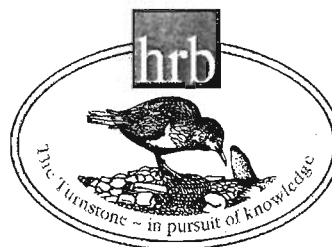


E.M.C.D.D.A.



**DRUG MISUSE RESEARCH DIVISION
HEALTH RESEARCH BOARD**

FINAL REPORT

Literature Review on the Relation between Drug Use, Impaired Driving and Traffic Accidents

CT.97.EP.14

Research Team: Colin Gemmell

Trinity College, Dublin

Rosalyn Moran

Drugs Misuse Research Division,
Health Research Board

James Crowley

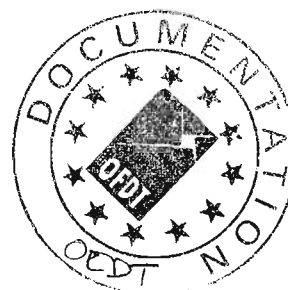
Professor, Transport Policy Research
Institute, University College Dublin

Richeal Courtney

Medical Expert, for the Health Research
Board

EMCDDA: Lucas Wiessing

February 1999



Please use the following citation:

European Monitoring Centre for Drugs and Drug Addiction. *Literature Review on the Relation between Drug Use, Impaired Driving and Traffic Accidents.* (CT.97.EP.14) Lisbon: EMCDDA, February 1999.

Contact Details

Drugs Misuse Research Division
Health Research Board
73 Lower Baggot Street
Dublin 2
Ireland

European Monitoring Centre for Drugs and Drug Addiction
Rua Cruz de Santa Apolónia 23/25
1100, Lisboa
Portugal.

Further copies of this report can be obtained from the EMCDDA at the above address.

This report presents findings from research conducted by the Health Research Board, Dublin, under contract for the European Monitoring Centre for Drugs and Drug Abuse (EMCDDA), Lisbon. It is accompanied by a second report, which provides an Annotated Bibliography addressing the *Relation between Drug Use, Impaired Driving and Traffic Accidents*.

We acknowledge gratefully the assistance given to the project by Irish and international members of a Collaboration Network which was formed for the project.

Contents

Credits	iii
Foreword	iv
Executive Summary	vi
1 METHODOLOGICAL ISSUES IN DETERMINING THE RELATIONSHIP BETWEEN DRUG CONSUMPTION, IMPAIRED DRIVING AND TRAFFIC ACCIDENTS	1
1.1 Introduction	1
1.2 Epidemiological Studies	1
1.3 Performance Tests	3
1.4 Simulation Techniques and 'Real' Driving	3
1.5 Problems with Experimental Studies	4
1.6 General Issues	6
1.7 Models of Driving Behaviour and Effect Models	6
1.8 Recent Proposals	7
1.9 Conclusion	10
2 EVIDENCE FROM EXPERIMENTAL AND FIELD STUDIES OF A RELATIONSHIP BETWEEN DRUG USE, DRIVING IMPAIRMENT AND TRAFFIC ACCIDENTS	12
2.1 Introduction	12
2.2 Alcohol	12
2.3 Methadone	14
2.3.1 Experimental Studies	15
2.3.2 Field Studies	17
2.3.3 Summary	18
2.4 Cannabis	18
2.4.1 Experimental Studies	19
2.4.2 Field Studies	21
2.4.3 Summary	23
2.5 Benzodiazepines (Anxiolytics and Hypnotics)	23
2.5.1 Experimental Studies	24
2.5.2 Field Studies	26
2.5.3 Summary	28
2.6 Antihistamines	30
2.6.1 Experimental Studies	30
2.6.2 Field Studies	31
2.6.3 Summary	32
2.7 Antidepressants	33
2.7.1 Experimental Studies	33
2.7.2 Field Studies	36
2.7.3 Summary	36
2.8 Amphetamines	37
2.8.1 Experimental Studies	38

