liver of three drug overdose cases were determined ultraviolet-spectrophotometrically. (JAM)

1974 9refs

UM-72-M0040

IDENTIFICATION OF METHAQUALONE METABOLITES FROM URINE EXTRACT BY GAS CHROMATOGRAPHY-MASS SPECTROMETRY, R. Bonnichsen; C.-G. Fri; C. Negoitai R. Ryhage, Clinica Chimica Acta v40 n2 p309-18 (Sep 1972)

A rapid and sensitive method for identifying methaqualone metabolites by means of gas chromatography-mass spectrometry (GC-MS) was presented. The mass spectra of the trimethylsilyl derivatives of ten synthetic metabolites of methaqualone have been studied and compared with the components of three silylated human extracts. Four to five metabolites were identified in each extract. Mass spectra were reproduced. (JAM)

1972 9refs

UM-74-M0041

QUALITATIVE AND QUANTITATIVE DETERMINATION OF METHAQUALONE IN SERUM BY GAS CHROMATOGRAPHY, M. A. Evenson; G. L. Lensmeyer, Clinical Chemistry v20 n2 p240-54 (Feb 1974)

A rapid (15 minute), qualitative and quantitative gas chromatographic method was reported for methaqualone in serum. A single extraction of pH 10.5 serum with chloroform containing an internal standard sufficed to obtain a reproducible assay with a sensitivity of 0.2 mcg/ml. No commonly used drugs or extreme serum conditions significantly interfered with the method. A non-

drug internal standard was used to compensate for variables in extraction, injection, and instrumental changes during analysis. The daily coefficient of variation was 5.6%. Mean recovery of added methaqualone was 80%. All analytical methaqualone standards were prepared in serum to compensate for the nonquantitative yield. The authors characterized the procedure as a time-saving and reliable method for drug analysis in a clinical toxicology laboratory. (JAM)

1974 14refs

UM-73-M0042

GLC DETERMINATION OF METHAQUALONE IN PLASMA, J. F. Douglas; S. Shahinian, Journal of Pharmaceutical Sciences v62 n5 p835-6 (May 1973)

A simple and sensitive (0.1 mcg/ml) gas-liquid chromatographic method for the determination of plasma methaqualone was described. Plasma made alkaline was extracted with chloroform, and the organic phase concentrated. Peak plasma levels in human subjects after 400 and 800 mg oral doses were 2.3 mcg/ml (1 hour) and 4.3 mcg/ml (2 hours), respectively. (HSRI)

1973 4refs

UM-75-M0043

QUANTIFICATION OF PHENCYCLIDINE IN BODY FLUIDS BY GAS CHROMATOGRAPHY CHEMICAL IONIZATION MASS SPECTROMETRY AND IDENTIFICATION OF TWO METABOLITES, D. C. K. Lin; A. F. Fentiman, Jr.; R. L. Foltz; R. D. Forney, Jr.,; I. Sunshine, Biomedical Mass Spectrometry v2 n4 p206-14 (Aug 1975)

A method was developed for quantification of phencyclidine in body fluids using gas chromatography chemical ionization mass spectrometry with selected ion recording. Pentadeuterated phencyclidine was synthesized and used as an internal standard. The sensitivity and specificity of the method permits determination of 1 ng phencyclidine in 1 ml of body fluid.

Phencyclidine blood levels in five individuals ranged from 50 ng/ml to 2.7 mg/ml after ingestion of unknown quantities. Two urinary metabolites in man and dog were identified and their structures were confirmed by synthesis. (JAM)

1975 16refs

UM-75-M0044

DETERMINATION OF PHENCYCLIDINE (PCP) IN URINE AND ILLICIT STREET DRUG SAMPLES, R. C. Gupta; I. Lu; G.-L. Oei; G. D. Lundberg, Clinical Toxicology v8 n6 p611-21 (Dec 1975)

The extraction and analysis of phencyclidine was reported for urine and non-biologic specimens. Methods employed were spectrophotometry, gas chromatography (GC), and thin-layer chromatography. Urine extraction efficiency (82.6%) and GC sensitivity (0.1 mg/ml urine) was sufficient to follow the excretion pattern of a comatose patient for nine days. A table describing the clinical condition along with urine concentrations of PCP in overdose patients was presented. (HSRI)

1975 15refs

UM-75-M0045

A GAS CHROMATOGRAPHIC METHOD FOR THE DETERMINATION OF AMITRIPTYLINE AND NORTRIPTYLINE IN HUMAN SERUM, A. Jørgensen, Acta pharmacologia et toxicologia v36 n1 p79-90 (Jan 1975)

The gas chromatographic (GC) determination of amitriptyline (AMT) and nortriptyline (NT) featured their simultaneous extraction from serum, the selec-

tive derivatization of NT, and GC analysis with a nitrogen sensitive detector. The lower limits of detection were 5 ng/ml (AMT) and 10-15 ng/ml (NT).

After a single dose to human volunteers, NT was not detectable, while peak concentrations of 40-50 ng/ml AMT were found. Both AMT (19-289 ng/ml) and NT (48-453 ng/ml) were found with marked individual variations following repeated administration to hospital patients. (HSRI)

1975 10refs

UM-68-M0046

SEPARATION AND DETERMINATION OF IMIPRAMINE AND ITS METABOLITES FROM BIOLOGICAL SAMPLES BY GAS-LIQUID CHROMATOGRAPHY, H. J. Weder; M. H. Bickel, Journal of Chromatography v37 n2 p181-9 (8 Oct 1968)

Gas-liquid chromatography (GLC) procedures and the determination of partition coefficients between organic solvents and aqueous buffers were reported for imipramine and its metabolites. Extraction procedures based on partition properties were followed in some cases by derivatization (acetylation). The sensitivity achieved using GLC with hydrogen flame ionization detection was 0.01-0.05 mcg. Examples of analyses using tissues, bile, and liver perfusion medium were given. (JAM)

1968 20refs

UM-69-M0047

GAS CHROMATOGRAPHIC IDENTIFICATION OF THIORIDAZINE IN PLASMA, AND A METHOD FOR ROUTINE ASSAY OF THE DRUG, S. H. Curry; G. P. Mould, Journal of Pharmacy and Pharmacology v21 n10 p674-7 (Oct 1969)

A gas chromatographic (GC) method for the detection and quantitation of thioridazine in plasma was reported. Extraction procedures using n-heptane containing 1.5% isoamyl alcohol or 20% toluene resulted in 100% recoveries of drug added to plasma, and clean blank samples. Thioridazine had a retention time of approximately 4 minutes on a 3% OV-17 gas chromatographic column at 260°; using flame or argon ionization detectors, samples as low as 0.01 mcg could be detected. Two patients receiving chronic treatment with oral thioridazine (100 and 300 mg twice daily) had drug concentrations of 0.24 mcg/ml and 1.80 mcg/ml, respectively, 2 hours after morning dose. (HSRI)

1969 9refs

UM-74-M0048

CHLORPROMAZINE ANALYSIS BY GAS CHROMATOGRAPHY WITH AN ELECTRON-CAPTURE DETECTOR, S. H. Curry, in The Phenothiazines and Structurally Related Drugs, I. S. Forrest; C. J. Carr; E. Usdin, eds., Raven Press, New York, p335-45 (1974)

The author discusses the difficulties experienced in the application of his gas chromatographic method for plasma chlorpromazine since its introduction in 1968. Contamination with benzodiazepine drugs, detector sensitivity, extraction recoveries, and nonagreement of duplicate assays are treated at length. The author concludes that the analytical problems can be overcome by careful application of the chemical, analytical, and statistical principles described. (HSRI)

1974 13refs

UM-74-M0049

CONCENTRATION OF GLUTETHIMIDE AND ASSOCIATED COMPOUNDS IN HUMAN SERUM AND CEREBROSPINAL FLUID AFTER DRUG OVERDOSE, M. Gold; E. Tassoni; M. Etzl; G. Mathew, Clinical Chemistry v20 n2 p195-9 (Feb 1974)

Serum and cerebrospinal fluid of patients in coma owing to glutethimide over-

dose were assayed for glutethimide and presumed metabolites. Chloroform extracts were concentrated and injected into a gas chromatograph. Patterns of serum concentration changes for the compounds were discussed in relationship to duration of and emergence from coma. (HSRI)

1974 7refs

UM-74-M0050

RAPID GAS CHROMATOGRAPHIC METHOD FOR QUANTITATION OF ETHCHLORVYNOL ("PLACIDYL") IN SERUM, M. A. Evenson; M. A. Poquette, Clinical Chemistry v20 n2 p212-6 (Feb 1974)

The development of a rapid, simple, and sensitive method for quantitation of ethchlorvynol was reported. The method required a single extraction with an internal standard, and could be applied to therapeutic as well as toxic concentrations of the drug in plasma. Evaluation of the assay for accuracy, precision, and interfering substances was presented. The statistical comparison with a colorimetric procedure was performed. (HSRI)

1974 14refs

UM-74-M0051

ROUTINE USE OF A FLEXIBLE GAS CHROMATOGRAPH-MASS SPECTROMETER-COMPUTER SYSTEM TO IDENTIFY DRUGS AND THEIR METABOLITES IN BODY FLUIDS OF OVERDOSE VICTIMS, C. E. Costello; H. S. Hertz; T. Sakai; K. Biemann, Clinical Chemistry v20 n2 p255-65 (Feb 1974)

The rapid identification of drugs, drug metabolites, and other toxic substances by a gas chromatograph-mass spectrometer-computer system described. The advantages of a computer searchable library of standard mass spectra is stressed. The system, including sample handling procedures, is particularly useful for such emergency situations as coma induced by drug overdose. Case histories illustrate the utility and flexibility of the system in the detection and identification of unknown substances in various body fluids. (HSRI)

1974 13refs

UM-75-M0052

A SEMIAUTOMATED RADIOIMMUNOASSAY FOR MASS SCREENING OF DRUGS OF ABUSE, T. S. Sulkowski; G. D. Lathrop; J. H. Merritt; J. H. Landez; E. R. Noe, Journal of Forensic Sciences v20 n3 p524-36 (Jul 1975)

The use and evaluation of radioimmunoassay (RIA) techniques is reported for the mass screening of urine specimens for opiates, barbiturates, and amphetamines. Semiautomation is accomplished by the use of an automatic pipetting station which performs 600 pipetting operations per hour. Assay factors, such as reproducibility, specificity, reagent shelf life, quality control, and criteria for positive detection, are discussed. (HSRI)

1975 8refs

UM-74-M0053

EVALUATION OF IMMUNOASSAY METHODS FOR DETECTION, IN URINE, OF DRUGS SUBJECT TO ABUSE, S. J. Mulé; M. L. Bastos; D. Jukofsky, Clinical Chemistry v20 n2 p243-8 (Feb 1974)

Results for abused drugs in urine, as obtained by radioimmunoassay (RIA), the "Enzyme Multiplied Immunoassay Technique" (EMIT), and hemagglutination inhibition (HI), were compared with each other, with fluorimetry, and with thin-layer chromatography (TLC). Among the drugs tested were opiates, opoids, barbiturates, amphetamine, and cocaine. The immunoassays and fluorimetric methods were highly sensitive (30 mcg/liter to 2 mg/liter).

Cross-reactivity (lack of specificity) varied with the method tested and the drug, ranging from no reaction to one exceeding that of the assay drug. The percentage of false positives for the immunoassays in comparison to TLC ranged from 3 to 31. The practical level of sensitivity for TLC, however, was only 1-5 mg/liter. False negatives were less than 2%. With the EMIT system (amphetamine, barbiturates, cocaine, opiates, and methadone assays), the total percentage of false values (negative and positive) ranged from 5 to 13.

All the immunoassays were reliable within the limitations of the assay, relatively easy to use, did not require sample treatment, and several hundred samples could be analyzed during an eight-hour period. The cost was moderate to high, depending on the assay and sample volume. Judicious use of immunochemistry, spectrofluorimetry, and thin-layer chromatography to the detection of psychoactive drugs in urine permits rapid, reliable, and effective surveillance of drug use or abuse. (JAM)

1974 20refs

UM-71-M0054

APPLICATION OF FLUORESCENCE AND GAS CHROMATOGRAPHY TO MASS DRUG SCREENING, P. H. Santinga, Fluorescence News v6 n3 p1-7 (Dec 1971)

The advantages of gas-liquid chromatography and spectrofluorometry in drug screening were emphasized. A general isolation procedure was presented for basic, neutral, and acidic drugs in urine. In this method, morphine and quinine (0.2 mcg/ml) were detected by a fluorometric procedure, while other drugs (1 mcg/ml) were identified by gas chromatography. (HSRI)

1971

Publisher: Biochemical Instrumentation Div., American Instrument Co., Siver Spring, Md. 20910

UM-75-M0055

MASS FRAGMENTOGRAPHIC DETERMINATION OF UNLABELED AND DEUTERIUM LABELED METHADONE IN HUMAN PLASMA. POSSIBILITIES FOR MEASUREMENT OF STEADY STATE PHARMACOKINETICS, H. R. Sullivan; F. J. Marshall; R. E. McMahon; E. Änggård; L.-M. Gunne; J. H. Holmstrand, Biomedical Mass Spectrometry v2 n4 p197-200 (Aug 1975)

To investigate possible changes in the pharmacokinetics of methadone in opiate dependent subjects undergoing methadone maintenance therapy, a method combining the use of quantitative mass fragmentography and pulse dosing with deuterium labeled methadone was developed.

N-butylchloride extracts of pH 9.5 plasma were evaporated, and the residue reconstituted in toluene for analysis. Plasma concentrations were determined down to 5 ng/ml, and were quantified by the use of an internal standard. As demonstrated in one application, the method will be of value in the study of methadone pharmacokinetics in the steady state and in other in vivo situations where multiple drug pools must exist. (JAM)

1975 15refs

UM-76-M0056

MASS SCREENING AND CONFIRMATION OF BARBITURATES IN URINE BY RIA/GAS CHROMATOGRAPHY, N. C. Jain; R. D. Budd; T. C. Sneath; D. M. Chinn; W. J. Leung, Clinical Toxicology v9 n2 p221-33 (Apr 1976)

A rapid, sensitive (0.5 mcg/ml), and specific procedure was described for mass screening and confirmation of barbiturates in urine specimens. Initial screening by radioimmunoassay was followed by gas chromatographic (GC) confirmation using a flame ionization detector. The barbiturates were analyzed

both as free acids and their dimethyl derivatives following a single extraction, thus eliminating false positive results. GC quantitation was achieved by inclusion of an internal standard, ibomal, in the extraction solvent. (HSRI)

1976 18refs

UM-76-M0057

EXTRACTION PROCEDURES FOR SOME COMMON DRUGS IN CLINICAL AND FORENSIC TOXICOLOGY, L. P. Hackett; L. J. Dusci; I. A. McDonald, Journal of Forensic Sciences v21 n2 p263-74 (Apr 1976)

The purpose of this study was to identify an extraction procedure suitable for general drug screening. Four extraction systems were investigated, and the distribution of 86 drugs was studied. The gas-liquid chromatography properties of these drugs were also studied, and relative retention times and column temperatures were tabulated for an OV-17 column. The incorporation of ultraviolet spectroscopy proved to be an asset in the identification of drugs in aqueous solutions. (HSRI)

1976 20refs

UM-71-M0058

A GLC BASED SYSTEM FOR THE DETECTION OF POISONS, DRUGS, AND HUMAN METABOLITES ENCOUNTERED IN FORENSIC TOXICOLOGY, G. S. Finkle; E. J. Cherry; D. M. Taylor, Journal of Chromatographic Science v9 n7 p393-419 (Jul 1971)

A simple yet comprehensive gas-liquid chromatography (GLC) system was presented and discussed. Four columns and three liquid phases were utilized, and the system was complemented by a direct solvent extraction scheme designed to detect substances to a sensitivity limit of two mcg/ml in blood, urine, and tissue specimens.

Relative retention data for almost 600 different substances were tabulated in two indices, one providing reference gas chromatographic information for any of the chemicals prior to an analysis; and the other allowing tentative identification of unknown gas chromatography (GC) peaks, which require further confirmation. The strength of the system is realized in the rapid determination of a negative analysis. A positive GC response and matching relative retention time requires further confirmation for certain identification. Techniques such as derivtive formation, infrared spectrophotometry, and mass spectrometry are mentioned. (JAM)

1971 7refs

UM-74-M0059

THE QUANTITATIVE DETERMINATION OF MORPHINE IN URINE BY GAS-LIQUID CHROMATOGRAPHY AND VARIATIONS IN EXCRETION, D. E. Fry; P. D. Willis; R. G. Twycross, Clinica Chimica Acta v51 n2 p183-90 (15 Mar 1974)

The authors reported a quantitative gas chromatographic method for total morphine in urine and its application in correlating the dose administered to the amount excreted. Following enzymatic hydrolysis, samples were extracted with ether; [^{14}C] morphine was added to correct for recovery losses.

Significant variations were found in the percentage of the daily dose of diamorphine or morphine excreted in 37 terminal cancer patients (20-112%) and in an individual over nine consecutive days (40-124%). Authors advise that extreme caution be exercised in drawing conclusions from results of morphine estimations on isolated urine specimens. (JAM)

1974 10refs

UM-75-M0060

PHARMACOKINETICS OF A SINGLE DOSE OF PHENYTOIN IN MAN MEASURED BY RADIOIMMUNOASSAY, J. D. Robinson; B. A. Morris; G. W. Aherne; V. Marks, British Journal of Clinical Pharmacology v2 n4 p345-9 (Aug 1975)

Serum concentrations of phenytoin (diphenylhydantoin) were studied by radioimmunoassay in five normal volunteers following a single oral dose of phenytoin sodium (100 mg). The radioimmunoassay was extremely sensitive (321 ± 41 pg/ml) and virtually specific for phenytoin.

Blood (1 ml) was collected by venipuncture before drug ingestion and additional 1 ml samples were collected at intervals over the next 102 hours. Two distinct peaks were found at 2.5-3.5 and 10-12 hours after ingestion. Maximum serum concentrations ranged from 1.56 mcg/ml to 2.76 mcg/ml. The mean plasma half-life of the drug under these conditions was 9.81 ± 0.66 (s.e. mean) hours. (JAM)

1975 15refs

UM-75-M0061

PHARMACOKINETICS OF N-DEMETHYLDIAZEPAM IN PATIENTS SUFFERING FROM INSOMNIA AND TREATED WITH NORTRIPTYLINE, G. Tognoni; R. Gomeni; D. De Maio; G. G. Alberti; P. Franciosi; G. Scieghi, British Journal of Clinical Pharmacology v2 n3 p227-32 (Jun 1975)

Hospitalized patients suffering from insomnia were treated with N-demethyldiazepam (30 mg p.o.) for 10 days, while continuing treatment with nortriptyline (75 or 100 mg daily). Plasma levels of N-demethyldiazepam were determined by gas-liquid chromatography, and clinical evaluation performed by objective rating scales.

While a positive therapeutic effect was observed, no correlation between plasma levels and clinical efficacy was noted. Plasma concentrations 22 hours after drug administration increased over time, from 639 ± 121 ng/ml (fifth day) to 976 ± 109 ng/ml (tenth day). Compared with diazepam, the tested drug had a longer plasma apparent half-life (51 ± 7 hours) with remarkable interpatient variability. A significant correlation was found between plasma levels at 10 hours in day 10 and the plasma half-life. (HSRI)

1975 21refs

UM-71-M0062

ROUTINE IDENTIFICATION OF DRUGS OF ABUSE IN HUMAN URINE. II. DEVELOPMENT AND APPLICATION OF THE XAD-2 RESIN COLUMN METHOD, S. J. Mulé; M. L. Bastos; D. Jukofsky; E. Saffer, Journal of Chromatography v63 n2 p289-301 (23 Dec 1971)

This drug extraction method was reported for application to the screening of large numbers of urine samples on a daily basis. The presence of morphine and quinine was determined fluorometrically and positive samples were confirmed by thin-layer chromatography. Aliquots of urine (25 ml) were applied to columns containing Amberlite XAD-2 resin. Drugs adhering to the resin were eluted with an organic solvent mixture, and bicarbonate-washed organic phases were dried. Methanolic residues thus obtained were applied equally to silica gel plates and sheets.