2.8.2	Field Studies	38
2.8.3	Summary	40
2.9	Ecstasy, Other Synthetic Drugs and Diet Pills	40
2.9.1	Ecstasy	41
2.9.2	GHB	43
2.9.3	Ketamine	44
2.9.4	PCP	46
2.9.5	Fentanyl	47
2.9.6	Ephedrine and Phentermine	49
2.9.7	Summary	50
3	DESCRIPTION OF DRUG TESTING PROCEDURES IN THE CONTEXT OF DRIVING IN THE EU, ISSUES RAISED BY TESTING, AND ASSESSMENT OF THE CRITERIA USED OR PROPOSED IN RELATION TO THE SCIENTIFIC EVIDENCE	52
3.1	The Existing Situation in the European Union Countries	52
3.1.1	Belgium	52
3.1.2	Denmark	52
3.1.3	Austria	53
3.1.4	France	53
3.1.5	Sweden	53
3.1.6	Germany	54
3.1.7	Spain	54
3.1.8	Italy	54
3.1.9	Netherlands	54
3.1.10	Ireland	55
3.1.11	United Kingdom	55
3.1.12	Portugal	55
3.1.13	Luxembourg	56
3.1.14	Greece	56
3.1.15	Finland	56
3.1.16	Summary	56
3.2	Existing and Proposed Methods of Testing	57
3.3	Issues Involved in Testing for Drug Use	60
3.3.1	Mandatory Drug Testing	60
3.3.2	Warning Labels	62
3.4	The Possibility of Registering New Drugs	62
3.5	Towards a Unified Approach	62
	APPENDIX: Expert Workshop – Programme	65
	REFERENCES	66
	LIST OF TABLES	
	Table 1: Impairment ratings for acute effects of benzodiazepines	28
	Table 2: Impairment ratings for residual effects of benzodiazepines	29
	Table 3: Impairment ratings for various antihistamines	32
	Table 4: Impairment ratings for various antidepressants	37

CREDITS

Principal Researchers

Ms Rosalyn Moran, *Project Leader, Health Research Board*
Professor James Crowley, *Professor, Transport Policy Research Institute, UCD*
Dr Richeal Courtney, *Medical Expert, on behalf of the Health Research Board*

Research Assistants

Colin Gemmell (*Synthesis and Final Reports*)
Sarah Heywood (*Literature Search and Collaborative Network*)

For the EMCDDA

Lucas Wiessing

Collaborative Network (Ireland)

Dr Alan Baird, *Department of Pharmacology, University College Dublin*
Dr Bridin Brady, *The State Laboratory*
Dr Denis Cusack, *Medical Bureau of Road Safety, University College Dublin*
Professor James Heffron, *Department of Biochemistry, University College Cork*
Dr Alan Keenan, *Department of Pharmacology, University College Dublin*
Ms Pauline Leavy, *Medical Bureau of Road Safety, University College Dublin*
Inspector Brendan Mangan, *Garda National Traffic Policy Bureau*
Dr Anya Pierce, *Department of Toxicology, Beaumont Hospital Dublin*
Ms Mary O'Brien (*Health Research Board*)
Ms Siobhan Stokes, *The State Laboratory*

Collaborative Network (International)

Sr Javier Alvarez, *Universidad Valladolid, Spain*
Dr Rainer Christ, *Kuratorium für Verkehrssicherheit, Wien*
Mr Olaf Drummer, *Victoria Institute of Forensic Medicine, Australia*
Dr Reinhard Fous, *Bundespoliziedirektion, Wien*
Ms Sofia Freire, *Reitox Focal Point, Lisbon*
Mr Klaus Fuchs, *Council of Europe, Strasbourg*
Mr Johan de Gier, *University of Utrecht, The Netherlands*
Dr Sabine Haas, *Austrian Ministry of Health, Wien*
Mr A Aad Hage, *Ministry Verkeer en Waterstaat, The Netherlands*
Professor Ian Hindmarch, *University of Surrey, UK*
Professor Anna Kokkevi, *Reitox Focal Point, Greece*
Professor Hans Peter Krüger, *University of Würzburg, Germany*
Mr Hans Laurell, *National Road Administration, Borlänge, Sweden*
Prof Dr G Leroux-Roels, *Universiteit Gent, Belgium*
Dr John Oliver, *Glasgow University, UK*
Herr Andreas Pinzker, *Federal Ministry of Science and Transport, Wien*
Ms Inge Spruit, *Trimbos Institute, The Netherlands*
Ms Hilde van Lindt, *EU Commission, Brussels*
Dr Alain Verstraete, *Universiteit Gent, Belgium*
Mr Gilles Vincent, *EU Commission, Brussels*

FOREWORD

This review of the Literature on the Relation between Drug Use, Impaired Driving and Traffic Accidents was undertaken for the European Monitoring Centre for Drugs and Drug Addiction - EMCDDA, Lisbon. The health consequences of drug use are a priority area for the EMCDDA and impaired driving and road traffic accidents linked to drugs constitute an important topic on which comprehensive information is lacking.

There is increasing concern across the EU Member States about the role drug use may play in traffic accidents. This finds expression in different issues related to driving, for example the risks associated with late night driving and ecstasy/amphetamine use in dance and night club contexts, the implications for driving of methadone maintenance, or the consequences of the increasing levels of cannabis use reported in some countries. In a number of Member States a debate on drug testing of drivers, comparable to that already existing for alcohol, is gaining momentum.

The literature review addressed inter alia the relationship between different patterns of drug consumption, impaired driving and traffic accidents. In addition drug testing procedures and associated legislation regarding drug-impaired driving in the different EU Member States were described and the issues raised by such testing reviewed. The outcomes of the study included a scientific literature review and annotated bibliography on the relation between drug use, impaired driving and traffic accidents.

A multidisciplinary approach was considered essential in order to address the wide scope of the project. Accordingly a research consortium was formed which included scientists with expertise in the areas of drug abuse, psychology, driving behaviour, biomedical sciences, transportation and road safety. Additional expertise where required was contributed to the project through the Collaboration Network and Local Workshop – integral aspects of the methodology developed to achieve the aims of the project.

A Work Programme involving six work packages was developed for the project as follows

- Workpackage 1: Elaboration of Methodological Issues in determining the relationship between drug consumption, impaired driving and traffic accidents
- Workpackage 2: Investigation of Experimental and Laboratory Evidence of the effects of different drugs on driving skills
- Workpackage 3: Investigation of Evidence from Field Studies of a relation between drug use and traffic accidents
- Workpackage 4: Description of Drug Testing Procedures in the context of driving in the EU, and identification of issues raised by such testing
- Workpackage 5: Ongoing development of a Collaboration Network

- Workpackage 6: Fine tuning of the report material at a Local Workshop involving members of the Collaboration Network based in Ireland.

The project was carried out over the ten month period April 1998 to January 1999.

The literature review, which is the subject of this report, is presented in three main chapters. Chapter 1, based on Workpackage 1, discusses the methodological issues which arise in the literature in the area. Chapter 2, based on Workpackages 2 and 3, reviews the epidemiological and experimental evidence on the relation between various medicinal and illicit drugs and driving impairment. Chapter 3 outlines the situation in the Member States of the European Union regarding drug testing and discusses some recent proposals for screening. Workpackages 5 and 6 informed all three chapters of the report.

The second main outcome of this study – *An Inventory of Literature on the Relation between Drug Use, Impaired Driving and Traffic Accidents*¹ – is a compendium of annotated references, and is available as a separate report. The material was sourced from CD-ROM searches, libraries, web pages, professional organisations, government offices and individuals. The literature spans several disciplines including psychology, economics, medicine, forensic science, sociology, politics, law, addiction studies and transport studies and should be an important resource document for those interested in the drugs-driving issue.

We acknowledge gratefully the assistance given to the project by Irish and international members of a Collaboration Network which was formed for the project. Every effort has been made to reflect the current position of literature in the field in the report. We trust the outcome of the study will be of benefit to the work of the EMCDDA and to the community generally.

¹ European Monitoring Centre for Drugs and Drug Addiction. *An Inventory of Literature on the Relation between Drug Use, Impaired Driving and Traffic Accidents*. (CT.97.EP.14) Lisbon : EMCDDA, February 1999.

EXECUTIVE SUMMARY

There is increasing concern across the EU Member States about the role drug use may play in traffic accidents. This literature review addresses inter alia the relationship between different patterns of drug consumption, impaired driving and traffic accidents. In addition drug testing procedures and associated legislation regarding drug-impaired driving in the different EU Member States are described and the issues raised by such testing reviewed. An annotated bibliography on the relation between drug use, impaired driving and traffic accidents has been compiled and is available as a separate document².