Opiates, opoids, barbiturates, amphetamines, phenothiazines, antihistamines, and minor tranquilizers were detected by specific color reactions and R_F values. The plates and sheets were cross-compared for final interpretation of results. The authors considered the method to be simple, rapid, inexpensive and very effective in detecting psychoactive drugs at concentrations ranging from 0.1 to 3 mcg/ml of urine. (JAM)

1971 9refs

UM-71-M0063

AN ULTRA RAPID METHOD FOR THE EXTRACTION OF DRUGS FROM BIOLOGICAL FLUIDS, J. Ramsey; D. B. Campbell, Journal of Chromatography v63 n2 p303-8 (23 Dec 1971)

A rapid quantitative method is described for the extraction of amphetamine, methamphetamine, methadone, and pethidine. The method involves the addition of a small amount of chloroform containing a suitable internal standard to a larger volume of aqueous phase. After mixing and centrifugation, a few microliters of solvent are withdrawn and injected into a gas-liquid chromatographic apparatus or spotted onto a thin-layer plate. Volatility problems of solvent and drug are overcome, since the solvent is covered by aqueous phase throughout and no evaporation step is involved.

The method as applied to the above compounds is simple, sensitive (1 mcg/ml of urine), accurate, and reproducible. The use of the procedure for the extraction of other drugs and its application to gas-liquid and thin-layer chromatography is discussed. (HSRI)

1971 10refs

UM-71-M0064

ROUTINE IDENTIFICATION OF DRUGS OF ABUSE IN HUMAN URINE. I. APPLICATION OF FLUOROMETRY, THIN-LAYER AND GAS-LIQUID CHROMATOGRAPHY, S. J. Mulé, Journal of Chromatography v55 n2 p255-66 (3 Mar 1971)

The methods described in this report were developed for the rapid analysis of over 500 urine samples (50-60 ml each) per day for psychoactive drugs. The techniques include extraction of drugs from biological material; semiautomated spectrofluorometry; extensive use of thin-layer chromatography with sequential chromogenic spraying for detection; and gas-liquid chromatography as an adjunct tool for positive identificaiton and confirmation.

In general procedure, morphine and quinine were detected spectrofluorometrically. Acidic and basic urine extractions were performed separately. Among the drugs which could be detected were barbiturates, diphenylhydantoin, glutethimide, amphetamines, phenothiazines, opiates, opoids, and tranquilizers. The methods and techniques were relatively simple to perform and the drugs could be detected in the range of 1-5 mcg/ml of urine. (JAM)

1971 10refs

UM-68-M0065

EXTRACTION PROCEDURES IN CHEMICAL TOXICOLOGY, S. L. Tompsett, Analyst v93 n1112 p740-8 (Nov 1968)

Investigations into the separation of drugs from urine by distillation, solvent extraction, and use of ion exchange resins are described and discussed. The following screening procedures were developed and used in conjunction with ultra violet spectrophotometry: distillation of urine in the presence of sodium bicarbonate; neutral extraction of urine with chloroform; basic urine extraction with chloroform. Ultraviolet spectrophotometry was used to assess recoveries of drugs after distillation or solvent extraction procedures. It was emphasized that the screening procedures, while they covered may drugs and compounds, were not to be considered complete. (HSRI)

1968 33refs

UM-72-M0066

A PROCEDURE FOR THE RAPID ANALYSIS OF LARGE NUMBERS OF URINE SAMPLES FOR DRUGS, L. R. Goldbaum; P. Santinga; A. M. Dominguez, Clinical Toxicology v5 n3 p369-79 (Fall 1972)

This method for urinary drug analysis utilizes gas-liquid chromatography (GLC)

with a number of columns with different liquid phases. Chloroform-5% isobutanol extracts of urine samples are washed with a sodium borate solution; then are submitted to separate acidic and basic extractions. Neutral drugs are detected in the remaining solvent phase. Morphine is detected by a highly sensitive and specific spectrofluorometric procedure, while acidic and basic drugs are determined by GLC following reextraction by solvent from their respective aqueous phases. A 5 ml sample containing 1 mcg/ml of drugs and 0.1 mcg/ml of morphine can be accurately determined by this procedure. (HSRI)

1972 2refs

UM-73-M0067

RAPID IDENTIFICATION OF DRUGS IN BODY FLUIDS OF COMATOSE PATIENTS, A. J. Rice; W. R. Wilson, Clinical Toxicology v6 n1 p59-73 (Spring 1973)

This report describes a gas chromatographic method for the identification and quantitation of a variety of drugs commonly involved in suicide attempts. Separate 4 ml plasma samples are required for acidic (barbiturates, glutethimide, methyprylon, meprobamate), neutral (benzodiazepines, chlorpromazine), and basic (antidepressants) extractions. The method can detect levels of drugs far below those seen in drug intoxicated patients, with the exception of diazepam and chlordiazepoxide. Detection limits for the drugs listed above were 1-2.5 mcg/ml of plasma. (HSRI)

1973 14refs

UM-71-M0068

PROFILE OF SEDATIVES AND TRANQUILIZERS IN SERUM, AS MEASURED BY GAS-LIQUID CHROMATOGRAPHY, H. F. Proelss; H. J. Lohmann, Clinical Chemistry v17 n3 p222-8 (Mar 1971)

A comprehensive screening method for 40 commonly used sedatives and tranquilizers utilized gas-liquid chromatography and two liquid phases. Barbiturates, nonbarbiturate sedatives, and tranquilizers of the phenothiazine, benzodiazepine, and dibenzazepine types could be identified and measured in serum; limits of detectability ranged from 0.1-0.5 mcg/ml of serum.

Simple solvent extractions at different pH values, with subsequent solvent partition, effected a preliminary separation into acid, neutral, and basic drugs; recovery data was presented for some of the compounds. The three fractions were separated on two columns: acid and neutral drugs with liquid phase XE-60 (3.5%) and basic drugs with liquid phase OV-17 (3%). Substances were examined for possible interference with the analysis. Clinical applications of the method were reported, and the serum concentrations of several drugs were given. (JAM)

1971 14refs

UM-71-M0069

GAS CHROMATOGRAPHIC DETERMINATION OF DOXEPIN IN HUMAN URINE FOLLOWING THERAPEUTIC DOSES, L. J. Dusci; L. P. Hackett, Journal of Chromatography v61 n2 p231-6 (14 Oct 1971)

A gas-liquid chromatographic method for the estimation of doxepin (Sinequan) in human urine is described. Chloroform extracts of a 50 ml urine sample are combined, washed, and dried; the residue is redissolved in chloroform containing the internal standard, and an aliquot is injected into the gas chromatograph. The method allows the determination of concentrations of doxepine as low as 0.1 mcg/ml. Recoveries using blood samples and a similar procedure are reported; the limit of detection in blood is 1/mcg/ml.

In 24 hours, an average of only 0.4% of doxepin appeared in the urine of subjects who had ingested single oral doses of 50 mg doxepin hydrochloride.

The drug could not be detected in subjects' blood 4 hours after administration of 20-50 mg. Results are presented showing urine levels of the drug 4, 8, 12, 16, and 24 hours after a therapeutic (50 mg) dose. (HSRI)

1971 9refs

UM-73-M0070

THIN-LAYER CHROMATOGRAPHY OF PHENOTHIAZINE DERIVATIVES AND ANALOGUES, A. De Leenheer, Journal of Chromatography v75 n1 p79-86 (3 Jan 1973)

A thin-layer chromatographic system was developed for the characterization of phenothiazines, azaphenothiazines, thioxanthines, dibenzazepines and dibenzocycloheptadienes. Two solvent systems were examined and the relative R_F values of the compounds were reported. After preliminary ultraviolet inspection, group differentiation of compounds at the microgram level was achieved by the sequential use of spray reagents with increasing oxidative properties. (HSRI)

1973 20refs

UM-72-M0071

ANALYSIS OF ALCOHOL. I. A REVIEW OF CHEMICAL AND INFRARED METHODS, N. C. Jain; R. H. Cravey, Journal of Chromatographic Science v10 n5 p257-62 (May 1972)

Selected chemical, biochemical and instrumental methods, excluding gas chromatographic methods, for the analysis of ethanol in blood, breath and urine samples are briefly described. The review is limited solely to methodologies; no attempt was made to discuss interpretation of alcohol levels. Special emphasis is placed on the review of breath methods because of their widespread use by law enforcement agencies. (JA)

1972 59refs

UM-75-M0072

COMPARISON OF COSTS FOR TESTING A WIDE VARIETY OF DRUGS OF ABUSE PER URINE SPECIMEN IN A DRUG ABUSE URINE SCREENING PROGRAM AND FREQUENT URINE COLLECTIONS, K. K. Kaistha; R. Tadrus, Journal of Chromatography v109 n1 p149-62 (4 Jun 1975)

Urine testing techniques, including thin-layer chromatography (TLC), gas-liquid chromatography, spectrophotofluorometry, and several immunoassay variants, are examined for their applicability in a drug abuse urine screening program. Comparisons are made on the basis of a technique's capacity to analyze urine specimens, the start up cost and cost per specimen using each technique, and the sensitivity, specificity, and range of compounds characterizing the method.

In the authors' opinion, TLC appears to be the only technique which is simple, inexpensive, reliable and versatile. Costs and other details concerning a TLC method developed by the authors were presented. (HSRI)

1975 16refs

UM-74-M0073

CHEMICAL EVALUATION OF "DRUG COCKTAILS" IN AUTOPSY SPECIMENS, A. E. Robinson; A. T. Holder, Journal of Chromatographic Science v12 n5 p281-4 (May 1974)

A full chemical analysis of autopsy specimens is essential if the cause of death is to be scientifically established in situations where several drugs have been taken. Suitable methods for the identification and determination of drugs in autopsy specimens, and the associated problems, are discussed.

Preliminary, qualitative analysis of urine and stomach content involves the extraction of acidic, neutral and basic fractions into ether. Thin-layer chromatography of the concentrated solvent extracts allows detection and partial characterization of many basic substances along with the benzodiazepines. Barbiturates are determined spectrophotometrically. A gas-liquid chromatography system is described for quantitation and confirmation purposes. (HSRI)

1974 8refs

UM-74-M0074

COMPARISON OF METHODS FOR DETECTION OF AMPHETAMINES, COCAINE AND METABOLITES, M. L. Bastos; D. B. Hoffman, Journal of Chromatographic Science v12 n5 p269-80 (May 1974)

This article is a comprehensive review and analysis of the available methods for detection of amphetamines, cocaine and metabolites in biological material and in street drug samples. Extraction procedures reflecting the special analytical requirements of amphetamine and cocaine are presented. Immunologic, spectrophotometric, and fluorescent methods are described and referenced. The principal solvent systems for the silica gel thin-layer chromatography of the compounds are tabulated for their ionized and un-ionized forms; visualization techniques are discussed. Gas chromatography (column packing, derivatization techniques) and microcrystallography are also discussed at some length. (HSRI)

1974 191refs

UM-74-M0075

ISOLATION AND IDENTIFICATION OF METHAQUALONE FROM POST-MORTEM TISSUES, G. N. Christopoulos; N. W. Chen; A. J. Toman, Journal of Chromatographic Science v12 n5 p267-8 (May 1974)

Procedures for the isolation, identification, and quantitation of methaqualone in tissues and biological fluids are described. Methaqualone present in specimens is quantitated by ultraviolet spectrophotometry; thin-layer and gas-liquid chromatographic procedures are given as confirmatory techniques. Data is presented from 17 cases which indicate that without prior hydrolysis of samples, low levels of methaqualone could remain undetected; levels of the drug are shown to increase between 47 and 60% after hydrolysis. (HSRI)

1974 6refs

UM-74-M0076

THIN-LAYER AND GAS CHROMATOGRAPHIC IDENTIFICATION OF LSD, A. R. Sperling, Journal of Chromatographic Science v12 n5 p265-6 (May 1974)

Methods suitable for the identification of lysergic acid diethylamide (LSD) and related compounds in powder form are presented. Two solvent systems were developed for use with silica gel GF thin-layer plates. After visualization with long wave ultraviolet light, the plates are sprayed with p-dimethylaminobenzaldehyde reagent. Used in conjunction, the two systems will distinguish LSD from other ergot alkaloids. In a gas chromatographic procedure, the trimethylsilyl derivative is prepared, and is free from interference by proteinaceous material, lactose, starch, and calcium carbonate as found in LSD tablets. (HSRI)

1974 7refs

UM-74-M0077

A REVIEW OF SOME GLC-FID DERIVATIZATION TECHNIQUES FOUND USEFUL IN FORENSIC TOXICOLOGY, G. Cimbura; J. Kofoed, Journal of Chromatographic Science v12 n5 p261-4 (May 1974)

An important reason for the employment of gas-liquid chromatographic derivatization techniques is to increase the sensitivity of the analysis either by improving the chromatographic behavior of a drug or by formation of derivatives which make it possible to utilize the high sensitivity of the electron capture detector. This report reviews gas-liquid chromatography-flame ionization detector (GLC-FID) techniques found useful by the authors in their forensic toxicological casework.

GLC-FID derivatization techniques covered include acetylation for the determination of amphetamines and morphine; methylation for the determination of diphenylhydantoin; chemical reduction for the confirmation of ethylene glycol, formaldehyde and drugs such as methadone; and bromination for the determination of bromides. (HSRI)

1974 17refs

UM-74- M0078

ANTIEPILEPTIC DRUGS: A CURRENT ASSESSMENT OF SIMUTANEOUS DETERMINATION OF MULTIPLE DRUG THERAPY BY GAS LIQUID CHROMATOGRAPHY-ON COLUMN METHYLATION, E. B. Solow; J. M. Metaxas; T. R. Summers, Journal of Chromatographic Science v12 n5 p256-60 (May 1974)

A revised gas chromatographic procedure for antiepileptic drugs made possible rapid and accurate serum level determinations. The method involves extracting buffered serum with toluene containing either 2 or 3 internal reference standards. Drugs in the toluene extract are concentrated in 25 mcl tetramethylammonium hydroxide, 2 M in methanol; an aliquot is then injected into the gas chromatograph. Methylated derivatives formed on-column require 20 or 60 minutes analysis time depending on drug therapy and choice of oven temperature. The resolution of nine drugs is shown by this method. (JAM)

1974 24refs

UM-74-M0079

PERFORMANCE EVALUATION IN THE TOXICOLOGY LABORATORY, J. K. Jones, Journal of Chromatographic Science v12 n5 p254-5 (May 1974)

A performance evaluation system using quality control and proficiency testing programs is recommended as an integral part of the procedural operation of a toxicology laboratory. The purpose of such an evaluation is to test the quality of results from routine analyses and not to test the greatest skill of which an analyst is capable.

Quality control is an in-house program utilizing the inclusion of standards on a daily and run-to-run basis. Adequate standards and the use of blind samples are required. Proficiency testing is accomplished through interlaboratory comparisons; the use of without-the-house known standards is recommended. Constructive aspects of such a performance evaluation program are to be emphasized. (HSRI)

1974 5refs

UM-74-M0080

THE IDENTIFICATION OF BARBITURATES FROM BIOLOGICAL SPECIMENS, N. C. Jain; R. H. Cravey, Journal of Chromatographic Science v12 n5 p228-36 (May 1974)

Selected methods for the extraction, screening, and subsequent identification of barbiturates from blood and other tissues are reviewed. These include spectrophotometric, microcrystalline, chromatographic, and gas chromatographic-

mass spectrometric methods. A brief description of the more recent approaches, including immunoassays, high pressure liquid chromatography, and the automated analysis of barbiturates, is included. (JAM)

1974 112refs

UM-74-M0081

EMERGENCY HOSPITAL TOXICOLOGY, C. B. Walberg; G. D. Lundberg; V. A. Pantlik, Journal of Chromatographic Science v12 n5 p225-7 (May 1974)

A patient-oriented emergency toxicology service in a large metropolitan hospital is described. Emergency toxicology tests are defined and differentiated from routine clinical toxicology tests. Methodology is described in general terms for simultaneous assay of multiple specimens within prescribed time limits. Reference to methods equally applicable to large and small laboratories and used in the program described is given. Workload figures for 1972 include number of tests, type of drug analyzed, type of assay, and the method. (JAM)

1974 28refs

UM-74-M0082

A REVIEW OF BREATH ALCOHOL METHODS, N. C. Jain; R. H. Cravey, Journal of Chromatographic Science v12 n5 p214-8 (May 1974)

This article provides a brief review of the current methods used in the determination of alcohol from breath. Only selected recent developments are discussed to supplement recently published reviews, which are referenced. The methodologies discussed in this paper are based on chemical, conductance, electrochemical, heat of oxidation, infrared absorption, dehydrogenation, and gas chromatographic methods. No attempt is made to correlate the breath, blood or urine alcohol levels; the review is devoted solely to the methods of breath alcohol analysis. (JAM)

1974 33refs

UM-74-M0083

CURRENT STATUS OF BLOOD ALCOHOL METHODS, R. H. Cravey; N. C. Jain, Journal of Chromatographic Science v12 n5 p209-13 (May 1974)

This article reviews current methods used in blood alcohol analysis. However, any method suitable for blood is also applicable to urine alcohol determination. An attempt is made to discuss the most recent work involving chemical, enzymatic, osmometric, gas chromatographic (GC) and computerized GC-mass spectrometric methods used in blood/urine alcohol analysis. No discussion of the correlation of blood:urine alcohol levels is presented. (JAM)

1974 33refs

UM-72-M0084

PREPARATORY PROCEDURES IN SCREENING FOR DRUGS OF ABUSE: "CLEAN-UP" METHODS IN CURRENT USE, D. Sohn; J. Simon; M. A. Hanna; G. Ghali, Journal of Chromatographic Science v10 n5 p294-6 (May 1972)

Procedures used to extract, concentrate, and purify drugs from urine and blood are noted, especially in regard to the analytical requirements of thin-layer and gas-liquid chromatography. Solvent extractions, resin loaded papers, and resin impregnated columns are included among the referenced techniques. The use of the Amberlite XAD-2 column as a "clean-up" procedure is compared to a quick solvent extraction for gas chromatography. (HSRI)

1972 23refs

UM-72-M0085

BARBITURATE ANALYSIS--A CURRENT ASSESSMENT, G. Kananen; R. Osiewicz; I. Sunshine, Journal of Cromatographic Science v10 n5 p283-7 (May 1972)

Since gas chromatography (GC) provides simultaneous qualitative and quantitative data, existing GC techniques for the determination of barbiturates were evaluated. Using both screening and quantitative procedures, the absolute and relative retention times of commonly occurring barbiturates were obtained and tabulated.

A comparison of the GC method with an ultraviolet-thin-layer chromatographic (UV-TLC) analysis was made. Both procedures yield clinically comparable analyses for barbiturate determinations. Depending on the available personnel and equipment, one or the other may be used satisfactorily. When a large number of samples (20 or more) are required to be analyzed, the described GC procedure is faster and more sensitive than the UV procedure. The GC method involves on-column methylation and the methylated barbiturates thus formed require only twenty minutes for quantitative analysis. (HSRI)

1972 11refs

UM-72-M0086

ANALYSIS OF HALLUCINOGENIC DRUGS, A. Sperling, Journal of Chromatographic Science v10 n5 p268-75 (May 1972)

Methods recently applied to the problem of hallucinogenic drug determination as well as those older methods appropriate to the general area of drug analysis were reviewed. Among the drugs and drug classes included were lysergic acid diethylamide, ergoline alkaloids, tryptamines, and delta-9-tetrahydrocannabinol (THC).