This report is divided into three main sections. Chapter One covers the methodological issues which arise in studying a relationship between drug use and driving. Chapter Two discusses experimental and field evidence of a relationship between various medicinal, illicit and new synthetic drugs and driving impairment. Chapter Three outlines the situation in European Union countries regarding testing for drugs and discusses some recent proposals for screening. Some of the main issues and findings emerging from the review are presented in summary form below.

Some of the main issues discussed in Chapter One are as follows:

- Whilst the relationship between alcohol and driving has been the subject of intensive research for many years and clear results have emerged, the same is not true of other drugs.

Epidemiological studies

- It often remains unclear whether accidents occur as a direct result of medicinal drug consumption *per se* or as a result of the underlying reasons why the drugs were being taken.
- Data are often presented with no reference to a comparison group (for example, the prevalence of drugs in the remainder of the driving population).
- Drug traces found in crash victims are often mixed with alcohol and/or other drugs, hence making it difficult to isolate the effects of a single drug.
- The fact that drug traces may be discovered in the body does not necessarily imply that they were producing impairing effects in the user.

Performance tests

- Subjects tend to be young, healthy (and non drug-abusing) volunteers, and hence unrepresentative of the general driving population.
- The post drug-administration performance is likely to be different between healthy volunteers and real patients/abusers.
- Testing often occurs soon or immediately after drug administration, hence only acute effects are demonstrated when side-effects are greatest.

² European Monitoring Centre for Drugs and Drug Addiction. *An Inventory of Literature on the Relation between Drug Use, Impaired Driving and Traffic Accidents*. (CT.97.EP.14) Lisbon : EMCDDA, February 1999.

- Frequent use of small numbers of subjects which may result in a Type 2 error (i.e. the non-detection of existing effects and a lack of statistical power).
- Content validity problems (the extent to which the individual tests actually represent facets of real driving).
- Construct validity of tests: it is not always the case that tests measure what they are meant to measure.
- The development of a reliable and valid battery of powerfully predictive performance tests remains as much of a priority now as it has ever done.
- In addition, well-conceptualised theories and paradigms underpinning models of driving behaviour are still lacking and without these any isolated findings remain of limited use.

Simulation techniques and 'real' driving

- They are generally inadequate representations of real-life driving.
- No simulator is capable of representing every aspect of the driving act simultaneously.
- Artificiality of the situation may cause motivational changes which result in biased performances.
- It is generally the case that only the more automatic processes associated with driving such as lane positioning and distance negotiation can be studied since it would be unethical and dangerous to arrange for situations to be encountered with accident or crash potential.
- Ethical considerations also prevent the administration of high doses of drugs to subjects and therefore the results may not reflect the actual amounts used by drug abusers.

Models of driving behaviour

- Several models exist, although most are based on a hierarchical resources model, consisting of three levels:
 - The strategic level (general trip planning, route selection and risk assessment);
 - The tactical level (actual vehicle manoeuvring and involves overtaking, distance between vehicles, avoidance of obstacles);
 - The operational level (tracking and adjustment of speed, etc).
- Recent proposals put forward by the Institute for Human Psychopharmacology in the Netherlands (Vermeeren et al, 1993), are cited as a good and comprehensive solution to the methodological problems involved in this area.

In Chapter Two, the following conclusions are drawn regarding the weight of evidence surrounding the various drugs:

In the case of ***Alcohol:***

- Field studies have shown that, where involvement in traffic accidents is concerned, no drug or drug group has ever been found with a frequency that compares to that of alcohol.
- Most experimental studies have demonstrated impairment on one or several performance skills at one or more BAC's (blood alcohol content), with the majority of impairments beginning at BAC's at or below 0.07g/dl.

- Simulator and on-the-road experiments have generally shown alcohol to have deleterious effects on a range of driving skills including brake reaction time, 'collision' frequency, steering responsiveness and lane control, as well as the requisite cognitive skills such as risk-taking appreciation, decision making and planning.
- The causal effects of alcohol on impaired driving are well established to the extent where it has been possible to enact legislation for the use of alcohol by drivers based on a valid classification system. This is not the case for other drugs.
- The impairing effects of alcohol are generally potentiated by the presence of other drugs.

In the case of ***Methadone***:

- Experimental studies have suggested that, in *naïve* individuals, the effect of acute methadone administration is to produce a dose-dependent reduction in reaction time, in visual function and in information processing. Significant psychomotor impairments are seldom evident when *non-naïve* subjects have been tested however.
- Where new patients on a maintenance programme are concerned, the literature suggests that it is advisable to allow a period of up to a month during which they should not drive.
- Field studies have shown that, where body fluids have been examined for drug traces, narcotic analgesics [including methadone] have not featured prominently.
- In general the effects of the opioids are slight when compared to other drugs such as benzodiazepines.
- As is the case with numerous drugs, methadone can potentiate the deleterious effects of alcohol.
- Both experimental and field studies suggest that methadone use does not result in sufficient driving impairments to merit users being designated as 'unfit'; experimental studies would suggest that this is particularly the case with *non-naïve or experienced* users.

In the case of ***Cannabis***:

- Where experimental studies are concerned, although there is some conflicting evidence, cannabis does not seem to significantly impair very basic perceptual mechanisms.
- However cannabis does impair more subtle aspects of perceptual performance such as attention and short-term memory, although these are typically observed at higher doses.
- Most experimental studies have used fairly low doses of cannabis and this may not reflect the doses ingested by heavy marijuana users.
- Field studies have demonstrated that cannabis is one of the most prevalent drugs discovered in fluid samples taken from drivers. However, assessment of the causal role of cannabis in accident occurrence is complicated by the fact that alcohol is also present in the majority of samples.
- When mixed with alcohol, cannabis is much more likely to be a risk factor than when consumed alone.

In the case of ***Benzodiazepines***:

- Where experimental results are concerned there is often little consistency, even where similar doses are given before similar tasks. The sedating effects of the drugs may cause some impairments on psychomotor tests.
- Field studies reveal that benzodiazepines are the most frequently detected licit drugs in all driver populations.
- Some authors have concluded that using benzodiazepines approximately doubled the risk of motor vehicle accidents. In addition, the risk was higher for drivers older than sixty-five.
- In general, combining alcohol with benzodiazepines results in additive impairing effects on psychomotor performance.
- In general, some benzodiazepine tranquillisers may impair driving skills in the first few weeks of treatment, but effects may dissipate with continued use.

In the case of ***Antihistamines***:

- Experimental evidence suggests that peripherally active as opposed to centrally active antihistamines are less likely to cause impairing sedative effects.
- Some antihistamines which are slow to cross the blood brain barrier and thus produce tolerance without central effects, such as astemizole, and especially terfenadine, are likely to have little detrimental effect on skill performance.
- The centrally active first generation agents commonly cause greater performance decrements as compared with the newer, non-sedating second generation antihistamines.
- Since antihistamines vary in the extent of their impairing effects it is important that pharmacists in particular, as well as general practitioners, nurses and the public in general, are informed about the necessity of using the less sedating drugs available.
- Where field studies are concerned, antihistamines are seldom suggested as causative factors in traffic accidents. When antihistamine traces have been found in fluid samples, alcohol is often also present.
- Although there is some experimental evidence that antihistamines potentiate the effects of alcohol, field evidence suggests that alcohol is by far the greater danger.
- In general, the use of peripherally acting antihistamines is not likely to result in impaired driving performance.

In the case of ***Antidepressants***:

- Experimental investigations suggest that antidepressants can have both beneficial and detrimental effects on psychomotor performance.
- Experimental studies indicate that antidepressants may impair performance in healthy subjects taking the drugs for a week or more.
- Some studies suggest that patients' performance may actually improve as the result of the drugs relieving their depressive symptoms; more needs to be known about the effects of depression *per se* on driving abilities.
- There is no clear picture from field studies regarding the antidepressant levels in drivers responsible for accidents compared to the wider driving population.
- If possible, the less sedating drugs should be prescribed in preference to older more sedating drugs such as amitriptyline.
- There is little research available on the newer, less sedative antidepressants in relation to their effects (other than sedation) on psychomotor performance.