The alkaloidal content of morning glory seeds was summarized. A spectrofluorometric study of hallucinogens was reported in which the optimum solvent and the practical limits of detection were presented. The stability of stored, purified THC and the cannabinoid content of fresh marijuana plant material were also given. (HSRI)

1972 48refs

UM-72-M0087

ANALYSIS OF ALCOHOL. II. A REVIEW OF GAS CHROMATOGRAPHIC METHODS, N. C. Jain; R. H. Cravey, Journal of Chromatographic Science v10 n5 p263-7 (May 1972)

In this review, selected gas chromatography (GC) methods used in the analysis of alcohol are discussed. The separation of alcohol from biological samples is achieved by means of head space, distillation, or extraction. Methods which eliminate sample preparation by direct injection of blood or urine are also described. Newly developed breath methods utilizing GC are cited. Recent advances in automation in the analysis of alcohol by GC are elaborated. (JA)

1972 31refs

UM-75-M0088

STEADY-STATE PLASMA NORTRIPTYLINE CONCENTRATIONS IN EPILEPTIC PATIENTS, R. A. Braithwaite; R. J. Flanagan; A. Richens, British Journal of Clinical Pharmacology v2 n5 p469-71 (Oct 1975)

A number of antiepileptic drugs in current clinical use have been shown to be potent inducers of the hepatic microsomal enzyme system. One result is that the metabolism of other drugs used in the epileptic patient is accelerated, leading to reduced plasma concentrations and possible therapeutic failure. The present study was designed to investigate the effect of chronic anticon-

vulsant therapy on steady-state nortriptyline concentrations in a group of six epileptic patients.

Plasma nortriptyline was measured by gas chromatography. Compared to two control groups of depressed patients and six volunteer students, the reduction in plasma concentration in patients receiving anticonvulsant therapy was 50%. It was, therefore, considered important to allow for the effects of hepatic microsomal enzyme induction by increasing the dose or frequency of administration in the epileptic patient. Monitoring the plasma concentration of the antidepressant would be valuable under the circumstances. (HSRI)

1975 20refs

UM-76-M0089

PROFICIENCY TESTING IN FORENSIC TOXICOLOGY: CRITERIA FOR EXPERIMENTAL DESIGN, R. C. Kelly; I. Sunshine, Clinical Chemistry v22 n8 p1413-4 (Aug 1976)

This letter to the editor concerned a published study in which the proficiency of nine forensic laboratories was evaluated. The survey was described, and its results were presented in table form. Problems in the interpretation of the results were discussed. Recommendations relevant to proficiency testing in analytical toxicology were made. (HSRI)

1976 6refs

UM-76-M0090

ENZYME-IMMUNOASSAY, G. B. Wisdom, Clinical Chemistry v22 n8 p1243-55 (Aug 1976)

Principles of the different enzyme-immunoassay techniques are described and their applications to the identification and quantification of antigens, haptens, and antibodies in biological fluids are discussed. Substances for which enzyme-immunoassays have been developed are listed. The enzymes used as labels, the methods of linking them to proteins, and the methods for separating free and bound labeled material are described. The reliability, practicality, disadvantages, and method improvement are reviewed. (JA)

1976 119refs

UM-76-M0091

PROPOXYPHENE AND NORPROPOXYPHENE CONCENTRATIONS IN BLOOD AND TISSUE IN CASES OF FATAL OVERDOSE, A. J. McBay, Clinical Chemistry v22 n8 p1319-21 (Aug 1976)

Propoxyphene and its major metabolite, norpropoxyphene, have been quantitated in tissue specimens obtained from autopsies of people suspected of dying from propoxyphene overdosage. Gas-chromatographic determination of both propoxyphene and norpropoxyphene is essential because the blood concentration of the parent drug should be about 1.0 mg/liter or greater to attribute a death to the drug. The metabolite concentration in blood may help to establish when the drug was ingested. Concentrations in the blood after high oral therapeutic doses are about 0.3 mg of propoxyphene per liter, and norpropoxyphene concentrations may be as high as 3 mg/liter. Methods of determining propoxyphene are discussed. (JA)

1976 8refs

UM-71-M0092

THE MASS SPECTROMETER AS A GAS-CHROMATOGRAPHIC DETECTOR, C. J. W. Brooks; B. S. Middleditch, Clinica Chimica Acta v34 n2 p145-57 (Sep 1971)

Qualitative and quantitative aspects of mass spectrometry, as applied to gas-chromatographic (GC) studies, are briefly discussed. Measurements of ion currents produced by electron impact, before separation in the magnetic sector, indicate that sensitivity factors are of the same order of magnitude for many

steroids. The utility of "single ion monitoring," in which ions of one characteristic m/e value are selectively detected during chromatography, is illustrated with particular reference to steroidal analogues. The detector response is proportional to the amount of sample injected: data are given for the range 50-1000 pg. The stationary phases OV-1 and Dexsil-300 GC are compared. (JAM)

1971 20refs

UM-71-M0093

ANALYTICAL AND PHARMACOKINETIC STUDIES ON BUTYROPHENONES, F. Marcucci; E. Mussini; L. Airoldi; R. Fanelli; A. Frigerio; F. De Nadai; A. Bizzi; M. Rizzo; P. L. Morselli; S. Garattini, Clinica Chimica Acta v34 n2 p321-32 (Sep 1971)

A gas-liquid chromatographic method to measure butyrophenones was developed and applied to the determination of these drugs in biological materials. Haloperidol and trifluperidol show many properties in common when they are injected in rats. They penetrate very rapidly into the brain where they reach levels several times higher than in plasma. The brain concentration able to inhibit completely the effects of amphetamine is between 30 and 40 ng/g for both drugs.

The method was employed for the determination of haloperidol in the plasma of psychiatric patients treated with this drug for therapeutic reasons. Haloperidol was present in the range of 100-200 ng/ml during chronic administration, but it could not be detected after an acute treatment. The limit of detection for the method was 20 ng/ml of plasma. (JAM)

1971 14refs

UM-71-M0094

DETERMINATION OF TRANQUILLIZERS BY GLC IN BIOLOGICAL FLUIDS, E. Van Der Kleijn; G. C. Beelen; M. A. Frederick, Clinica Chimica Acta v34 n2 p345-56 (Sep 1971)

This paper deals with procedures for the rapid qualitative and quantitative gas-chromatographic assay of various hypnosedative and ataractic drugs in blood and urine. Barbiturates, benzodiazepines, carbamates, and other agents are included. The use of such assays in clinical toxicology, the evaluation of drug treatments, forensic toxicology, and bioavailability studies is outlined, and the relevance of plasma concentrations for these purposes is described. The advantages of gas-liquid chromatographic procedures over spectrophotometric and colorimetric assays are mentioned where applicable, and the relative sensitivity of gas-chromatographic detectors is noted along with procedure modifications necessitated by their choice. The relation of plasma concentrations to pharmacologic effect and the mode of action of ataractic drugs are discussed. (HSRI)

1971 33refs

UM-71-M0095

DETERMINATION OF BARBITURATES IN BLOOD BY GLC, H. V. Street, Clinica Chimica Acta v34 n2 p357-64 (Sep 1971)

Methods for gas-liquid chromatographic (GLC) determination of barbiturates (a) unmodified, (b) as their methyl derivative, and (c) as their trimethylsilyl (TMS) derivatives are discussed in relation to a concentration range of 1-10 mcg of barbiturate per ml of plasma. The need to use a column packing showing minimum solute adsorption is stressed, and the importance of identification of a particular GLC peak is emphasized. A procedure is recommended which uses the unmodified barbiturate for quantitative estimation and "on-column" formation of methyl- and TMS-derivatives for qualitative identification. (JA)

1971 15refs

UM-72-M0096

METHODS FOR THE ANALYSIS OF NARCOTIC ANALGESICS AND AMPHETAMINES, S. J. Mulé, Journal of Chromatographic Science v10 n5 p275-82 (May 1972)

The primary purpose of this review was to report the most recent developments in the identification and detection of narcotic analgesics and amphetamines. Emphasis was placed upon detection in biological materials which required extraction of the drugs and/or metabolites prior to analysis.

The reviewed methods included qualitative and quantitative color tests, microcrystallography, ultraviolet spectrophotometry, gas-liquid chromatography (GLC), thin-layer chromatography (TLC), and spectrophotofluorometry. Extensive chromatographic data for the narcotic analgesics in GLC and TLC systems was provided by the author. These latter techniques were deemed methods of choice for identifying drugs subject to abuse extracted from biological material. (HSRI)

1972 84refs

UM-72-M0097

REVIEW OF METHODS OF ANALYSIS FOR PHENOTHIAZINE DRUGS, G. Cimbura, Journal of Chromatographic Science v10 n5 p287-93 (May 1972)

Methods of analysis of phenothiazine drugs in biological material were reviewed. The methods covered include direct screening tests, extraction techniques. photometry, ultraviolet spectrophotometry, thin-layer and paper chromatography, gas-liquid chromatography, and spectrofluorometry. The main advantages and limitations of the methods reviewed are briefly discussed. (JA)

1972 55refs

UM-76-M0098

SIMULTANEOUS MEASUREMENT OF IMIPRAMINE AND DESIPRAMINE BY SELECTED ION RECORDING WITH DEUTERATED INTERNAL STANDARDS, M. Claeys; G. Muscettola; S. P. Markey, Biomedical Mass Spectrometry v3 n3 p110-6 (Jun 1976)

A gas chromatographic-mass spectrometric method for the quantitative determination of imipramine and its N-demethylated metabolite, desipramine, in plasma samples at the nanogram level is reported. The method involves derivatization of the extracted drugs with trifluoroacetylimidazole. Specificity is provided by selected ion recording of the M + 1 ions formed upon chemical ionization with methane as reagent gas. Quantitation is achieved by stable isotope dilution techniques, using deuterium labeled analogs as internal standards.

Preliminary results were reported summarizing the maximum daily dosage of imipramine, the steady state plasma levels of imipramine, desipramine and their total, and the mean steady state ratio for eight patients. Large variability and lack of correlation between plasma drug levels and clinical outcome were evident in the preliminary study. (HSRI)

1976 27refs

UM-76-M0099

PLASMA PHENCYCLIDINE PHARMACOKINETICS IN DOG AND MONKEY USING A GAS CHROMATOGRAPHY-MASS FRAGMENTOGRAPHY ASSAY, A. E. Wilson; E. F. Domino, The Pharmacologist v18 n2 p142 (Fall 1976)

The pharmacokinetic application of a published mass fragmentography assay for phencyclidine (PCP) was reported. Using phencyclidine-d_5 and monitoring the most abundant ions, the authors obtained a sensitivity of 1 ng/ml for the method.

Aliquots of venous blood were obtained following the injection of 1.0 and 1.1 mg/kg i.v. PCP in 6 dogs and 7 Macaca Mulatta monkeys, respectively. In both species, a complex plasma disappearance curve of PCP was observed. (HSRI)

1976

UM-76-0100

SENSITIVE GLC PROCEDURE FOR SIMULTANEOUS DETERMINATION OF PHENYTOIN AND ITS MAJOR METABOLITE FROM PLASMA FOLLOWING SINGLE DOSES OF PHENYTOIN, K. K. Midha; I. J. McGilveray; D. L. Wilson, Journal of Pharmaceutical Sciences v65 n8 p1240-3 (Aug 1976)

An improved method was reported for the simultaneous determination of phenytoin (diphenylhydantoin) and its metabolite, 5-(p-hydroxyphenyl)-5-phenylhydantoin, in plasma and urine. After sample hydrolysis by incubation with β-glucuronidase (4 hours, 37°), an ether extraction, a back extraction into basic buffer, and reextraction with ether were performed. The drug, its metabolite, and internal standard were determined in dried extracts dissolved in trimethylanilinium hydroxide by gas-liquid chromatography (GLC) with flame-ionization detection as their respective methyl derivatives following flash-heater methylation. A sensitivity of 150 ng of phenytoin and 125 ng of metabolite per ml of sample was reported; recoveries were 76 and 64%, respectively.

A 200 mg dose of phenytoin was given to a healthy male volunteer (84 kg), blood was withdrawn at different time intervals over 96 hours, and aliquots of plasma were assayed. Plasma phenytoin was found to be 1-3 mcg/ml during the first hour after drug administration. Comparison with an ultraviolet method was made, and the results presented. (HSRI)

1976 19refs

UM-76-M0101

GLC DETERMINATION OF DOXEPIN PLASMA LEVELS, J. E. O'Brien; O. N. Hinsvark, Journal of Pharmaceutical Sciences v65 n7 p1068-9 (Jul 1976)

A procedure is described for the three step extraction of doxepin, a tricyclic antidepressant, from plasma and its determination by gas-liquid chromatographic (GLC)-flame ionization detection. The method permits the resolution and quantitative determination of the cis- and trans-isomer of doxepin, as well as its desmethyl metabolite. Doxepin levels in the plasma of chronically treated patients were determined to demonstrate that the method had adequate sensitivity (10 ng/ml) for measuring drug levels in the blood after therapeutic doses. (JAM)

1976 3refs

UM-76-M0102

GLC DETERMINATION OF METHOTRIMEPRAZINE AND ITS SULFOXIDE IN PLASMA, S. G. Dahl; S. Jacobsen, Journal of Pharmaceutical Sciences v65 n9 p1329-32 (Sep 1976)

A gas-liquid chromatographic (GLC)-flame ionization detection method was developed for the assay of methotrimeprazine and its sulfoxide metabolite in plasma. Sample clean up was accomplished by a three step extraction procedure with two washes. Silylation of glassware and gas-chromatographic (GC)-column was necessary for reproducible quantitation of low concentrations of the compounds. For a 6 ml aliquot, the sensitivity was 2-3 ng/ml for unchanged drug, and 4-5 ng/ml for metabolite. The coefficient of variation, calculated from duplicate analyses of plasma samples, was 8-15% for concentrations between 10 and 100 ng/ml.

The method, suitable for the analysis of chlorpromazine, its sulfoxide, and promazine as well, was used to determine plasma levels of the compounds after single and multiple therapeutic doses. Patients treated with orally administered methotrimeprazine had higher plasma levels of the sulfoxide than of unmetabolized drug. (JAM)

1976 13refs

UM-75-M0103

INDUCTION EFFECT OF DIAZEPAM ON ITS OWN METABOLISM, R. Sellman; J. Kanto; E. Raijola; A. Pekkarinen, Acta pharmacologia et toxicologia v37 n5 p345-51 (Nov 1975)

The purpose of this study was to examine more closely the increased elimination of diazepam after long-term use in man by measurement of plasma concentrations after intravenous injection of diazepam (10 mg). Diazepam, N-demethyldiazepam, and oxazepam were determined in 0.5 ml plasma samples by a gas-liquid chromatography-electron capture detection method; recoveries for the compounds were greater than 90%.

An increased elimination rate of diazepam was indicated in psychiatric patients receiving continuous diazepam therapy as compared to a group of healthy volunteers and a group of psychiatric patients not given diazepam. A significantly lower increase of diazepam concentrations in the plasma was found at 15 minutes, 1, 3, 6, and 24 hours after drug administration in those given long-term diazepam therapy. The increase of N-demethyldiazepam was significantly higher in these patients suggesting increased formation of diazepam's principal metabolite. (HSRI)

1975 18refs

UM-75-M0104

CUMULATION IN CEREBROSPINAL FLUID OF THE N-DESMETHYL METABOLITE AFTER LONG-TERM TREATMENT WITH DIAZEPAM IN MAN, J. Hendel, Acta pharmacologia et toxicologia v37 n1 p17-22 (Jul 1975)

The purpose of this study was to evaluate possible differences in the relative distribution patterns of diazepam and its principal metabolite, N-desmethyldiazepam, between blood and cerebrospinal fluid (CSF) in man. Thirteen patients were given diazepam (10 mg) intramuscularly 12 hours and 1 hour before spinal puncture. Plasma and CSF concentrations of the compounds were determined simultaneously by gas chromatograpy-electron capture detection. The lower limit of the method was 1.0 ng/ml of plasma and 0.5 ng/ml of CSF; the recoveries of diazepam and N-desmethyldiazepam were greater than 95%.

Five patients treated with diazepam over several months showed a significantly higher N-desmethyldiazepam ratio (CSF/plasma) than eight patients not previously treated with diazepam. This result indicated a cumulation of this psychoactive metabolite in the brain of man during long-term treatment with diazepam. (JAM)

1975 15refs

UM-74-M0105

INTERPRETATION OF POST MORTEM SERUM LEVELS OF CARDIAC GLYCOSIDES AFTER SUSPECTED OVERDOSAGE, A. C. Moffat, Acta pharmacologia et toxicologia v35 n5 p386-94 (Nov 1974)

Post mortem serum concentrations of cardiac glycosides have been measured by radioimmunoassay in 13 patients who had suddenly died from suspected overdosage. With digoxin, the highest level observed was 71 ng/ml after an intramuscular injection to an infant, while levels of 7.2-24 ng/ml were found after oral administration to adults.

The levels found were much higher than the mean therapeutic levels, which were 1.34 ng/ml for optimally digitalised patients and 3.11 ng/ml for those showing evidence of toxicity, although some overlap did occur. Other cardiac glycosides (digitoxin, lanatoside C and deslanoside) showed a similar relationship between concentrations found during therapy and after overdosage. (JAM)

1974 28refs

UM-75-M0106

RAPID MASS SCREENING AND CONFIRMATION OF URINARY AMPHETAMINE AND METHAMPHETAMINE BY GAS CHROMATOGRAPHY, N. C. Jain; R. D. Budd; T. C. Sneath, Clinical Toxicology v8 n2 p211-24 (Apr 1975)

A procedure is described for the mass screening and confirmation of amphetamine and methamphetamine in urine using gas chromatography (GC) with flame ionization detector. The amphetamine drugs are screened as free drugs on a 10% Apiezon L-10% KOH column after a three step extraction, and confirmed as their trifluoroacetamide derivatives on a 3% OV-17 column. The dual approach eliminates false positives and interfering substances that may be present in the urine, and has been found specific for the amphetamines.

In screening, when a low percentage of positives are found, the authors recommend combining aliquots of the chloroform extracts of specimens for GC-injection. Such a procedure is advantageous if positive rates are less than 25%. Individual samples are subsequently determined and confirmed when a combined injection yields a positive result. (HSRI)

1975 33refs

UM-75-M0107

RAPID ANALYSIS OF THE CENTRAL NERVOUS SYSTEM STIMULANTS, AMPHETAMINES, VIA GAS CHROMATOGRAPHY-MASS SPECTROMETRY: RAPID ACYLATION IN THE PRESENCE OF A MERCURY CATALYST, A. Wu, Clinical Toxicology v8 n2 p225-32 (Apr 1975)

Acylation with trifluoroacetic anhydride in the presence of a catalyst, mercuric trifluoroacetate, was applied to the gas chromatographic-mass spectrometric (GS/MS) assay of amphetamine, methamphetamine, mescaline, and methylenedioxyamphetamine. Urine was extracted three times with portions of benzene/ether (3/1); the combined extracts were dried over anhydrous sodium sulfate and then concentrated. Following derivatization (80°, 30 seconds), aliquots were injected into the GC/MS unit; analysis time was 10 minutes. Detection of 300 pg were achieved in a preliminary trial. The technique was applied routinely for court samples and law enforcement authorities. (HSRI)

1975 4refs

UM-76-M0108

A PROCEDURE FOR DRUG SCREENING WITHOUT THE NEED TO TRANSPORT URINES: USE OF ION EXCHANGE PAPERS AND HEMAGGLUTINATION INHIBITION, G. J. Alexander, Clinical Toxicology v9 n3 p435-46 (Jun 1976)

A procedure was devised for drug abuse screening in urine specimens by absorbing the drugs onto papers loaded with ion-exchange resin. The preliminary treatment consists of local treatment of samples collected at many distant clinics with papers that absorb 50-65% of alkaloid drugs and 25% of barbiturates. After drying, the papers are sent via regular mail to a central analytical laboratory for processing. Portions of the specimens are reconstituted in aqueous saline buffers (2.9-9.7% recovery overall), while drugs from other portions are extracted with solvents at appropriate pH.