- The side effects of the most popular antidepressant, fluoxetine, such as nausea and insomnia, can themselves effect driving.
- Where alcohol is combined with antidepressants, especially the more sedative ones, the worst impairments are generally seen in the initial phase of treatment and diminish after prolonged treatment. Still alcohol is a bigger problem, and the effects of severe, untreated depression on driving capacities may be worse than the effects of antidepressants.

In the case of *Amphetamines*:

- Experimental studies suggest that at lower doses amphetamines have few effects on cognitive functioning, but at higher doses risk-taking increases and responses become inappropriate. Lower doses may actually result in an enhancement of some psychomotor tasks.
- Field evidence suggests that there is insufficient evidence to specifically implicate amphetamine use in traffic accidents, largely due to a lack of controlled studies.
- Only a few studies have directly examined alcohol-amphetamine interactions and the results are somewhat contradictory. In general, high doses of amphetamine are likely to increase the impairing effects of alcohol.
- In general therefore, there may be subjective positive stimulant effects associated with amphetamine use; however these same effects, especially at higher doses, could result in personality changes leading to an increased likelihood of impaired driving.

In the case of *Ecstasy and Other Synthetic Drugs* (GHB, Ketamine, PCP, Fentanyl, Ephedrine and Phentermine):

- It is evident from the comparatively sparse literature on MDMA and other synthetic drugs and driving that much more research is required in order to increase understanding of the impairing effects of this drug. At present, one must extrapolate from the few studies available on psychological effects to the driving act.
- In particular, most medical research has concentrated on the short-term effects of MDMA and little is known of its consequences following long-term usage.
- Ecstasy tablets are often comprised of numerous, potentially toxic constituents, the combined effects of which are largely unknown.
- Similarly, there is very little evidence concerning the specific effects of GHB, ketamine, PCP, fentanyl and abused diet drugs on driving abilities and in field studies they have not been frequently detected.
- Given the known side-effects of these drugs however and especially given the perception-altering effects of some of them, notably PCP and fentanyl, it is likely that they constitute a danger where driving is concerned.
- At present, much more experimental work needs to be carried out in order to elucidate the effects of all these drugs on mental and psychomotor performance.

In Chapter Three, the current situation in most EU countries is outlined as regards drug testing procedures, and the following general conclusions are drawn:

Existing situation in EU countries:

- All EC Member States have legal provisions for prohibiting driving under the influence (DUI) of psychotropic substances besides alcohol in their respective Traffic Codes. However there are no specific criteria related to the different types of drugs (licit or illicit), extent of drug use, or definition of an influence.
- Although EC Legislation gives limits for alcohol, no limits are given for drugs.
- Countries in the European Union have no laws defining illegal blood limits of illicit drugs or medicines. At present there is insufficient evidence to define safe levels where drugs other than alcohol are concerned.
- Since 1994, European pharmaceutical package inserts have had to include some statement concerning the potential deleterious effects of the drug on driving, although it may be some time before this policy is adopted for all types of medication .

Drug testing procedures:

- One possible method of drug testing is to give police forces expert training in roadside behavioural evaluation of suspects. Such a scheme has been established in the United States and is relatively inexpensive to set up.
- Standard drug testing of biological fluids generally consists of immunoassay screening followed by gas chromatographic-mass spectrometric (GS/MS) confirmation conducted on a urine sample.
- At present there are no roadside drug tests available. Drugwipe devices using sweat or saliva samples (Securetec, Ottobrun, Germany) have been developed which can test for cannabis, amphetamines, MDMA, methadone, benzodiazepines, cocaine, barbiturates and opiates.
- Several other tests are now available including Triage, Ezscreen, Accupinch, Mach IV, Verdict, Biosign and I.D. Block.
- Newer methods using sweat or saliva samples are potentially preferable because they are virtually non-invasive, fast, and easy to execute by non-scientists (e.g. police officers).
- Saliva-testing or "lollipop" technologies (Cozart Bioscience LTD, Oxfordshire) can detect cannabis, amphetamines, MDMA, cocaine, benzodiazepines and opiates. There is ongoing work concerned with establishing the sensitivity and specificity of many of these tests.
- Although some techniques have been examined which test hair samples, the consensus of opinion indicates that they are not reliably effective due to the inconsistent relationship between results and recent drug ingestion.