Drugs are detected in the reconstituted aqueous media by hemagglutination inhibition and spectrophotofluorimetry, and confirmed in the solvent extracts by thin-layer chromatography. Recovery of labeled drugs after this treatment and urine screening data showed that the procedure is safe, convenient, and reliable for opiate alkaloids, methadone, amphetamines, and phenothiazine tranquilizers but is less suitable for barbiturates. (ASM)

1976 3refs

UM-76-M0109

STREET DRUG IDENTIFICATION PROGRAM, R. C. Gupta; G. D. Lundberg, Clinical Toxicology v9 n2 p281-93 (Apr 1976)

A monthly report (July 1975) from a drug investigation laboratory is presented. Tabulated results from street drug monitoring include appearance of sample (capsule, tablet form, powder, color, etc.), supposed drug name, qualitative and quantitative test results, source of sample, and street price. The relative increase of the incidence of phencylidine and cocaine were noted, in addition to a high percentage of falsely represented drug samples. (HSRI)

1976

UM-76-M0110

SPIN IMMUNOASSAY FOR OPIATES IN URINE--RESULTS OF SCREENING MILITARY PERSONNEL, J. Cate, IV; M. Clarkson; J. Strickland; N. A. D'Amato, Clinical Toxicology v9 n2 p235-43 (Apr 1976)

Described was a system for urinary opiate screening by spin immunoassay (FRAT), a technique utilizing the principles of competitive protein binding and free radical assay detection; sample positives were confirmed by gas-liquid chromatography (GLC) and spectrophotofluorometry. The authors used 0.35 mcg/ml morphine as the lower limit for morphine detection to increase the sensitivity for screening purposes; the GLC detection limit for morphine and codeine was 0.4 mcg/ml.

Results of screening and confirmation of opiates in 215,900 urine samples over a period of 15 months was reported. The system proved reliable and workable; its advantages included minimal sample processing, rapid turn around time, high sensitivity, nonradioactive reagents, and trouble free instrumentation. The relatively high cost of reagent kits and initial capital outlay for an electron spin resonance spectrometer were the principal disadvantages. The system would be most appropriately applied to screening a large population of mostly drug free individuals. (HSRI)

1976 7refs

UM-76-M0111

SCREENING FOR DRUGS OF ABUSE IN URINE SAMPLES FROM A DRUG ADDICTION CENTER, M. A. Peat, Clinical Toxicology v9 n2 p203-19 (Apr 1976)

Analytical methods used in a laboratory monitoring urine specimens collected from patients attending one of the Drug Dependency Units were described and compared with other published methods. A thin-layer chromatographic system and its application to urinary drug identification were described. Schemes for the pH-dependent solvent extraction of narcotics, barbiturates, and amphetamines were presented, and the chromatographic behavior of other drugs of abuse were reported.

A majority of drug dependent patients were found to be stabilized on their prescribed drugs. Continued monitoring of urine samples was held to be advisable in the treatment and control of drug abuse, especially for the detection of change in the patient's clinical or physiological behavior. (HSRI)

1976 30 refs

UM-76-M0112

GAMMAFLOW: A COMPLETELY AUTOMATED RADIOIMMUNOASSAY SYSTEM, G. Brooker; W. L. Terasaki; M. G. Price, Science v194 n4262 p270-6 (15 Oct 1976)

The development of a completely automated on-line radioimmunoassay system was reported. Gammaflow combines the sample or standard with the labeled ligand

and antibody, incubates the sample (up to 21 minutes), separates and determines the amount of labeled ligand bound, and then computes the amount of unknown sample by comparison to standard curves. Samples are processed at a rate of 20-40 per hour, and the unattended system was shown to have both long range stability and reproducibility.

Assays have been performed for digoxin, cyclic adenosine monophosphate, cyclic guanosine monophosphate, insulin, angiotensin I, and thyroxine. The standard curves thus obtained and the assay sensitivities compared favorably with those published using manual assays. The system was discussed in terms of assay variables, such as incubation time and temperature, flexibility in establishing new radioimmunoassay protocols, and different column separators. Descriptions of the assay conditions and a flow diagram of the automated process were included. (HSRI)

1976 20refs

UM-76-M0113

PROGRAMMED MULTIPLE DEVELOPMENT IN THIN-LAYER CHROMATOGRAPHY, T. H. Jupille; J. A. Perry, Science v194 n4262 p288-93 (15 Oct 1976)

Programmed Multiple Development (PMD) is a thin-layer chromatography (TLC) technique featuring repeated development of a TLC plate with the same solvent in the same direction for gradually increasing distances. Between developments, the plate is dried by controlled evaporation while it remains in contact with the solvent resevoir. An additional spot reconcentration step occurs during solvent removal, thus increasing the ability of the system to resolve sample components. Chromatographic principles of the method, a schematic diagram of a PMD developer, and descriptions of its adjustable parameters are presented.

Problems encountered in the application of the technique, such as solvent demixing and vapor phase transfer, are discussed. Applications are described which featured requirements for high sensitivity, resolution of closely related molecules, and the resolution of complex mixtures. The authors conclude that improvements in existing models for PMD spot behavior will allow easier and more rapid optimization of PMD program parameters as well as easier transfer of conventional TLC separation systems to PMD. (HSRI)

1976 35refs

UM-76-M0114

FORENSIC ASPECTS OF HIGH-PRESSURE LIQUID CHROMATOGRAPHY, B. B. Wheals, Journal of Chromatography v122 p85-105 (7 Jul 1976)

This paper reviews the applications of high-pressure liquid chromatography (HPLC) to forensic problems, and discusses some of the developments that have taken place in the use of this technique in the Metropolitan Police Laboratory, London. Preparation of octadecyltrichlorosilane-modified silica is described, and some of the chromatographic characteristics of this material are investigated.

Injection techniques and fluorimetric detection are also discussed. Applications of HPLC to the analysis of cannabis, opium alkaloids, amphetamine related materials, LSD, and polynuclear hydrocarbons are described. The author concludes that the importance of qualitative analysis in forensic drug work means that HPLC, excellent for quantitation, is considerably less important than thin-layer chromatography. Similarly, gas chromatography will probably remain where it serves adequately. Future prospects for the technique may include trace metal analysis with the fluorimetric detection of separated metal chelates, fluorimetric drug metabolite analysis, and as a preparative tool for subsequent spectroscopic examination. (HSRI)

1976 38refs

UM-76-M0115

THE RADIOIMMUNOASSAY OF DRUGS. A REVIEW, J. Landon, The Analyst v101 n1201 p225-43 (Apr 1976)

An extensive review (144 references) of basic principles and the requirements for a drug radioimmunoassay is followed by a discussion of the advantages and disadvantages of the available techniques. A table listing the drugs for which radioimmunoassays have been reported is furnished with references. Topics for discussion include the development of a suitable antiserum, the production of immunogens, the obtaining of an appropriate labelled antigen, and methods for the separation of antibody-bound and free fractions.

Concepts important for the evaluation of drug radioimmunoassays, such as sensitivity, specificity, and usefulness, are discussed. Anticipated trends in the area of research are the continued development of drug radioimmunoassay kits, increased automation of the assay procedure, and the use of alternative, but related, analytical techniques. The author concludes that radioimmunoassay techniques will be employed to an increasing extent in the determination of drug levels in biological fluids. Emphasis should be placed on quality control and assay result validity, especially in clinical applications, and use of both physicochemical and immunological means is recommended. (HSRI)

1976 144refs

UM-76-M0116

RAPID SCREENING AND CONFIRMATION OF AMPHETAMINE, METHAMPHETAMINE, METHADONE, AND METHADONE METABOLITE IN URINE BY GAS/THIN LAYER CHROMATOGRAPHY, N. C. Jain; R. D. Budd; W. J. Leung; T. C. Sneath, Journal of Chromatographic Science v14 n6 p293-5 (10 Jun 1976)

A method suitable for large scale screening and confirmation of urine specimens for amphetamine, methamphetamine, methadone, and its primary metabolite (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine) is described. The drugs are extracted from alkaline urine into organic solvent. The amphetamine drugs are then back-extracted into a small volume of acid; following reextraction into an organic phase, amphetamine and related compounds are identified by gas chromatography both as free bases on a 10% Apiezon L-10% KOH column and as their trifluoroacetamide derivatives on a 3% OV-17 column.

The initial organic layer, which contains methadone and its metabolite, is analyzed by split sample thin-layer chromatography using two solvent systems; this dual analysis allows one step screening and confirmation, and eliminates the possibility of false positives caused by other drugs or urinary substances. The possible behavior of these substances are reported. The sensitivity level of the method is 0.1 mcg/ml for amphetamine and methamphetamine in urine, and 0.5 mcg/ml for methadone and its metabolite. (JAM)

1976 14refs

UM-75-M0117

THIN-LAYER CHROMATOGRAPHIC SCREENING AND CONFIRMATION OF BASIC DRUGS OF ABUSE IN URINE, N. C. Jain; W. J. Leung; R. D. Budd; T. C. Sneath, Journal of Chromatography v115 n2 p519-26 (24 Dec 1975)

Thin-layer chromatographic procedures were presented for the identification of methadone, primary metabolite of methadone (2-ethylidine-1,5-dimethyl-3,3-diphenylpyrrolidine), propoxyphene, norpropoxyphene, cocaine, benzoylecgonine, methaqualone, and phencyclidine from urine specimens. The chromatographic behavior of the drugs of interest, as well as other drugs that may be found in the urine, was described on nine different solvent systems. Preferred solvent systems for screening and confirmation of individual drugs were indicated.

The procedure for initial screening requires only one extraction, but, by splitting the sample, dual analysis required for identification is possible.

The method is sensitive, detecting most of the listed drugs at levels of 1.0 mcg/ml or less. (JAM)

1975 15refs

UM-76-M0118

DETERMINATION OF CHLORIMIPRAMINE AND DESMETHYLCHLORIMIPRAMINE IN HUMAN PLASMA BY ION-PAIR PARTITION CHROMATOGRAPHY, B. Mellström; S. Eksborg, Journal of Chromatography v116 n2 p475-9 (21 Jan 1976)

The application of ion-pair chromatography to the determination of chlorimipramine (CIM) and its principal metabolite, desmethylchlorimipramine (DCIM), in human plasma was reported. Quantitative extraction was achieved by shaking alkalinized plasma with diethyl ether for 90 minutes, followed by a two step extraction procedure designed to reduce fluid volume and bring the compounds into the mobile phase. An ultraviolet detector was employed; quantitation was based on peak-height measurements and standard curves. Limits of sensitivity were approximately 25 ng/ml.

Plasma concentrations of both CIM and DCIM and their ratio in the first dosage interval of the day varied markedly between three patients treated with chlorimipramine hydrochloride for at least two weeks. Plasma levels of metabolite (100-500 ng/ml) were higher than those of the parent drug (100 ng/ml average). The possibility of assay interference by other tricyclic antidepressants was raised. (HSRI)

1976 11refs

UM-76-M0119

MAS FRAGMENTOGRAPHIC DETERMINATION OF DIPHENYLHYDANTOIN AND ITS MAIN METABOLITE, 5-(4-HYDROXYPHENYL)-5-PHENYLHYDANTOIN, IN HUMAN PLASMA, C. Hoppel; M. Garle; M. Elander, Journal of Chromatography v116 n1 p53-61 (7 Jan 1976)

A method is described for the mass fragmentographic determination of diphenylhydantoin (DPH) and its main metabolite, 5-(4-hydroxyphenyl)-5-phenylhydantoin (4-OH-DPH), in 0.01-0.1 ml of human plasma as their dimethyl and trimethyl derivatives, respectively. The derivatives are formed by extractive alkylation using tetrabutylammonium hydrogen sulphate. The synthesis of pentadeuterated 4-OH-DPH was reported, and the compound was used as the internal standard for mass fragmentography procedures.

Optimal conditions for the extractive alkylation technique were studied by gas chromatography-flame ionization detection, and the successful analyses of DPH and eight derivatives were accomplished. Following acidic hydrolysis of the plasma sample, conjugated 4-OH-DPH and a dihydrodiol metabolite are measured by the method. Using 100 mcl plasma samples, the lower limit of detection is about 10 ng/ml (0.03 nmole/ml). (JAM)

1976 28refs

UM-76-M0120

GAS CHROMATOGRAPHIC SEPARATION OF ALLYLBARBITAL AND BUTABARBITAL, N. C. Jain; T. Sneath; R. Budd; D. Chinn; W. Leung; B. Olson, Journal of Chromatography v116 n1 p194-6 (7 Jan 1976)

An investigation into the gas chromatographic separation of free and methylated barbiturates, with particular reference to allylbarbital and butabarbital, was reported. Of the 15 columns included in the study, four were found that could clearly separate the methylated derivatives of allylbarbital and butabarbital. Relative retention times of common barbiturates on these columns were tabulated. It was concluded that 4% OV-210 separated most free barbiturates, including allylbarbital and butabarbital, whereas 3% OV-17 and 3% OV-25 were most suitable to distinguish their methyl derivatives. (HSRI)

1976 5refs

UM-75-M0121

KINETICS OF HEROIN DEACETYLATION IN AQUEOUS ALKALINE SOLUTION AND IN HUMAN SERUM AND WHOLE BLOOD, G. R. Nakamura; J. I Thornton; T. T. Noguchi, Journal of Chromatography v110 n1 p81-9 (2 Jul 1975)

A kinetic study of heroin hydrolysis in alkaline aqueous solution at room temperature was conducted by a gas chromatography-flame ionization detection (GC-FID) method to measure the consecutive reactions of diacetylmorphine (heroin) to monoacetylmorphine and of monoacetylmorphine to morphine. A first order reaction was observed in both instances, and the rate for the deacetylation of heroin was greater than that of monoacetylmorphine.

The differences in the rate of heroin hydrolysis in fresh human serum and post-mortem whole blood was studied using GC-FIC and thin-layer chromatography. In the serum, no cleavage of 6-monoacetylmorphine was observed, while in whole blood both acetyl groups of heroin were cleaved, resulting in the formation of morphine. Relatively large amounts of monoacetylmorphine remained in the hydrolysate of both serum and whole blood. Hydrolysis proceeded at twice the rate in whole blood as in serum. Finally, spontaneous hydrolysis of heroin was eliminated as a possible deacetylation mechanism. (HSRI)

1975 15refs

UM-75-M0122

QUANTITATIVE DETERMINATION OF COCAINE AND ITS METABOLITES BENZOYLECGONINE AND ECGONINE BY GAS/LIQUID CHROMATOGRAPHY, J. I. Javaid; H. Dekirmenjian; E. G. Brunngraber; J. M. Davis, Journal of Chromatography v110 n1 p141-9 (2 Jul 1975)

A quantitative method was developed to determine cocaine and its metabolites, benzoylecgonine and ecgonine. The method involved the formation of fluorocarbon derivatives which were separated on 3% and 5% OV-1 columns, and detected in picomole quantities using an electron capture detector. Ecgonine and benzoylecgonine were derivatized with a mixture of hexafluoroisopropanol-heptafluorobutyric anhydride (1:2). Cocaine was first reduced by lithium aluminum hydride and then acylated by pentafluoroproprionic anhydride. By these techniques, cocaine and its metabolites could be determined in the same sample. It was demonstrated that cocaine could be determined in urine and plasma by this method. (JAM)

1975 19refs

UM-75-M0123

GAS CHROMATOGRAPHIC METHOD FOR THE MICRODETERMINATION OF BARBITURATES IN BLOOD USING A NITROGEN/SELECTIVE FLAME IONIZATION DETECTOR, B. H. Dvorchik, Journal of Chromatography v105 n1 p49-56 (19 Feb 1975)

A quantitative gas-liquid chromatographic method for the simultaneous determination of unmodified barbital, pentobarbital, secobarbital, and hexobarbital from whole blood was described. The method involved one extraction from whole blood into chloroform with subsequent injection into a gas chromatograph equipped with a nitrogen-sensitive flame ionization detector. Recommendations for increasing the sensitivity of the method (10 mcg/ml of whole blood) were noted. The applicability of the method to pharmacokinetic studies and to the analysis of barbiturates in small samples of blood was indicated. (JAM)

1975 19refs

UM-75-M0124

SENSITIVE METHOD FOR THE ROUTINE DETERMINATION OF TRICYCLIC ANTIDEPRESSANTS IN PLASMA USING A SPECIFIC NITROGEN DETECTOR, L. A. Gifford; P. Turner; C. M. B. Pare, Journal of Chromatography v105 n1 p107-13 (19 Feb 1975)

The sensitivity of the alkali flame ionization detector (AFID) as a specific

nitrogen detector was studied in relation to the tricyclic antidepressants, and the limits of detection for the 5-H-Dibenz[b,f]azepines and 5-H-Dibenzo[a,d]-cycloheptenes were measured. The system proved to be equally sensitive to secondary and tertiary amines, thus enabling routine analysis of imipramine and amitriptyline at therapeutic concentrations.

By use of the backflush system described, interference from extraneous extraction products were considerably reduced and reproducibility was improved by eliminating detector saturation. A simple extraction procedure was made possible by the improved detector sensitivity, and no derivatization procedures were necessary. A general method for the estimation of plasma tricyclic levels was described and exemplified; method sensitivity was in the nanogram/-ml of plasma range. (HSRI)

1975 12refs

UM-75-M0125

DETERMINATION OF TRICHLOROETHANOL AT THERAPEUTIC AND OVERDOSE LEVELS IN BLOOD AND URINE BY ELECTRON CAPTURE GAS CHROMATOGRAPHY, D. J. Berry, Journal of Chromatography v107 n1 p107-14 (9 Apr 1975)

A gas chromatographic (GC) method for the determination of trichloroethanol, the active metabolite of chloral hydrate, in blood and urine was reported using electron capture detection. A hundred-fold dilution of the sample with an ethanolic solution of internal standard preceded GC injection. The practice of purging the detector was obligatory. A sensitivity of 1 mcg/ml of body fluid was indicated for the method. Nonlinearity in the calibration graph made it necessary to prepare a standard curve on a daily basis.

Trichloroethanol plasma levels were determined in five subjects for the time period 0.5-24 hours following a single oral dose of chloral hydrate. Two dosage forms were studied. Plasma concentrations of trichloroethanol were also reported for some cases of self-poisoning. (HSRI)

1975 10refs

UM-75-M0126

RAPID AND SENSITIVE GAS CHROMATOGRAPHIC DETERMINATION OF DIACETYLMORPHINE AND ITS METABOLITE MONOACETYLMORPHINE IN BLOOD USING A NITROGEN DETECTOR, D. A. Smith; W. J. Cole, Journal of Chromatography v105 n2 p377-81 (26 Feb 1975)

A quantitative gas chromatographic method for the determination of plasma concentrations of diacetylmorphine (heroin, DAM) and its metabolite monoacetylmorphine (MAM) using as alkali flame detector (nitrogen detector) was described. Plasma samples (pH 9.0) containing ethylmorphine acetate as internal standard are extracted with benzene. The dried benzene extracts are analysed as their corresponding acetylated derivatives following treatment with trifluoroacetic anhydride-benzene (1:5). Quantitation of narcotic levels down to 100 ng/ml and detection to 20 ng/ml were reported.

Blood levels of DAM and MAM in a 25 kg dog following the intravenous administration of DAM (16 mg) were studied using the method described. No DAM was detectable in the blood after 3 minutes; MAM showed a slower rate of disappearance than the parent compound and was detectable for eight minutes. (JAM)

1975 8refs

UM-75-M0127

QUANTITATIVE GAS CHROMATOGRAPHIC DETERMINATION OF DIAZEPAM AND ITS MAJOR METABOLITE IN HUMAN SERUM, J. M. Steyn; H. K. L. Hundt, Journal of Chromatography v107 n1 p196-200 (9 Apr 1975)

A gas chromatographic method utilizing flame ionization detection was reported for the quantitative determination of diazepam and its major metabolite as

their respective benzophenones. Buffered serum samples containing an internal standard are extracted three times with diethyl ether. The combined ether extracts are extracted with 6 N HCl, which in turn is washed with ether three times. The benzophenones formed from the subsequent acid hydrolysis step are extracted from neutral solution into carbon tetrachloride, an aliquot of which is injected into the gas chromatograph. A summary of the results for the recovery of diazepam obtained with serum in the range between 10 and 100 mcg per 100 ml was presented. (HSRI)

1975 7refs

UM-75-M0128

SIMULTANEOUS DETECTION OF A WIDE VARIETY OF COMMONLY ABUSED DRUGS IN A URINE SCREENING PROGRAM USING THIN-LAYER IDENTIFICATION TECHNIQUES, K. K. Kaistha; R. Tadrus; R. Janda, Journal of Chromatography v107 n2 p359-79 (16 Apr 1975)

A single step extraction method and thin-layer chromatographic techniques capable of identifying a wide variety of drugs of abuse are presented. The drugs are absorbed from urine on paper loaded with cation-exchange resin; an ammonium chloride-ammonia buffer (pH 10.1) is used to elute compounds from the paper. A two-stage solvent system is used to obtain a chromatogram on pre-coated silica gel glass microfiber sheets, thus providing optimum separation of a wide range of drugs. Different detection reagents are then applied in succession to marked areas of the developed chromatogram.