Conclusion:

- In general it is concluded that, whilst alcohol still remains the biggest problem on the roads, the lesser problem posed by other drugs is still important. However much more experimental and epidemiological investigation regarding the impact of other drugs is required.
- Additionally there still remains a need for a reliable and valid battery of psychomotor tests which can predict driving impairment. Beyond this, on-site drug testing technology must be further developed so as to produce rapid, accurate and cost-effective results. Allied to this, there is a need for police officers to be trained in drug-related impairment recognition.

Chapter One

Methodological Issues in Determining the Relationship Between Drug Consumption, Impaired Driving and Traffic Accidents

1.1 Introduction

It is estimated that at least 10% of all people killed or injured in traffic accidents are taking some type of psychotropic substance (medicinal or illicit) and these may be contributory factors to the accident (de Gier, 1993). Since 1987 there has been a fourfold increase in the number of drivers killed who have been found to have traces of illegal drugs in their bodily fluids (AA Report, 1997). To date however, there is still little evidence that medicinal drugs are *causally* related to traffic accidents; the percentage of drivers killed and who have traces of medicinal drugs in their systems has stayed at about 5% (AA Report, 1997).

This raises the obvious question of the relationship between drug consumption and driving impairment. Whilst the relationship between alcohol and driving has been the subject of intensive research for many years and clear results have emerged, the same is not true of other drugs. In a recent review of the psychological literature over the past 25 years on driving behaviour, Sivak (1997) found that out of the relevant 346 publications, 25% examined alcohol effects and 9% investigated drugs other than alcohol. In addition, the main methodological approach adopted in these studies were experimental (55%) and survey (12%).

Klebensberg (1988) assessed the situation thus:

"The state of current research into the problem of drugs and driving seems to have made little progress over the last few years. On the one hand, evidence of individual, highly specific drug effects is accumulating, while on the other hand, all attempts to make any more generally valid, universal statements have met with no success," (p.32).

This chapter will outline the main methods which have been used to investigate the putative relationship between drugs and driving impairments, and will describe the problems associated with each approach.

1.2 Epidemiological Studies

Epidemiological studies can generally be categorised into five approaches (Hildegard and Berghaus, 1998).

(1) In the case of *reanalyses of blood specimens positive for alcohol*, blood samples suspected of containing alcohol are additionally screened for both licit and illicit drugs, thus allowing a quantification of the extent to which alcohol users also use drugs. For example, Augsberger and Rivier (1997) reanalysed samples from DUI drivers and found that 15% of those samples contained benzodiazepines. One of the central problems with this type of approach is that the presence of the alcohol makes it almost impossible to separately assess the effects of the other drugs involved. In addition, the population under scrutiny is highly selective and is unlikely to be comparable to the wider driving population.

(2) *Screening of blood specimens of injured or killed drivers* allows an assessment to be made of the extent to which drivers involved in accidents were carrying medicinal or illegal drugs in their systems. The sample is usually obtained from hospitals and spans a particular time period. In general these studies are not able to separate samples from drivers responsible for an accident from samples from non-responsible drivers.

(3) In *roadside surveys*, drivers are stopped at a set place and time and asked to submit themselves to a drug test or a questionnaire. As Hildegard and Berghaus (1998) point out, such surveys can merely give a general overview of the frequencies of intake of substances in drivers. Therefore it is not possible to say anything about the performance-impairing risks of particular drugs or dosages.

(4) By using *retrospective analysis*, information can be acquired from drivers who were involved or not involved in accidents at some point in their past concerning their usage of drugs at the time and subsequently (see for example Smart, 1974). This method is one of the poorer ones since it relies on the integrity of the memory of those questioned and there is no objective way to verify information or to establish causality.

(5) Finally, in *analysis of drivers at fault*, blood samples of drivers responsible for an accident can be compared with either a control group of drivers with no accident history, or with drivers who were not responsible for an accident. The rationale behind this method is that some statement about the likely contributing influence of a drug towards an accident can be made if that drug is found more often among drivers responsible for an accident than in the other groups. For example, the Benzodiazepine/Driving Collaborative Group (1993) found no significant difference between a 'responsible' and a 'non-responsible' group of drivers with respect to their consumption of benzodiazepines once the effects of alcohol were allowed for. Hildegard and Berghaus (1998) conclude that this type of methodology "represent the best approach," (p.5).