Extensive tabulations provide relevant data both for the color reactions obtained for the drugs using the consecutive application of detection reagents; and for the chromatographic behaviors of the drugs, alone and in various combinations, in two two-stage developing solvent systems. These techniques have been found to be well suited for urine screening programs; the cost of analysis per urine specimen is less than US $1 (1975). (JAM)

1975 61refs

UM-75-M0129

THE SEPARATION OF A WIDE RANGE OF DRUGS OF ABUSE BY HIGH-PRESSURE LIQUID CHROMATOGRAPHY, I. Jane, Journal of Chromatography v111 n1 p227-33 (20 Aug 1975)

The convenient analysis of illicit drug samples by high-pressure liquid chromatography was reported. The method described allowed the separation of a wide range of drugs by isocratic elution on a single column, and had been applied to the routine analysis of a large number of samples. A weighed amount of sample is dissolved in water or dilut hydrochloric acid, and an aliquot is injected onto the column. The ultraviolet-detector wavelength is adjusted to the maximum response for the compound of interest. Retention data for the phenethylamines, opium alkaloids and other drugs of forensic interest was given. (HSRI)

1975 6refs

UM-75-M0130

DETERMINATION OF THERAPEUTIC LEVELS OF AMITRIPTYLINE IN SERUM BY GAS-LIQUID CHROMATOGRAPHY, P. C. N. Eichholtz, Journal of Chromatography v111 n2 p456-8 (3 Sep 1975)

The modification of a published gas-liquid chromatographic method for the determination of serum amitriptyline was reported. A three-step extraction procedure was followed by derivatization of amitriptyline with hexamethyldisilazane. If an 8 ml serum sample is used, the limit of sensitivity for the method is 40 ng/ml. A sample of 8 ml of serum from a depressive patient who had been treated with 35 mg amitriptyline hydrochloride t.i.d. for two weeks contained 80 ng/ml. (HSRI)

1975 4refs

UM-75-M0131

DETERMINATION OF NITRAZEPAM IN SERUM BY GAS-LIQUID CHROMATOGRAPHY. APPLICATION IN BIOAVAILABILITY STUDIES, K. M. Jensen, Journal of Chromatography v111 n2 p386-96 (3 Sep 1975)

A gas chromatographic method with electron capture detection was used for measuring serum concentrations of nitrazepam in bioavailability studies. The analytical procedure consisted of extracting nitrazepam with benzene, converting the isolated nitrazepam into 2-amino-5-nitrobenzophenone by boiling in acidic medium, and dissolving the extracted residue in benzene containing an internal standard. The limit of detection was 5 ng/ml; the recovery of nitrazaepam (10-40 ng/ml of serum) was essentially quantitative. The metabolites of nitrazepam (the 7-amino and 7-acetamido compounds) were not included in the determination.

At an interval of one week, fifteen healthy volunteers each received one 5 mg tablet of nitrazepam of two different brands. Blood samples were drawn immediately before and 1/2, 1, 2, 4, 7, 24, 48, and 72 hours after administration. Peak serum concentrations of 25-50 ng/ml (mean 35 ng/ml) were obtained at 2 hours; a half-life of approximately 25 hours was obtained with both brands. A brief review of other methods developed for the determination of nitrazepam was included, and the results of this study were compared to published work. (HSRI)

1975 11refs

UM-75-M0132

GAS CHROMATOGRAPHIC-MASS FRAGMENTOGRAPHIC DETERMINATION OF "STEADY-STATE" PLASMA LEVELS OF IMIPRAMINE AND DESIPRAMINE IN CHRONICALLY TREATED PATIENTS, G. Belvedere; L. Burti; A. Frigerio; C. Pantarotto, Journal of Chromatography v111 n2 p313-21 (3 Sep 1975)

A method for the simultaneous determination of imipramine (IMI) and its principal metabolite, desipramine (DMI), in the blood plasma of depressed patients under chronic treatment was described. Following extraction, acetylation of DMI produced a derivative with suitable retention time and avoided on-column absorption. Overall recoveries of 80% were reported for the compounds. Concentrations were determined by focusing the mass spectrometer on the ions at m/e 280 and 235 for IMI, 308, 236, and 114 for DMI (N-acetyl derivative), and 284 and 238 for promazine (internal standard). Fragmentation patterns were reported and found similar for the three compounds. Determinations were possible at levels as low as 10 ng/ml in plasma.

Plasma levels of IMI and DMI were reported in two healthy volunteers after a single dose of IMI, and in four patients undergoing chronic treatment. In three of the four, imipramine plasma levels were significantly higher than those of desipramine. (JAM)

1975 28refs

DHEW(ADM) 76-339 UM-76-M0133

CANNABINOID ASSAYS IN HUMANS, R. E. Willette, ed., NIDA Research Monograph 7, U. S. Department of Health, Education and Welfare (May 1976)

This monograph contains "state of the art" techniques for determining levels of cannabinoids in the human body. Methods described range from those applicable to routine screening and survey work to others suitable for research or method validation purposes. Immunoassay, high-pressure liquid chromatographic,

electron capture gas chromatographic, and gas chromatographic-mass spectrometric procedures are presented. (HSRI)

1976 120p 144 refs

DHEW(ADM) 76-339

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UM-76-M0134

PROCEDURES COMPARED FOR EXTRACTING BENZODIAZEPINES FROM BLOOD, A. W. Missen, Clinical Chemistry v22 n6 p927-8 (Jun 1976)

Adsorption methods were compared for the analytical recovery from blood of therapeutic concentrations of nitrazepam, diazepam, and N-desmethyldiazepam. Activated charcoal, Amberlite XAD-2 ion-exchange resin, and Celite eluates were analyzed by electron capture/gas chromatography.

It was noted that results for authentic blood samples analyzed by each of the three procedures did not always correlate with corresponding recoveries from supplemented (spiked) blood samples. Application to the blood screening for benzodiazepines and other drugs in drivers was briefly mentioned. (HSRI)

1976 8refs

UM-76-M0135

MEASUREMENT OF CLOMIPRAMINE, N-DESMETHYLCLOMIPRAMINE, IMIPRAMINE, AND DEHYDROIMIPRAMINE IN BIOLOGICAL FLUIDS BY SELECTIVE ION MONITORING, AND PHARMACOKINETICS OF CLOMIPRAMINE, *J.-P. Dubois; W. Küng; W. Theobald; B. Wirz*, Clinical Chemistry v22 n6 p892-7 (Jun 1976)

The quantitative determination of tricyclic antidepressants in whole blood, plasma and urine was reported using a combined gas chromatograph-mass spectrometer system and deuterium-labeled internal standards. Recoveries exceeded 95% with a low coefficient of variation for compounds added to human whole blood; for clomipramine and dehydroimipramine hydrogen fumarate, the detection limits were 0.3 mcg/l.

Six healthy volunteers who received a single oral dose of 50 mg clomipramine hydrochloride showed peak drug concentrations in the blood 3 to 5 hours after administration with a range of 14.4-30.1 mcg/l. Plasma/whole blood concentration ratios varied from 0.70-1.20, and cumulative renal elimination from 0-72 hours is less than 0.2% of the dose. It was concluded that this method is suitable for in vivo bioavailiability studies of unchanged clomipramine, dehydroimipramine, and imipramine after a single oral dose of as little as 25 mg. (JAM)

1976 21refs

UM-76-M0136

DIAZEPAM ABUSE: INCIDENCE, RAPID SCREENING, AND CONFIRMING METHODS, T. A. Rejent; K. C. Wahl, Clinical Chemistry v22 n6 p889-91 (Jun 1976)

A quantitative gas-chromatographic method for the simultaneous analysis of diazepam and sedatives was described. A single extraction at low pH was used, and the balance of the sample preserved for confirmation by ultraviolet spectrophotometry and thin-layer chromatography. Because therapeutic concentrations of diazepam were below the range of sensitivity of the initial screening procedure, positive findings necessarily reflected overuse of the compound.

Blood samples from 2500 patients suspected to be drug overdose victims were screened for the most commonly abused drugs. Of these, 61% had positive find-

ings, including diazepam in one of every four; ethyl alcohol was detected most frequently, in 900 cases. The prevalence of ethanol, diazepam and other drugs, and the age distribution of their incidence both alone and in various combinations were reported. (JAM)

1976 12refs

UM-76-M0137

PHARMACOKINETIC INTERPRETATION OF DATA GATHERED DURING THERAPEUTIC DRUG MONITORING, B. H. Dvorchik; E. S. Vesell, Clinical Chemistry v22 n6 p868-78 (Jun 1976)

Some pharmacokinetic principles are reviewed that can facilitate interpretation of data obtained during therapeutic drug monitoring. Topics include discussion of the one- and two-compartment models, volume of drug distribution, drug clearance, organ clearance, first pass effect, chronic or repetitive dosing, and bioavailability. The use of urine and saliva to measure drug clearance and drug binding to plasma proteins, respectively, is also discussed. The use of saliva to estimate rapidly, conveniently and noninvasively the concentration of the free, pharmacologically active form of the drug as well as the fraction of drug bound to plasma protein is described. (JAM)

1976 73refs

UM-76-M0138

ANALYSIS OF RESULTS OF TOXICOLOGICAL EXAMINATIONS PERFORMED BY CORONERS' OR MEDICAL EXAMINERS' LABORATORIES IN 2000 DRUG-INVOLVED DEATHS IN NINE MAJOR U. S. CITIES, E. C. Dinovo; L. A. Gottschalk; F. L. McGuire; H. Birch; J. F. Heiser, Clinical Chemistry v22 n6 p847-50 (Jun 1976)

This report details intercity differences in methodology and practices of toxicological examination, as well as in the type and number of drugs reported. The 2000 cases comprised a representative sample of psychoactive drug deaths from each of the nine cities from 1972 through 1974.

Variations in the number of drugs quantitatively measured per case studied, the number of different drugs quantitatively measured, and the number and type of drugs found per case were reported. From the data as a whole, information is presented for 33 drugs as to the concentration in physiological tissues and fluids. Analysis of single psychoactive drug cases and single-drug-plus-ethanol cases shows that, in the presence of alcohol, the toxic blood concentration of imipramine, amitriptyline, meprobamate, thioridazine, morphine, propoxyphene, methaqualone, and all barbiturates was decreased by an average of 50%. (JAM)

1976 6refs

UM-76-M0139

RESULTS OF A NINE-LABORATORY SURVEY OF FORENSIC TOXICOLOGY PROFICIENCY, E. C. Dinovo; L. A. Gottschalk, Clinical Chemistry v22 n6 p843-6 (Jun 1976)

A brief proficiency testing program was performed on behalf of the National Institute on Drug Abuse in its effort to improve the investigating and reporting of drug-related deaths in nine major U. S. cities. Five standard drug samples were used in the study; three samples consisted of drugs, but no metabolites, added to drug-free urine, and two consisted of drugs added to 30 g/l solution of human albumin. Some samples were sent as complete unknowns, and partial information was supplied with others.

The results for the proficiency samples point out startling interlaboratory differences in accuracy and precision of detection of drugs. These observed variations in toxicological proficiency may introduce a significant source of error in drug-death statistics and in epidemiological deductions based on these statistics. (JAM)

1976 4refs

UM-76-M0140

TABULATION OF THERAPEUTIC, TOXIC, AND LETHAL CONCENTRATIONS OF DRUGS AND CHEMICALS IN BLOOD, C. L. Winek, Clinical Chemistry v22 n6 p832-6 (Jun 1976)

Therapeutic, toxic and lethal concentrations of drugs and chemicals in blood are presented. General factors affecting the pharmacological response to a drug and relevant to the use of the data, e.g., therapeutic monitoring, generic equivalency, efficacy of treatment in poisoning, and cause of death, are tabulated as well. Consideration of these factors is essential to the correct utilization of blood concentration data. Generally, the values represented are for the adult man, and via the oral route of administration. References containing additional collections of such data are given. (HSRI)

1976 11refs

UM-76-M0141

DETERMINATION OF CLOMIPRAMINE AND DESMETHYLCLOMIPRAMINE IN PLASMA OR URINE BY THE DOUBLE-RADIOISOTOPE DERIVATIVE TECHNIQUE, G. Carnis; J. Godbillion; J. P. Metayer, Clinical Chemistry v22 n6 p817-23 (Jun 1976)

A double isotope derivative method was developed for the determination of clomipramine (CM) and its principal metabolite (desmethylclomipramine, DCM) in plasma and urine. After addition of ^{14}C-labeled CM and DCM as internal standards and extractive isolation of both compounds, DCM is acetylated with ^{3}H-acetic anhydride. The derivative is separated from CM by thin-layer chromatography, and its radioactivity measured. CM, extracted from silica gel, is reacted with trichloroethyl chloroformate; the urethane is saponified and decarboxylated. The resulting DCM is acetylated, purified and its radioactivity measured as described.

The sensitivity of the method is 15 mcg/l for CM and 2 mcg/l for DCM. Specificity, precision, reproducibility, accuracy, and method sensitivity are fully reported. Concentrations of CM and DCM in plasma after single and repeated doses in volunteers and patients, respectively, are given. Concentrations of desmethylclomipramine tended to exceed the corresponding clomipramine concentrations and showed less variability. (JAM)

1976 14refs

UM-76-M0142

GAS-CHROMATOGRAPHIC ANALYSIS FOR THERAPEUTIC CONCENTRATIONS OF AMITRIPTYLINE AND NORTRIPTYLINE IN PLASMA, WITH USE OF A NITROGEN DETECTOR, D. N. Bailey; P. I. Jatlow, Clinical Chemistry v22 n6 p777-81 (Jun 1976)

A gas-chromatographic procedure for the simultaneous determination of amitriptyline and its active metabolite, nortriptyline, in human plasma was described. Both drugs are extracted at pH 10.5 into hexane/isoamyl alcohol; back-extracted into dilute HCl; and re-extracted into the solvent mixture after alkalinization of the HCl solution. The solvent residue is chromatographed with protriptyline as the internal standard. The sensitivity limit for the method was 5 mcg/l of plasma.

Forty-seven commonly used basic drugs were screened for interference in the assay; only doxepin and desipramine interfered with the proposed procedure. The method was applied to patients receiving therapeutic doses of both drugs and also to patients who had taken overdoses of amitriptyline. Plasma drug values in overdose ranged up to 1080 mcg/l for amitriptyline, to 337 mcg/l for nortriptyline, and to 1260 mcg/l for the sum of both. (JAM)

1976 20refs

UM-76-M0143

RAPID RADIOISOTOPIC PROCEDURE FOR DETERMINATION OF NORTRIPTYLINE IN PLASMA, K. P. Maguire; G. D. Burrows; J. P. Coghlan; B. A. Scoggins, Clinical Chemistry v22 n6 p761-4 (Jun 1976)

A double isotope derivative dilution procedure for measuring plasma nortriptyline is described. In the method, ^{14}C-nortriptyline is used for estimating procedural losses and ^{3}H-acetic anhydride for derivative formation. Samples may be purified by thin-layer chromatography following the addition of 10 mcg nortriptyline acetate to eliminate interference by the major metabolite of nortriptyline, 10-hydroxynortriptyline. Radioactive derivatives are located on silica gel sheets by the absorption of added marker at 254 nm. Recovery of the ^{14}C-indicator through the method was about 25%; the lower limit of sensitivity of the assay was 5 mcg/l, and was primarily due to the low specific activity of ^{14}C-nortriptyline.

The method was used to investigate the variation in steady-state drug concentrations in plasma of persons who were on a 150 mg/day dose of nortriptyline. Intra-individual variation from day to day was 10-14%. This variation was not significantly affected by the dosage schedule, the time of sampling after an oral dose, or the storage of plasma samples. For 19 patients on 150 mg/day, the mean concentration of plasma nortriptyline was 181 $\pm$ 22 (SE) mcg/l. (JAM)

1976 26refs

UM-76-M0144

RADIOIMMUNOASSAY, ENZYME IMMUNOASSAY, SPECTROPHOTOMETRY, AND GAS-LIQUID CHROMATOGRAPHY COMPARED FOR DETERMINATION OF PHENOBARBITAL AND DIPHENYLHYDANTOIN, V. Spiehler; L. Sun; D. S. Miyada; S. G. Sarandis; E. R. Walwick; M. W. Klein; D. B. Jordan; B. Jessen, Clinical Chemistry v22 n6 p749-53 (Jun 1976)

Sera from epileptic patients were assayed for phenobarbital and diphenylhydantoin by four different analytical procedures. Quantitative results obtained by radioimmunoassay (I) and enzyme immunoassay (II) were compared to each other and to the results obtained on aliquots of the same sample by gas-liquid chromatography (III) and ultraviolet spectrophotometry (IV). For phenobarbital the correlation coefficients were I vs. II, 0.909; I vs. III, 0.947; II vs. III, 0.917; I vs. IV, 0.950; II vs. IV, 0.953. For diphenylhydantoin the correlation coefficients were I vs. II, 0.953; I vs. III, 0.951; II vs. III, 0.957; I vs. IV, 0.862; II vs. IV, 0.898.

Immunoassays can be performed more quickly, while gas-liquid chromatography permitted simultaneous analysis for several drugs (primidone, phenobarbital, diphenylhydantoin) which, with batching of specimens, lends itself well to nonemergency analysis. The immunoassays can be substituted for gas-liquid chromatography or ultraviolet spectrophotometry without changing the resulting clinical interpretations. (JAM)

1976 19refs

UM-76-M0145

ANALYTICAL TOXICOLOGY: APPLICATIONS OF ELEMENT-SENSITIVE ELECTROLYTIC CONDUCTIVITY DETECTION FOR GAS CHROMATOGRAPHY, B. E. Pape, Clinical Chemistry v22 n6 p739-48 (Jun 1976)

A discussion of general detector principles precedes the report of selected applications of electrolytic conductivity detection (ElCD) to problems in analytical toxicology. The system components, the principles of ElCD operation, and detector variables, such as reactant gas, reaction catalysts, and furnace temperature, are described. The qualitative and quantitative analysis of ethchlorvynol, methaqualone, meprobamate, benzodiazepines, tricyclic antidepressants, and phenothiazines, as well as plasma drug screening, are reported.

The author concludes that the element-selective Hall ElCD is more sensitive than flame ionization detection, and permits gas-liquid chromatographic analysis with less sample clean-up, direct injection of sample extracts without prior concentration, and a more certain qualitative identification. Various ElCD furnace chemistry modes permit the detection of organic nitrogen, sulfur, or carbon, as contrasted to other less flexible element selective detectors. (HSRI)

1976 14refs

UM-76-M0146

QUANTITATIVE ENZYME IMMUNOASSAY: CURRENT STATUS, S. L. Scharpé; W. M. Cooreman; W. J. Blomme; G. M. Laekeman, Clinical Chemistry v22 n6 p733-8 (Jun 1976)

The current (1976) status of this group of techniques for the assay of endogenous and exogenous compounds in biological fluids is briefly reviewed. General features of quantitative radio- and enzyme-immunoassays, enzyme-linked immunosorbent assay and the homogenous enzyme immunoassay (EMIT) are described. Applications of the homogeneous enzyme immunoassay in monitoring drugs in urine and plasma are referenced, and several are discussed in some detail. (HSRI)

1976 61refs

UM-76-M0147

DETECTION OF DRUGS OF ABUSE BY RADIOIMMUNOASSAY A SUMMARY OF PUBLISHED DATA AND SOME NEW INFORMATION, R. Cleeland; J. Christenson; M. Usategui-Gomez; J. Heveran; R. Davis; E. Grunberg, Clinical Chemistry v22 n6 p712-25 (Jun 1976)

The authors review the status of radioimmunoassays for drugs of abuse in regard to their applicability to rapid drug screening, quantitation of drugs in biological specimens, limits of sensitivity, specificity, and stability in terms of usable shelf life of reagents. General problems related to the development of all assays are discussed. Clinical and experimental results obtained with the use of these assays are discussed for morphine, barbiturates, methadone, amphetamine, methaqualone, and benzoylecgonine. The possible development of combined radioimmunoassays was investigated. (HSRI)

1976 23refs

UM-76-M0148

CLINICAL PHARMACOKINETICS OF LORAZEPAM. I. ABSORPTION AND DISPOSITION OF ORAL ^{14}C-LORAZEPAM, D. J. Greenblatt; R. T. Schillings; A. A. Kyriakopoulos; R. I. Shader; S. F. Sisenwine; J. A. Knowles; H. W. Ruelius, Clinical Pharmacology and Therapeutics v20 n3 p329-41 (Sep 1976)

Eight healthy male subjects received 2 mg oral doses of lorazepam containing 24 mcCi/mg of 2-^{14}C-lorazepam. Multiple venous blood samples were drawn during the first 96 hours after the dose, and all urine and stool samples were collected for 120 hours after dosing. Concentrations of lorazepam and its metabolites were determined by thin-layer chromatography/liquid scintillation spectrometry and by gas-liquid chromatography.

Following a lag time, lorazepam was absorbed with an apparent half-life of 15 minutes. The peak plasma concentration was 16.9 ng/ml, measured in the pooled sample drawn 2 hours after the dose. This corresponded to the time at which the clinical effects appeared to be maximal. The apparent elimination half-life of lorazepam was about 12 hours. Biotransformation to a pharmacologically inactive glucuronide metabolite appeared to be the major mechanism of lorazepam clearance. Two other minor metabolites were identified. (JAM)

1976 42refs

UM-76-M0149

AMITRIPTYLINE PLASMA LEVELS AND THERAPEUTIC RESPONSE, V. E. Ziegler; B. T. Co; J. R. Taylor; P. J. Clayton; J. T. Biggs, Clinical Pharmacology and Therapeutics v19 n6 p795-801 (Jun 1976)

Eighteen depressed outpatients were treated for 6 weeks with amitriptyline. Clinical improvement was monitored using the Hamilton Depression Rating Scale administered by two psychiatrists blind to the tricyclic used for treatment, dosage, and plasma levels. Amitriptyline and its desmethyl metabolite, nortriptyline, were assayed twice weekly by gas chromatography-mass fragmentography.

For the 17 patients having total tricyclic plasma levels between 0 and 250 ng/ml, there was a negative correlation between the Hamilton score and the mean total tricyclic level and amitriptyline level. The mean nortriptyline level did not significantly correlate with the Hamilton score. The 10 patients having mean total tricyclic levels above 95 ng/ml had lower median Hamilton scores at weeks 3 and 6 than those whose tricyclics were lower. The percentage of recovered patients increases significantly as the plasma levels rise to 250 ng/ml, the maximum plasma level considered in this study. (JAM)

1976 14refs

UM-76-M0150

PROPOXYPHENE AND NORPROPOXYPHENE: INFLUENCE OF DIET AND FLUID ON PLASMA LEVELS, P. G. Welling; L. L. Lyons; F. L. S. Tse; W. A. Craig, Clinical Pharmacology and Therapeutics v19 n5 pt1 p559-65 (May 1976)

The influence of various test meals and ingested fluid volumes on the bioavailability and pharmacokinetics of propoxyphene has been studied in healthy human subjects. Plasma was assayed for propoxyphene and its major metabolite, norpropoxyphene, simultaneously by a gas chromatographic method. Subjects received the same treatment at the same time. Treatments were administered 2 weeks apart, and the six subjects received all six treatments.

The absorption of drug was delayed by all test meals, but the overall efficiency of absorption was either not affected or was slightly increased. Increased fluid volume intake decreased propoxyphene bioavailability. Plasma levels of metabolite correlated well with levels of unchanged drug, particularly in the first 2 hours after dosing, but were not markedly influenced by treatments. (JAM)

1976 15refs

UM-76-M0151

PHARMACOKINETICS OF METHOTRIMEPRAZINE AFTER SINGLE AND MULTIPLE DOSES, S. G. Dahl, Clinical Pharmacology and Therapeutics v19 n4 p435-42 (Apr 1976)

Concentrations of methotrimeprazine (levomepromazine) and a metabolite, methotrimeprazine sulfoxide, were measured in plasma by a gas chromatographic method after a single intramuscular dose and after single and multiple oral doses of methotrimeprazine. The highest plasma concentrations of methotrimeprazine were found 30-90 minutes after intramuscular injection, and 1-3 hours after oral administration. On average, 50% of orally administered drug reached the general circulation as unchanged methotrimeprazine.

The sulfoxide could not be traced in plasma after a 25 mg intramuscular dose, but was found in higher plasma concentrations than the unmetabolized drug after a single and multiple oral doses. This could be due to oxidation of the drug either in the intestinal lumen or in the intestinal wall, or during its first passage through the liver. The apparent half-life of the sulfoxide was on the average 30% shorter than the half-life of methotrimeprazine (15-30 hours). (JAM)

1976 19refs

UM-76-M0152

PLASMA LEVELS AND ANTIDEPRESSIVE EFFECT OF IMIPRAMINE, L. F. Gram; N. Reisby; I. Ibsen; A. Nagy; S. J. Dencker; P. Bech; G. O. Petersen; J. Christiansen, Clinical Pharmacology and Therapeutics v19 n3 p318-24 (Mar 1976)

The relationship between the antidepressant effect of imipramine, the plasma concentration of imipramine, and the active metabolite desipramine was studied in 24 patients suffering from endogenous depression. After a placebo period of 7 days, the patients received imipramine, 75 mg t.i.d. The dose was reduced in patients with pronounced side effects. Blood samples for drug assay were drawn in the morning, 15 hours after the last drug intake. Imipramine and desipramine in plasma were assayed by quantitative in situ thin-layer chromatography.

Individual variations in plasma concentration were 20- to 30-fold in both imipramine and desipramine. Severity of depression was assessed on the Hamilton Rating Scale. Eleven of 12 patients who responded satisfactorily to the treatment had plasma concentrations of imipramine greater than or equal to 45 mcg/L, and desipramine greater than 75 mcg/L; whereas the 12 patients not responding satisfactorily all had concentrations of imipramine or desipramine or both below these limits. The study reveals that the pharmacokinetic variability among patients explains the variability in therapeutic response. (JAM)

1976 18refs

UM-76-M0153

PHENYTOIN: PHARMACOKINETICS AND BIOAVAILABILITY, R. Gugler; C. V. Manion; D. L. Azarnoff, Clinical Pharmacology and Therapeutics v19 n2 p135-42 (Feb 1976)

The pharmacokinetics of a single 300 mg oral and intravenous, and 14 daily 300 mg oral doses were studied in 6 healthy volunteers. Plasma levels were determined by a highly specific radioimmunoassay permitting analysis of concentrations less than 0.1 mcg/ml. The mean plasma elimination half-life was the same (about 17 hours) following intravenous and oral doses of phenytoin (diphenylhydantoin); however, following chronic oral administration, the half-life increased to about 19 hours.

The absolute bioavailability of an oral dosage form varied from 57.7% to 85.6% when based on the relationship between the corresponding single dose areas under the curve (ACUs). When based on the comparison of the AUC for multiple oral dosing with the single intravenous dose area, average bioavailability was 85.9% (71.8-106.3). Since the variation in the bioavailability and elimination of phenytoin does not allow accurate prediction of the steady state plasma concentration, monitoring plasma levels may be of special importance. (JAM)

1976 31refs

UM-76-M0154

INFLUENCE OF MAGNESIUM AND ALUMINUM HYDROXIDE MIXTURE ON CHLORDIAZEPOXIDE ABSORPTION, D. J. Greenblatt; R. I. Shader; J. S. Harmatz; K. Franke; J. Koch-Weser, Clinical Pharmacology and Therapeutics v19 n2 p234-9 (Feb 1976)

Ten healthy male subjects ingested 25 mg of chlordiazepoxide hydrochloride (Librium) with 100 ml of water or with 100 ml of magnesium and aluminum hydroxide (Maalox) in a single dose crossover study. Multiple venous blood samples drawn during the first 24 hours after each dose were assayed for concentrations of chlordiazepoxide and its major metabolite, desmethylchlordiazepoxide, by a spectrofluorometric procedure.

The antacid prolonged the mean chlordiazepoxide absorption half-time from 11 to 24 minutes, and in 6 of 10 subjects delayed achievement of the peak

blood concentration by 0.5 to 3.0 hours. The formation of the metabolite was also slowed. The areas under the 24 hour blood concentration curve for chlordiazepoxide and its metabolite were not influenced by the antacid. The apparent elimination half-life of chlordiazepoxide was not significantly affected. Administration of chlordiazepoxide with antacid reduces the rate of its absorption but does not alter the completeness of absorption or the apparent rate of elimination. (JAM)

1976 35refs

UM-75-M0155

FIRST-PASS METABOLISM OF IMIPRAMINE IN MAN, L. F. Gram; J. Christiansen, Clinical Pharmacology and Therapeutics v17 n5 p555-63 (May 1975)

Test doses of carbon-14-imipramine were given twice to each of four subjects, one time by intravenous infusion (1 hour) and one time by oral administration (in aqueous solution). Blood samples were drawn at intervals for 72 or 96 hours, and urine was collected up to 6 days. Imipramine and desipramine in plasma were measured by direct densitometry of thin-layer chromatograms.

The systemic availability of orally administered imipramine varied from 29 to 77%. The decrease in availability was due to an excess in metabolism after oral administration. This first pass metabolism did not correlate with plasma half-life, apparent clearance, or the rate of metabolite excretion in urine. There was close correlation with the excess in formation of demethylated metabolites after oral administration, which suggests that the first pass metabolism is mediated by demthylation; the first pass metabolism did not correlate to the total rate of demethylation.

From a clinical point of view, the pharmacokinetic measurement of interest is plasma concentration of active compounds. The relative potency of imipramine and its active metabolite, desipramine, is unknown. Clinical studies relating plasma levels of the compounds to therapeutic effect will give information as to the relative potency of the two compounds, and, therefore, to the clinical significance of the first pass metabolism of imipramine. (HSRI)

1975 20refs

UM-75-M0156

DETERMINATION OF PROPOXYPHENE AND NORPROPOXYPHENE BY CHEMICAL IONIZATION MASS FRAGMENTOGRAPHY, R. L. Wolen; E. A. Ziege; C. M. Gruber, Jr., Clinical Pharmacology and Therapeutics v17 n1 p15-20 (Jan 1975)

The kinetics of propoxyphene and its primary metabolite, norpropoxyphene, have been simultaneously reevaluated in man using gas-liquid chromatography-mass spectrometry, deuterium labeled mass internal standards, and multiple ion monitoring. Four normal adult males received molar equivalents of two propoxyphene salts (300 mg of napsylate and 195 mg of hydrochloride) in a crossover design with a 6 week washout interval between the doses.

Plasma concentrations were determined for as long as 240 hours after a single oral dose. Peak plasma levels were 200-250 ng/ml 1.5-4.0 hours after administration. The overall half-life of propoxyphene was 11.8 hours, while that of its metabolite was 36.6 hours. (JAM)

1975 10refs

UM-75-M0157

THE DISPOSITION OF MORPHINE IN SURGICAL PATIENTS, B. A. Berkowitz; S. H. Ngai; J. C. Yang; J. Hempstead; S. Spector, Clinical Pharmacology and Therapeutics v17 n6 p629-35 (Jun 1975)

The disposition of serum morphine following administration of 10 mg/70 kg was determined by a sensitive and specific radioimmunoassay in 31 anesthetized

surgical patients ranging in age from 23 to 75 years. Following intravenous injection, 93% of the morphine disappeared from the serum within 5 minutes. The early serum levels of the drug (2 minutes) correlated directly with the patients' age. Patients 23 to 50 years of age averaged 0.29 mcg/ml, whereas patients 51 to 75 years of age averaged 70% higher, 0.49 mcg/ml.

Following intramuscular administration, morphine was rapidly absorbed with peak levels occurring within 10 to 20 minutes. The serum half-life between 10 and 240 minutes was independent of age and averaged about 2 hours after either mode of administration. The decline in morphine serum levels paralleled the decline in morphine analgesia and was coincident with the appearance of morphine glucuronide in the serum. These studies demonstrate the applicability and specificity of the radioimmunoassay for morphine and suggest that serum levels of morphine may be a useful and objective indicator of its pharmacologic activity. (JAM)

1975 19refs

UM-75-M0158

PHARMACOKINETICS OF CARBAMAZEPINE IN NORMAL MAN, R. H. Levy; W. H. Pitlick; A. S. Troupin; J. R. Green; J. M. Neal, Clinical Pharmacology and Therapeutics v17 n6 p657-68 (Jun 1975)

The bioavailability of commercial carbamazepine tablets with and without meals was compared to a propylene glycol solution with respect to extent of absorption in 6 normal humans after a dose of 6 mg/kg. The presence of dose dependent kinetics within a clinically significant range was also investigated. Serum and urine samples were assayed by gas-liquid chromatography.

Carbamazepine is rapidly absorbed from the propylene glycol solution. Eight per cent of the dose was absorbed from the commercial tablet resulting in therapeutic serum concentrations (3 to 6 mcg/ml). The data were consistent with dissolution rate-limited absorption. Mean half-lives ranged from 31 to 35 hours. No dose-dependent kinetics were observed following doses of 3, 6, or 9 mg/kg.

The fraction of dose absorbed, the fraction excreted unchanged in urine, the time of maximum serum concentration, and absorption and elimination half-lives appear to be independent of dose. The time course of side effects could not be correlated with serum carbamazepine levels suggesting that metabolites contributed to side effects. (JA)

1975 21refs

UM-75-M0159

MEPERIDINE KINETICS IN MAN. INTRAVENOUS INJECTION IN SURGICAL PATIENTS AND VOLUNTEERS, L. E. Mather; G. T. Tucker; A. E. Pflug; M. J. Lindop; C. Wilkerson, Clinical Pharmacology and Therapeutics v17 n1 p21-30 (Jan 1975)

The plasma concentration time profiles of meperidine following intravenous injection in surgical patients and volunteers were investigated by reference to a classical two compartment open model. Physiologic characteristics of the subject and variables associated with the surgery and anesthesia were screened as determinants of the kinetic patterns observed.

Type of anesthesia or premedication, patients' sex, or cigarette smoking did not appear to be important factors in this evaluation. Increasing alcohol consumption was associated with increasing volumes of distribution. Increasing age was associated with increasing fraction of drug unbound in plasma. These factors may relate directly to clinical observations that heavy alcohol consumers tend to be more refractory to central nervous system depressants, and that elderly patients are more susceptible to respiratory depression from narcotics. (JAM)

1975 31refs

UM-74-M0160

VALIDITY OF SCREENING METHODS FOR DRUGS OF ABUSE IN BIOLOGICAL FLUIDS. I. HEROIN IN URINE, C. W. Gorodetzky; C. R. Angel; D. J. Beach; D. H. Catlin; S.-Y. Yeh, Clinical Pharmacology and Therapeutics v15 n5 p461-72 (May 1974)

In evaluating methods of detecting drugs of abuse in biological fluids, it is of special importance to determine the ability of detecting a drug or its metabolites in biological fluids. To evaluate several methods of detecting heroin use by urine analysis for morphine and its metabolites, single intravenous doses of 2.5 and 5 mg/70 kg heroin were administered a week apart in random order to 10 nontolerant subjects. Urine was collected for the week following.

Along with pre-drug control urines, each sample was coded, randomized, and analyzed by the following methods: (1) thin-layer chromatography (TLC) with iodoplatinate preceded by each of 4 extraction procedures, including organic solvent and ion exchange resin impregnated paper extraction both with and without prior acid hydrolysis; (2) the free radical assay technique (FRAT); (3) radioimmunoassay (RIA); and (4) the Technicon Autoanalyzer.

There was a high probability of detection for the first 8 hours by all the methods except the Technicon Autoanalyzer, which gave a low proportion of positives 8 hours after the 2.5 mg/70 kg heroin dose; up to 16 hours with TLC procedures with hydrolysis and FRAT; and up to 32 to 48 hours with RIA. (JA)

1974 *26refs*

UM-74-M0161

VALIDITY OF SCREENING METHODS FOR DRUGS OF ABUSE IN BIOLOGICAL FLUIDS. II. HEROIN IN PLASMA AND SALIVA, C. W. Gorodetzky; M. P. Kullberg, Clinical Pharmacology and Therapeutics v15 n6 p579-87 (Jun 1974)

Five subjects received 3 single intravenous doses of heroin (2.5, 5, and 10 mg/70 kg) and 1 oral dose of dextromethorphan (60 mg/70 kg). Another 4 subjects received morphine (30 mg, subcutaneously) four times a day for three months. Saliva and plasma samples were collected at intervals for 48 hours following each single dose and hourly for 6 hours between chronic doses. Plasma samples were analyzed for opiate by radioimmunoassay (RIA), and saliva samples by RIA, a modified free radical assay technique (FRAT), and the enzyme multiplied immunoassay technique (EMIT).

The low dose of heroin was not consistently detectable at any sampling time in either the plasma or saliva. The medium and high doses were detectable with high probability for 2 to 4 hours in plasma, 1 to 2 hours in saliva. Dextromethorphan was not detectable in plasma but was detected with high probability in saliva for 30 minutes by EMIT and 2 hours by FRAT. During chronic administration, there were high probabilities of detection of morphine in plasma for at least 6 hours and in saliva for 3 to 4 hours after the last morphine dose. While these fluids do not appear to be as useful as urine in routine screening for heroin, they may be useful in the detection of high dose chronic abuse. (JA)

1974 17refs

UM-74-M0162

DISPOSITION OF PROPOXYPHENE AND NORPROPOXYPHENE IN MAN AFTER A SINGLE ORAL DOSE, K. Verebely; C. E. Inturrisi, Clinical Pharmacology and Therapeutics v15 n3 p302-9 (Mar 1974)

The disposition of propoxyphene and its major biotransformation product, norpropoxyphene, was studied in normal subjects following a single 130 mg oral dose. The concentration of the two compounds in samples of plasma and urine was determined by use of gas-liquid chromatography. The peak plasma level of propoxyphene occurs at 2 hours followed by a rapid elimination with

an average apparent half-life of 3 hours (1.6 to 4.1 hours range). The plasma level of norpropoxyphene reaches a peak at 4 hours and lowly decays with an apparent half-life of 16.8 hours (range 11.5 to 28.8 hours).

For a given subject, the ratio of the concentration of propoxyphene over the norpropoxyphene in plasma at 4 hours is well correlated with the apparent plasma half-life of propoxyphene. This suggests that this single plasma sample may provide an indication of the relative rate of N-demethylation in a population. The data indicate that individual differences in absorption and biotransformation may be responsible for the substantial variation of the plasma propoxyphene levels seen in subjects receiving the same dose. (JA)

1974 12refs

UM-75-M0163

PHENYTOIN AND PHENOBARBITAL CONCENTRATIONS IN SALIVA AND PLASMA MEASURED BY RADIOIMMUNOASSAY, C. E. Cook; E. Amerson; W. K. Poole; P. Lesser; L. O'Tuama, Clinical Pharmacology and Therapeutics v18 n6 p742-7 (Dec 1975)

Saliva and plasma levels of phenytoin (diphenylhydantoin, DPH) and phenobarbital (PB) in a series of epileptic patients were compared by means of a radioimmunoassay (RIA) that required only 10 mcl of saliva or plasma. There was an excellent linear relation (r = 0.98) between the logarithms of the concentrations of DPH in the two fluids. The ratio saliva/plasma was remarkably constant at 0.10 and was unaffected by varying levels of PB. The ratio was close to the fraction of DPH reported unbound in plasma at 37 degrees.

PB plasma and saliva levels were also closely related (r = 0.98 for logarithms of plasma and saliva levels). This relation was nonlinear but could be approximated by the ratio plasma/saliva = 3.4. The simplicity of sample collection and the sensitivity of the RIA procedure suggest that clinical monitoring of these anticonvulsant levels may be carried out by RIA on saliva samples. (JAM)

1975 30refs

UM-75-M0164

SALIVARY EXCRETION OF AMOBARBITAL IN MAN, T. Inaba; W. Kalow, Clinical Pharmacology and Therapeutics v18 n5 pt1 p558-62 (Nov 1975)

The concentration of amobarbital in saliva and serum were determined in 5 normal adults following ingestion of 120 mg of sodium amobarbital. Drug levels were measured by gas-liquid chromatography, and protein binding of amobarbital in serum was determined by equilibrium dialysis.

There was excellent linear relationship between amobarbital concentrations in a saliva and serum (r = 0.993); saliva levels were 36.1% of serum levels. Since the pH of saliva was generally lower than that of blood in man, the degree of ionization of amobarbital in serum and saliva had to be taken into consideration. Estimation of protein binding of amobarbital in serum from concentration of amobarbital in saliva and serum was in good agreement with the two in vitro data of equilibrium dialysis.

The salivary data may provide an estimate of plasma protein binding in the living subject. In principle, such a set of data should permit an experimental assessment of the influence of plasma protein binding on the rate of drug metabolism. In addition, the determination of amobarbital in saliva is not only painless and noninvasive but also less time consuming than that in serum. (JAM)

1975 13refs

UM-75-M0165

TRICYCLIC ANTIDEPRESSANT OVERDOSE: CLINICAL PRESENTATION AND PLASMA LEVELS, D. G. Spiker; A. N. Weiss; S. S. Chang; J. F. Ruwitch, Jr.; J. T. Biggs, Clinical Pharmacology and Therapeutics v18 n5 pt1 p539-46 (Nov 1975)

Fifteen patients were studied at 8- to 12-hour intervals during the first 24 hours after overdosing with tricyclic antidepressants, and subsequently followed daily for up to 144 hours. The severity of the overdose was determined by measuring the plasma tricyclic antidepressant level using gas chromatography-mass fragmentography. No correlation was found between total, tertiary, or desmethyl tricyclic antidepressant plasma levels and maximum heart rate, lowest blood pressure, degree of unconsciousness, or electrocardiogram (EKG) changes involving the P-R interval or ST-T wave changes.

There was a weak correlation between drug plasma level and maximum pupil size, and a strong correlation between the duration of the QRS complex and tricyclic antidepressant levels. All patients with a total tricyclic plasma level greater than 1000 ng/ml had a QRS interval greater than 100 msec. As the total plasma tricyclic level fell, the duration of the QRS complex returned to normal. Thus, the most reliable clinical sign for evaluating the seriousness of tricyclic antidepressant overdosage, appears to be the duration of the QRS complex on the electrocardiogram. (JAM)

1975 21refs

UM-74-M0166

HUMAN BRAIN, CEREBROSPINAL FLUID, AND PLASMA CONCENTRATIONS OF DIPHENYLHYDANTOIN AND PHENOBARBITAL, F. Vajda; F. M. Williams; S. Davidson; M. A. Falconer; A. Breckenridge, Clinical Pharmacology and Therapeutics v15 n6 p597-603 (Jun 1974)

The concentrations of diphenylhydantoin (DPH) and phenobarbital (PB) have been measured in plasma, lumbar cerebrospinal fluid (CSF), and samples of temporal lobe in 12 epileptic patients undergoing a temporal lobectomy. The brain:plasma ratio of DPH was 0.75 ± 0.19:1, and the CSF:plasma ratio was 0.12 ± 0.04:1. For PB, the mean brain:plasma ratio was 0.59 ± 0.21:1 and the CSF:plasma ratio was 0.46 ± 0.12:1. The significant correlation between brain and plasma drug concentrations supports the value of monitoring plasma concentrations of anticonvulsant drugs in patients with epilepsy. (JA)

1974 18refs

UM-75-M0167

METHADONE IN MAN: PHARMACOKINETIC AND EXCRETION STUDIES IN ACUTE AND CHRONIC TREATMENT, K. Verebely; J. Volavka; S. Mulé; R. Resnick, Clinical Pharmacology and Therapeutics v18 n2 p180-90 (Aug 1975)

The biologic disposition of methadone in acute and during chronic administration was studied in 12 human volunteers. In the acute study, a biexponential methadone plasma level decay was observed. The acute primary half-life of 14.3 hours in combination with the acute secondary half-life of 54.8 hours were longer than the single exponential chronic half-life of 22.2 hours determined in the same subjects.

The urinary and fecal excretion of methadone and its mono-N-demthylated metabolite increased from 22.2% in the acute to 62.0% in the chronic phase of the study. The pupillary effects of methadone monitored throughout 24 hours were nearly the same in magnitude in the acute and chronic studies, whereas the plasma levels increased 3- to 8-fold following chronic methadone medication. The urinary metabolite 1 to methadone ratio tripled from the acute to the chronic phase. These findings suggest that both dispositional and pharmacologic tolerance are involved in the development of tolerance following chronic administration of methadone. (JA)

1975 27refs

UM-76-M0168

A MASS FRAGMENTOGRAPHIC METHOD FOR THE DETERMINATION OF CHLORPROMAZINE AND TWO OF ITS ACTIVE METABOLITES IN HUMAN PLASMA AND CSF, G. Alfredsson; B. Wode-Helgodt; G. Sedvall, Psychopharmacology v48 n2 p123-31 (28 Jul 1976)

A mass fragmentographic method for the quantitation of chlorpromazine (CPZ), monodemethyl-chlorpromazine, and 7-hydroxychlorpromazine in plasma, cerebrospinal fluid (CSF), and tissues has been developed. The deuterated analogues of the compounds serve as internal standards, and high specificity is attained by multiple ion determination. Experimental error for the method is below 10%, and the sensitivity allows determination of sub-nanogram quantities of CPZ per ml of CSF.

The method has been applied to the analyses of drug concentrations in plasma and CSF of chlorpromazine-treated patients. The amount of CPZ in CSF was about 3% of the plasma level. The CPZ levels in plasma and CSF were significantly correlated. The method as described has a high specificity and reliability, and offers good opportunities to analyze the possible relations between pharmacokinetics and clinical parameters in relation to CPZ treatment. (JAM)

1976 19refs

UM-76-M0169

CLINICAL SIGNIFICANCE OF PLASMA CHLORPROMAZINE LEVELS. II. PLASMA LEVELS OF THE DRUG, SOME OF ITS METABOLITES AND PROLACTIN IN PATIENTS RECEIVING LONG-TERM PHENOTHIAZINE TREATMENT, T. Kolakowska; D. H. Wiles; M. G. Gelder; A. S. McNeilly, Psychopharmacology v49 n1 p101-7 (26 Aug 1976)

Plasma levels of chlorpromazine (CPZ), three of its metabolites and prolactin were measured repeatedly in 18 chronic schizophrenic patients. The patients were studied while on chronic phenothiazine medication (more than 5 years), during 4-6 weeks on placebo, and during 6-12 weeks of CPZ treatment. The findings were compared with those obtained during acute CPZ treatment in patients who had received similar CPZ doses but no previous phenothiazine medication.

Plasma CPZ levels were similar in the chronic and the acute groups and so was their relation to dose. In neither group was therapeutic effect related to plasma CPZ level. In these chronic patients, in contrast to the findings during acute CPZ treatment, neither prolactin nor the appearance of parkinsonian symptoms was related to plasma drug level, and both effects were less pronounced in those who had received chronic phenothiazine therapy. Since plasma CPZ levels of the two groups were similar, these differences may be due to an acquired tolerance of the nervous system to some of the antidopaminergic effects of the drug. (JAM)

1976 20refs

UM-74-M0170

THE CONCENTRATIONS OF DIAZEPAM AND ITS METABOLITES IN THE PLASMA AFTER AN ACUTE AND CHRONIC ADMINISTRATION, J. Kanto; E. Iisalo; V. Lehtinen; J. Salminen, Psychopharmacologia (Berlin) v36 n2 p123-31 (Apr 1974)

Plasma levels of diazepam, N-demethyldiazepam, and free oxazepam were studied in 12 neurotic outpatients during subchronic use, in 14 outpatients after chronic use, and in 8 test subjects after an acute intravenous administration. The psychic condition of the patients was estimated both by a psychiatrist and by the patients themselves. A gas chromatographic procedure using a nickel-63-detector was employed to determine plasma levels of diazepam and its metabolites.

Experimental evidence was presented to support the contention that diazepam induces its own metabolism in man. The authors conclude that diazepam should

be administered in small doses and for short periods of time, or intermittently, since with long-term therapy diazepam may become less effective. (JAM)

1974 15refs

UM-74-M0171

PERPHENAZINE CONCENTRATIONS IN HUMAN WHOLE BLOOD. A PILOT STUDY DURING ANTIPSYCHOTIC THERAPY USING DIFFERENT ADMINISTRATION FORMS, C. E. Hansen; N.-E. Larsen, Psychopharmacologia (Berlin) v37 n1 p31-6 (18 Jun 1974)

Perphenazine (PPZ, Trilafon^{R}) has been studied in human whole blood under therapeutic conditions. By means of a highly sensitive gas chromatographic method, concentrations of 0.2 mcg/l of whole blood could be assayed with a sufficient degree of accuracy. In three acutely psychotic patients, the PPZ levels were studied after administration in each of three different ways: A) as single doses of PPZ (5 mg) given intramuscularly; B) as multiple doses (8 mg b.i.d., 22 days), given orally; and C) as single doses of PPZ enanthate (100 mg i.m.).

The PPZ levels reached in experiment B were not higher than those of experiment A despite the higher dose given to the patients. This result indicated the possibilities that there was incomplete absorption and/or a "first pass effect," and that during protracted oral administration PPZ increases the rate of its own metabolism. In B, the elimination rate was rapid compared to the dose interval, leading to considerable blood concentration variations between the two doses. The highest PPZ concentration, 7.4 mcg/l, was measured in experiment C. Neurological side effects were registered, and their relation to blood concentrations of PPZ are briefly discussed. (HSRI)

1974 13refs

UM-75-M0172

FIRST-PASS METABOLISM OF NORTRIPTYLINE IN MAN, L. F. Gram; K. F. Overø, Clinical Pharmacology and Therapeutics v18 n3 p305-14 (Sep 1975)

The kinetics of nortriptyline were studied after oral and intravenous (i.v.) administration of test doses of 50 mg carbon-14-nortriptyline. The systemic availability of orally administered nortriptyline varied from 0.46 to 0.59 in six healthy male volunteers. The decrease in availability was due to metabolism after administration. Systemic clearance varied from 0.31 to 0.66 L/minute. From these measurements indirect estimates of the hepatic blood flow could be made, and a variation from 0.6 to 1.5 L/minute was found.

Quantitative measurements of first-pass metabolism could also be obtained from urinary metabolite excretion when the kinetics of metabolite formation and elimination were taken into account. Analysis of the data from the i.v. test according to a 2-compartment open model showed that there was a close correlation between the rate constant of distribution from the central to peripheral compartment and the elimination rate constant in the central compartment. Still, there was some variation in the ratio of the two constants, and this was attributed to the variation of the estimated hepatic blood flow. (JAM)

1975 29refs

UM-74-M0173

MORPHINE METABOLISM IN MAN, S. F. Brunk; M. Delle, Clinical Pharmacology and Therapeutics v16 n1 pt1 p51-7 (Jul 1974)

Morphine metabolism was studied in 6 normal men at weekly intervals after intravenous, intramuscular, subcutaneous, and oral administration. Morphine was rapidly absorbed after intramuscular and subcutaneous injection, producing plasma levels of free morphine, from 15 minutes to 3 hours, which are significantly higher than levels after intravenous administration. Intravenous morphine, while initially higher, undergoes more rapid distribution, metabolism, and excretion.

Morphine is well absorbed from the gastrointestinal tract, but is so rapidly conjugated with glucuronide in the cells of the intestinal mucosa and liver that significant levels of free morphine are not found in either the plasma or urine, whereas the levels of conjugated morphine are high. N-demethylation of morphine is greater after oral than after parenteral administration. While route of administration alters plasma levels of free morphine, it does not alter plasma half-life. (JA)

1974 10refs

UM-74-M0174

PLASMA NORTRIPTYLINE AND CLINICAL RESPONSE, G. Burrows; B. A. Scoggins; L. R. Turecek; B. Davies, Clinical Pharmacology and Therapeutics v16 n4 p639-44 (Oct 1974)

The relationship of plasma nortriptyline levels to clinical response of 80 depressed patients was studied. Plasma nortriptyline levels were estimated 4 weeks after commencing treatment by a modified isotope derivative method. Percentage change in the Hamilton Depression Rating Scale was used to measure clinical response. There was no simple relationship between these two measures.

Twelve of the 80 patients were studied further. Clinical response to variations of plasma nortriptyline levels was studied. Calculation of regression coefficients showed a positive relationship between clinical change and plasma nortriptyline levels. While this relationship differed significantly among patients, it was not related to age or sex.

The twelve patients also responded to altered oral doses of nortriptyline within a few days of the alteration of plasma levels. This is in contrast to the 10-14 day delay that is a feature of the pharmacologic response to tricyclic medication. The relationship appeared to be associated with the development of steady-state plasma levels, and indicated the need to study the value of rapid steady-state development in antidepressant therapy with tricyclic drugs. The study as a whole reemphasized the difficulty of identifying that subgroup of depressive patients who respond to tricyclic medication. (JAM)

1974 16refs

UM-74-M0175

ESTIMATION OF PHARMACOKINETIC PARAMETERS OF LITHIUM FROM SALIVA AND URINE, U. Goth; W. Prellwitz; E. Jähnchen, Clinical Pharmacology and Therapeutics v16 n3 p490-8 (Sep 1974)

The salivary and urinary excretion of lithium was studied in three healthy male subjects after oral administration of two or three different doses spaced 7 weeks apart. In all individuals the concentration of lithium in salivary fluid was found to be 2.2 to 3.3 times as high as the concentration in plasma. In each subject the saliva:plasma concentration ratio remained constant over more than a 100-fold concentration range for at least three months. This ratio was not markedly affected by about tenfold changes in saliva flow rate.

Pharmacokinetic parameters obtained from salivary excretion data are in agreement with those obtained from plasma concentration and urinary excretion rate data. Renal clearance of lithium can be estimated from salivary excretion data. Diurnal rhythms in the urinary excretion rate of lithium were observed. Once the saliva:plasma concentration ratio is established (by taking only a few blood samples), the measurement of saliva concentrations should provide all pharmacokinetic information necessary for rational dose regimens. (JA)

1974 21refs

UM-74-M0176

PHARMACOKINETICS OF THIOTHIXENE IN MAN, D. C. Hobbs; W. M. Welch; M. J. Short; W. A. Moody; C. D. van der Velde, Clinical Pharmacology and Therapeutics v16 n3 pt1 p473-8 (Sep 1974)

A specific and sensitive gas chromatographic assay which incorporates mass fragmentography was developed and used to measure concentrations of thiothixene to less than 1 ng/ml of plasma in psychotic patients on long-term therapy. Fifteen chronic schizophrenic patients were treated orally with commercial thiothixene capsules over a period of 1 to 25 months, and the dose was adjusted such that adequate control of symptomatology was obtained. Although total daily doses in two groups of patients ranged from 15 to 60 mg, a four-fold difference, plasma drug concentrations 2.1 to 2.5 hours after dosing in one group, and at peak in the other group, fell within the range of 10.0 to 22.5 ng/ml. This indicated that during prior adjustments of dose to achieve therapeutic control, optimum plasma levels were also being achieved. The effective plasma level appears to be approximately the same for all patients despite the widely differing dosage necessary. (HSRI)

1974 5refs

UM-74-M0177

ABSORPTION AND CLEARANCE OF SECOBARBITAL, HEPTABARBITAL, METHAQUALONE, AND ETHINAMATE, J. M. Clifford; J. H. Cookson; P. E. Wickham, Clinical Pharmacology and Therapeutics v16 n2 p376-89 (Aug 1974)

The absorption and clearance of secobarbital, heptabarbital, methaqualone, and ethinamate were studied by measurements of blood and plasma drug levels after single oral dosage in the therapeutic range to nonfasting subjects. Determinations of blood and plasma levels were carried out to the limits of sensitivity of the gas-liquid chromatographic method employed in the study.

The mean maximum plasma level of ethinamate and methaqualone was observed after 1 and 2 hours, respectively. Mean maximum blood level of secobarbital and heptabarbital was observed after 3 and 6 hours, respectively. Half-lives of the drugs were reported for secobarbital (28.9 hours), heptabarbital (9.7 hours), and ethinamate (2.3 hours). Methaqualone plasma levels decayed in a biphasic manner; the half-life of the fast component was calculated as 0.9 hour and the slow one as 16 hours. Of the four drugs, only ethinamate could not be detected in the body 24 hours after they were administered. (JAM)

1974 36refs

UM-74-M0178

PHARMACOKINETIC CONTROL AND CLINICAL INTERPRETATION OF STEADY-STATE BLOOD LEVELS OF DRUGS, G. Levy, Clinical Pharmacology and Therapeutics v16 n1 pt2 p130-4 (Jul 1974)

Average steady-state blood levels are a function of the dose, fraction of dose absorbed, dosing interval, biologic half-life, and apparent volume of distribution of drugs that have apparently linear pharmacokinetic characteristics. The rate of accumulation of such drugs, when administered at regular intervals, is inversely proportional to the half-life of their slowest (terminal) elimination phase. "Hidden accumulation" may occur if the terminal elimination phase of a drug reflects the characteristics of a relatively very small pharmacokinetic compartment; this may account for a gradual increase in the intensity of a pharmacologic effect at a time when drug concentrations in plasma are apparently at the steady state.

Fluctuations of drug levels during a dosing interval at the steady state due to the effects of absorption, distribution, and elimination can complicate the assessment and interpretation of these levels. Control of steady-state levels is particularly difficult in the case of drugs with distinct nonlinear (Michaelis-Menten) characteristics. A change in dose (or fraction absorbed)

will cause a more than proportional change in the steady-state drug level. The clinical interpretation of steady-state drug levels must take into consideration the possible effects of pharmacologically active metabolites and of changes in drug distribution that may modify the relationship between drug concentration in plasma and the intensity of a pharmacologic effect. (JA)

1974 22refs

UM-74-M0179

FACTORS CAUSING INTERINDIVIDUAL VARIATIONS OF DRUG CONCENTRATIONS IN BLOOD, E. S. Vesell, Clinical Pharmacology and Therapeutics v16 n1 pt2 p135-48 (Jul 1974)

Multiple factors in carefully controlled studies produce individual variations in drug blood levels. Environmental and genetically controlled factors to which the hepatic microsomal enzyme system is sensitive can induce such variations, as can factors which alter drug absorption, distribution, and excretion. For several commonly used drugs, including phenylbutazone, antipyrine, ethanol, and nortriptyline, large interindividual variations in plasma half-lives have been shown to be controlled predominantly by genetic factors in man. When a variety of environmental perturbations are imposed on this genetically controlled basal drug-metabolizing capacity, alterations can also occur in drug absorption, distribution and excretion.

Co-administration of other drugs, disease states, and swiftly changing cardiovascular or renal status can also alter drug blood levels. In various disease states, the drug receptor site may become altered so that it no longer responds as expected to a given drug level. Operation of several of these factors in severely ill patients renders interpretation of drug blood levels difficult. (JAM)

1974 36refs

UM-74-M0180

APPLICATION OF RADIOIMMUNOASSAY TO PHARMACOLOGY, S. Spector, Clinical Pharmacology and Therapeutics v16 n1 pt2 p149-52 (Jul 1974)

The principles underlying the radioimmunoassay are briefly described and are illustrated by the development of a radioimmunoassay for morphine and related compounds. The radioimmunoassay measures the inhibition of binding of a labeled ligand by the antibody. The sensitivity of the system is a function of the avidity of the antiserum used and the specific activity of the labeled drug. Factors which can lead to discrepancies with the radioimmunoassay are noted. (HSRI)

1974 7refs

UM-74-M0181

DRUG LEVELS IN THE TARGET TISSUE AND EFFECT, E. J. Ariëns, Clinical Pharmacology and Therapeutics v16 n1 pt2 p155-75 (Jul 1974).

The dose-response relationship in drug therapy, and the dose-effect curve and how it is affected by many variables and differences between individuals, are discussed and schematized. The sequence of events is considered under three phases: (1) pharmaceutical (disintegration of the dosage form); (2) pharmacokinetic (processes determining the drug concentration in the various compartments); and (3) pharmacodynamic (interaction of the drug molecules with their sites of action or receptors).

The bioactivity of the compound in relation to receptor molecules is in part based on the concentration in the target tissue; mass-action law may therefore be expected to govern the relationship between this concentration in the target tissue and the effect. The role of feedback mechanisms in regulating the biochemical sequence of conversions is analyzed in terms of the steps

that are involved in a rate-limiting process; the effect of a particular dose is modified by counterbalancing feedback mechanisms, unless it interferes with the appropriate homeostatic maintenance of the parameter involved.

Other factors which influence the drug concentration/effect relationship are discussed. Issues in drug design, including bioactivation and biotoxification in target tissues, are presented. Recommendations concerning metabolism resistant drugs and research needs are given. (JAM)

1974 45refs

UM-74-M0182

APPLICATION OF BLOOD LEVEL DATA TO CLINICAL TRIALS, D. L. Azarnoff, Clinical Pharmacology and Therapeutics v16 n1 pt2 p183-8 (Jul 1974)

In the evaluation of drugs, especially in the early phases, interpatient variation in response to a fixed dose may give misleading results concerning both efficacy and toxicity. Unless blood level determinations are made during the clinical trial, an effective drug could unnecessarily be lost or discarded. Factors which can contribute to a lack of correlation between the administered dose of drug and its effect are identified and discussed. Measurement of plasma concentrations of drugs during clinical investigations, while not an infallible aid, can be useful when applied under proper circumstances. (JAM)

1974 29refs

UM-75-M0183

PROFICIENCY TESTING IN FORENSIC DRUG CHEMISTRY, R. S. Frank, presented at the 7th International Meeting of Forensic Sciences, Zurich, Switzerland (8-12 Sep 1975)

It is the responsibility of the forensic scientist to ensure the accuracy of information provided a court or law enforcement investigator regarding the composition of drug evidence. The forensic science program of the Drug Enforcement Administration undertook a program to assess the accuracy of information generated by its field laboratories, and to determine whether significant differences existed between the laboratories or between the methods employed.

In each of six laboratories, duplicate analyses of a supplied sample were made by three analysts, each using three different, specified methods. Results were analyzed with regard to a set of defined parameters: consistency, accuracy, bias, and variability. A new mode of presentation was developed for the results.

The results were both tabulated and graphically presented for each laboratory and method. It was concluded that no significant problems existed with either the laboratories or the methods, and that the proficiency testing program was successful in meeting the aims of the Drug Enforcement Administration and the needs of the forensic scientists. (HSRI)

Forensic Sciences Division, Office of Science and Technology, Drug Enforcement Admin., Washington, D. C. 20537.

1975 18p 6refs

UM-76-M0184

MASS SPECTROMETRY, A. L. Burlingame; B. J. Kimble; P. J. Derrick, Analytical Chemistry v48 n5 p368R-403R (Apr 1976)

The widely divergent and increasingly heterogeneous field of mass spectrometry is reviewed. The initial sections cover instruments, techniques, and computers. The authors emphasize organic chemistry in their treatment of

developments in ion chemistry, and biomedical and environmental studies in the discussion of analytical applications. The review covers the literature from the cutoff of a previous review to the end of 1975. (HSRI)

1976 1266refs

UM-76-M0185

GAS CHROMATOGRAPHY, S. P. Cram; R. S. Juvet, Jr., Analytical Chemistry v48 n5 p411R-42R (Apr 1976)

This review, as one of a series, surveys developments in the field of gas chromatography, and covers the years 1974-75. Books and reviews related to the area are cited. Columns and detectors are extensively treated. Qualitative and quantitative analyses using gas chromatography and gas chromatography in conjunction with ancillary techniques such as mass spectrometry and infrared detectors are reported. Developments in general methodology related to gas chromatography are also covered. (HSRI)

1976 1748refs

UM-76-M0186

STATISTICAL AND MATHEMATICAL METHODS IN ANALYTICAL CHEMISTRY, P. S. Shoenfeld; J. R. DeVoe, Analytical Chemistry v48 n5 p403R-11R (Apr 1976)

This review focuses on those subjects which have experienced a considerable increase in activity since the last review in the series (1972), and covers the period October 1971 to January 1976. A computer-based literature search was used, and the key words employed were given. Only those applications which have a direct and demonstrated application to analytical chemistry are presented. Active areas reviewed include spectral resolution, chracterization and evaluation of the measurement process, optimization techniques, pattern recognition, and digital signal processing.

In their final comments, the authors emphasize the importance of the correctness of the result as opposed to the acknowledged emphasis on the reproducibility of measurement and signal interpretation in real world terms. Techniques for numerical and statistical analysis of the data should be supplanted with careful studies of systematic errors in analysis, according to the authors. (HSRI)

1976 192refs

UM-76-M0187

ION EXCHANGE AND LIQUID COLUMN CHROMATOGRAPHY, H. F. Walton, Analytical Chemistry v48 n5 p52R-66R (Apr 1976)

Aspects of ion exchange and liquid column chromatography are reviewed. This report updates an earlier review and covers the literature on a selected basis through December 1975. Chromatographic absorbents, the properties of resins, and the nonchromatographic uses of resins and absorbents are covered. Column techniques and studies of column behavior are surveyed. Applications are presented, and two tables are included which summarize reports concerning inorganic ions and compounds, including bio-organic and drug substances, respectively. (HSRI)

1976 675refs

UM-76-M0188

ULTRAVIOLET SPECTROMETRY, R. Hummel; D. Kaufman, Analytical Chemistry v48 n5 p268R-73R (Apr 1976)

This review, an update of a previous review by the authors, covers the period from December 1973 to November 1975. Sections of the review covering different aspects of ultraviolet spectrometry include instrumentation, spectral

studies, solvent and pH effects, structure elucidation, and theory and calculation. Applications in the areas of inorganic, organic, biological, and pharmaceutical analysis are surveyed. (HSRI)

1976 255refs

UM-75-M0189

SEPARATION AND QUANTITATIVE DETERMINATION OF TRICYCLIC ANTIDEPRESSANTS BY HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY, I. D. Watson; M. J. Stewart, Journal of Chromatography v110 n2 p389-92 (16 Jul 1975)

Aqueous solutions containing different proportions of amitriptyline, nortriptyline, and protriptyline in the range of 20-200 ng/ml were made basic and extracted twice with 2.5 volumes of light petroleum. Pooled extracts were filtered and evaporated; residues were dissolved in 100 mcl aliquots of methanol and applied to the column. The liquid chromatograph was fitted with an ultraviolet detector, and ammonia-methanol, used as the eluting solvent, resulted in no peak tailing. The method described combines the advantages of sensitivity (20 ng/ml of aqueous solution) and simple work-up with complete resolution of the three tricyclic antidepressants. (HSRI)

1975 7refs

UM-75-M0190

A SIMPLE METHOD FOR DETERMINING DIAZEPAM AND ITS MAJOR METABOLITES IN BIOLOGICAL FLUIDS: APPLICATION IN BIOAVAILABILITY STUDIES, E. Arnold, Acta pharmacologia et toxicologia v36 n4 p335-52 (Apr 1975)

A gas chromatographic-electron capture detection method was described for the determination of diazepam and its major metabolites in blood, urine, and muscle homogenate. A benzene extract is evaporated to dryness and reconstituted with an internal standard. Human bioavailability studies following single doses (10 mg) of diazepam in the form of tablets and suppositories were performed using a cross-over design in a four week experiment. Rats were used to study the absorption of injection fluids.

The sensitivity of the method was 5 ng diazepam per ml of serum. The accuracy of the analysis is limited by the non-linear response of the detector. Both brands of tablets resulted in similar serum levels (300-400 ng/ml). Maximum serum concentrations differed when two brands of suppositories were tested, but the serum concentrations obtained (100-200 ng/ml) after three hours did not differ.

The biological half-life of diazepam in the elimination phase was calculated to be about 50 hours. N-desmethyldiazepam, a principal metabolite, tended to accumulate during the administration of 10 mg diazepam even with weekly intervals of drug administration. Three-day urine samples from four subjects given two 10 mg tablets 7 days apart, exhibited a uniform excretion pattern: small quantities of free diazepam (less than 0.5% of dose) and considerable quantities of conjugated oxazepam, N-desmethyldiazepam, and hydroxydiazepam (about 20% of dose). (HSRI)

1975 18refs

UM-75-M0191

METHODS OF IDENTIFICATION AND CONFIRMATION OF ABUSIVE DRUGS IN HUMAN URINE, D. L. Roerig; D. Lewand; M. Mueller; R. I. H. Wang, Journal of Chromatography v110 n2 p349-59 (16 Jul 1975)

A thin-layer chromatography (TLC) procedure using the non-ionic resin Amberlite XAD-2 to absorb water soluble organic molecules from urine is described. The technique can be used as the initial drug detection method for urine surveillance in a drug abuse treatment program. While the TLC method is sufficiently sensitive (morphine, 0.2 mcg/ml; methadone, 0.5 mcg/ml;

barbiturates, between 0.5 and 1.0 mcg/ml; 0.5 mcg/ml, amphetamine), it is prone to false positive results.

Radioimmunoassay (RIA) is used to confirm all positive and questionable positive results for morphine observed with TLC; in addition, RIAs for barbiturates and amphetamines are being evaluated for possible inclusion in the screening system. Gas-liquid chromatography (GLC) is used as a confirmatory method for other drugs, as it is more sensitive, has greater separation ability, and is less prone to false positives. The increased time for analysis and its greater cost have made GLC less attractive than TLC as a primary method for urine surveillance. As two confirmation methods, GLC can detect a wider range of drugs, while RIA is faster and less expensive. The combined methadologies result in a urine surveillance procedure that is versatile, sensitive and highly reliable. (HSRI)

1975 21refs

UM-76-M0192

DETECTION OF AMPHETAMINE AND METHAMPHETAMINE-TYPE MATERIALS IN PHARMACEUTICAL AND BIOLOGICAL FLUIDS BY FLUOROMETRIC LABELING, T. J. Hopen; R. C. Briner; H. G. Sadler; R. L. Smith, Journal of Forensic Sciences v21 n4 p842-50 (Oct 1976)

This report outlines a procedure by which amphetamine- and methamphetamine-like compounds can be detected in drug preparations and in human urine (sensitivity of 0.1 mcg/ml). Fluorescent derivatives of the compounds are synthesized using NBD-Cl (7-chloro-4-nitrobenzo-2-oxo-1,3-diazole) and are separated by thin-layer chromatography (TLC) using two solvent systems. Urine is made basic (pH 7 to 8) with sodium bicarbonate, if necessary, and 0.4 M NBD-Cl in dioxane is added. After sufficient reaction time, the solution is extracted twice with choloroform; the extracts are dried and evaporated. The residue is reconstituted in dichloroethane, and the fraction is passed through an activated Fluorisil^{R} column. Eluates are dried, reconstituted in a smaller volumn of dichloroethane, and spotted on TLC plates. Following two solvent system development, the plates are viewed with an ultraviolet lamp.

Interfering substances have not been found as long as both solvent systems are used. The procedure can be used for general screening of suspected amphetamine-type preparations. (HSRI)

1976 12refs

UM-76-M0193

IDENTIFICATION OF DRUGS AND OTHER TOXIC COMPOUNDS FROM THEIR ULTRAVIOLET SPECTRA. PART 3: ULTRAVIOLET ABSORPTION PROPERTIES OF 22 STRUCTURAL GROUPS, T. J. Siek; R. J. Osiewicz; R. J. Bath, Journal of Forensic Sciences v21 n3 p525-51 (Jul 1976)

The ultraviolet absorption spectra of 22 different chemical (structural) groups of drugs and toxic compounds were studied. This paper completes a three-part series in which more than 500 individual compounds have been grouped according to structure as it pertains to characteristics of the ultraviolet absorption scan. Each group has a typical absorption profile with respect to the number of bands between 200 and 340 nm, the intensity of the band(s), and the changes in absorption pattern with solvent and pH changes.

Phenothiazines, xanthines, coumarins, quinolines, naphthalene derivatives, 0-alkyl benzene derivatives, opiates, ergot alkaloids, benzodiazepines, and various heterocyclic compounds are among the groups of compounds covered in this paper. In addition, an appendix is included which presents a summary of the ultraviolet absorption characteristics of compounds in the different structural groups. (ASM)

1976 19refs

UM-76-M0194

THE IDENTIFICATION OF QUINAZOLINONES ON THE ILLICIT MARKET, P. Daenens; M. Van Boven, Journal of Forensic Sciences v21 n3 p552-63 (Jul 1976)

This paper describes the analytical data for the identification of three commercially available hypnotics of the quinazolinone series (methaqualone, mecloqualone, and nitromethaqualone) by their ultraviolet (UV), infrared (IR), nuclear magnetic resonance (NMR), and mass spectra. Thin-layer (TLC) and gas-liquid (GLC) chromatographic data are also presented.

Following extraction with chloroform from alkaline medium, identification of the different quinazolinone compounds can best be done by combined gas chromatography-mass spectrometry (GC-MS). While UV data only shows the presence of the quinazolinone nucleus, IR spectra provide sufficient details for individual identification despite the great similarity of the spectra. GC and TLC, which make probable identifications, have potential for isolation and purification prior to further analysis. NMR spectra allow quick identification provided there is sufficient pure product available for the determination (15 mg). (HSRI)

1976 17refs

UM-76-M0195

IDENTIFICATION OF DRUGS AND THEIR DERIVATIVES, D. R. Wilkinson; F. Pavlikowski; P. Jenson, Journal of Forensic Sciences v21 n3 p564-74 (Jul 1976)

This paper represents a brief review of traditional procedures for the analysis of confiscated drugs and the application of these procedures to the products formed after reductive fragmentation and halocarbon-acetylation of the drugs. The purpose of this investigation was to prepare reference spectra (ultraviolet spectroscopy (UV), infrared spectroscopy (IR) and to characterize the gas chromatographic (GC) behavior of the compounds; to develop drug derivatization procedures; to determine minimum pill quantities necessary for their complete analysis; and to develop proposals for the derivatization of other drugs for analysis.

Confiscated pills, already tentatively identified by some previous procedure as meperidine or propoxyphene, were analyzed by use of UV, IR, and GC. The same drugs were confirmed by analyzing the alcohols obtained after reductive fragmentation with lithium aluminum hydroxide as well as their derivatives formed by reaction with trichloroacetic and pentafluoroproprionic anhydrides. No procedures were specifically included to remove filler material, nor were microtechniques developed for the analysis of small amounts of material. The procedure described may be performed easily with approximately five confiscated pills. (ASM)

1976 9refs

UM-76-M0196

ANTEMORTEM CONVERSION OF CODEINE TO MORPHINE IN MAN, G. R. Nakamura; E. C. Griesemer; T. T. Noguchi, Journal of Forensic Sciences v21 n3 p518-24 (Jul 1976)

Forty-five drug overdose cases involving codeine were investigated. Concentrations of codeine and morphine were determined in blood, bile, liver, kidney, and urine. Ratios of codeine to morphine were compared for each of these specimens and evidence was developed that codeine was metabolized partially into morphine in the antemortem stage.

Morphine concentration was less than that of codeine in blood, liver, kidney, and urine. However, bile analyses showed that the amount of morphine exceeded that of codeine, suggesting a more active demethylation activity in the hepatic system than in the blood and other tissues studied. Controlled in

vitro studies showed that no codeine demethylation occurred in post-mortem tissues during cold storage for a period as long as 30 days. (AS)

1976 11refs

UM-76-M0197

A DESCRIPTIVE APPRECIATION OF MODERN LABORATORY INSTRUMENTATION USED FOR MEDICOLEGAL PURPOSES; WITH SPECIAL EMPHASIS ON GAS CHROMATOGRAPHY AND MASS SPECTROMETRY, B. S. Finkle, in Legal Medicine Annual: 1975, C. H. Wecht, ed., New York: Appleton-Century-Crofts, p67-81 (1976)

Forensic toxicological analyses, especially drug analyses, requiring rapid procedures, ultrasensitivity, qualitative specificity, and purity of separation can be achieved by integrated gas chromatograph-mass spectrometer-computer (GC-MS-COM) systems. The advent of relatively low-cost, production-model gas chromatograph-mass spectrometers (GC-MS) followed the introduction of the practical quadrupole mass filter and the all-glass jet separator. Thus, final and specific identification of unknown compounds utilizes the extraction and gas chromatographic characteristics of the compound in conjunction with its unique molecular fragmentation pattern.

The dedicated computer or interactive data system greatly extends the GC-MS capability for routine analyses. Computer-managed data collection with computer-assisted data manipulation and interpretation is complemented by established mass spectral libraries in dedicated or time-share computers. The flexibility of GC-MS-COM operation is illustrated by discussions of multiple ion detection-mass fragmentography, alternate methods of ionizing compounds in the mass spectrometer source, and quantitative analysis with GC-MS-COM. Despite its seemingly high cost, this powerful analytical tool is cost-effective when its quality, reliability, and operational aspects are considered. (HSRI)

1976 30refs

UM-73-M0198

RAPID DRUG ANALYSIS IN BIOLOGICAL SAMPLES BY GAS CHROMATOGRAPHY, R. F. Adams; J. E. Purcell; L. S. Eltro, American Laboratory v5 n5 p51-60 (May 1973)

A gas chromatographic system incorporating methodological advances was used to develop an integrated drug analysis procedure. The improvements discussed were sample treatment, solvent-free injection, the use of an additive to the carrier gas to reduce peak tailing, the use of dual columns and sample splitting for positive identification, and automatic data reduction by a gas chromatography (GC) data system.

The procedure was tested for a number of drugs, including barbiturates, methyprylon, glutethimide, meprobamate, amphetamine and methamphetamine, codeine, cocaine, methadone, promazine, clorpromazine, and morphine. GC characteristics of these and other drugs were reported for the system. Applications in drug analysis were presented and examples of typical GC chromatograms and computer print-outs were given. (HSRI)

1973 15refs

UM-76-M0199

SIMULATION OF BIOLOGICAL SYSTEMS: DISTRIBUTION OF DRUGS AND TRACERS, G. L. Atkins, Simulation v27 n4 p177-80 (Oct 1976)

Computer simulation of tracer and drug kinetics has been valuable in the areas of testing basic modelling assumptions, checking theoretical work, model validation and application, and designing and analyzing experiments. In modelling, simplifying concepts such as compartment homogeneity and linear kinetics must be tested. For example, there is no theoretical reason why kinetics should be linear; indeed, examples of non-linear relationships be-

tween concentration and rate have been reported. Other uses of computer simulation include predicting optimal dosing using known minimum and maximum effective drug concentrations and the investigation of numerical methods for the analysis of experiments.

Good data is essential for the successful modelling of tracer and drug kinetics experiments. Problems include limits on the number of samples which can be obtained from one subject and the lack of data precision. Often, data is inadequate for distinguishing between several similar models. Simulation is considered complementary to experimental work, and its continued application for the formulation and interpretation of experiments as well as the development of more complex models can be expected. (HSRI)

1976 19refs