In this area, epidemiological evidence is quite often inadequate when compared to the case of alcohol specifically, as it remains unclear whether accidents occur as a direct result of drug consumption *per se* or as a result of the underlying reasons why the drugs were being taken in the first place. It may well be the case, for example, that for most people taking prescribed drugs, their driving is actually safer due to the medication, for example schizophrenic patients taking antipsychotic drugs (Judd, 1985).

It is necessary therefore to investigate the possible interaction effects between a medical condition and the treatment medicine. One *fundamental* problem with many epidemiological studies is that the data are often presented with no reference to a comparison group (the prevalence of drugs in the remainder of the driving population), thus making interpretation of the results difficult at best. Mason and McBay (1984) make the point that, in order for epidemiological studies using fatality blood content results to be meaningful, figures need to be compared to (1) drug traces in the wider population of drivers, and (2) drivers in non-fatal accidents. It is extremely difficult to obtain blood samples from ordinary citizens in either of these groups, due to ethical and legal constraints.

Epidemiological approaches are primarily concerned with how prevalent a drug is in a population, and conversely, how large a proportion of drug users drawn from a random sample are involved in traffic accidents. Whether direct toxicological analysis or a questionnaire is used, it must be noted that the number of drivers involved in an accident (e.g. who were suspected of driving 'under the influence') is much larger than the rare cases which one would find if genuine random samples were drawn (Klebensberg, 1988).

A further practical consideration is that it is known that the rate of drug level increase is probably more relevant in terms of driving impairment than absolute levels detected hours after initial ingestion of a drug (Cosbey, 1986). There is also the problem that similar results are found in differing subject/patient cohorts such as suicide attempts and the acutely emotionally stressed (Sanders, 1986). In a recent meta-analysis of over two hundred epidemiological studies, Hildegard and Berghaus (1998) concluded that, "a valid estimation of the risk for road safety induced by medicines, based on the best methods, is hardly possible at present," (p.1).

1.3 Performance Tests

It is evident that determining the relationship between drug consumption and driving impairment is intrinsically fraught with difficulties. Other than epidemiological investigations, the other main approach is the experimental one. The standard laboratory approach to drug testing is to administer the drug of interest to the subject acutely or according to a regimen and subsequently measure performance on a behavioural task. These tasks generally include measures of short-term memory, tracking ability, decision/reaction time, perception, attention (sustained and divided), speed estimation and reactive loading.

Performance tests can be extremely inadequate in predicting real-life driving skills however and the standard laboratory tests may frequently be ecologically invalid ("woefully inadequate," O'Hanlon, 1988, p.71). Hindmarch (1980), after cataloguing a great number of laboratory psychomotor tests including auditory discrimination, perceptual learning and motor tests, concluded that as a whole the results could not justifiably be generalised to the driving act. A solid, reliable and valid battery of powerfully predictive performance tests remains as much of a priority now as it has ever done. In addition, well-conceptualised theories and paradigms underpinning models of driving behaviour are still lacking and without these any isolated findings remain of limited use. This is important because it is often the assumption in experimental studies that because one component of driving (e.g. vigilance) is impaired, that the driver will consequently be *generally* impaired because no interactions are assumed to occur between task components (Klebensberg, 1988).

1.4 Simulation Techniques and 'Real' Driving

One solution to the thorny issue of performance measurement is to use driving simulation tasks. This may include a computer interface, robotics or virtual reality applications. Generally simulators can be of two types (Irving, 1988): interactive (wherein the driver has control of the speed and the path of the vehicle), and non-interactive (wherein the driver is only capable of making decisions but cannot actually

control the vehicle). Sophisticated as such techniques have become however, they remain inadequate representations of real-life driving, especially in the domains of visual and vestibular integration. Moskowitz (1985) notes that no simulator is capable of representing every aspect of the driving act simultaneously, but only a subset of them, depending on the interest of the investigator and the sophistication of the technology.

Similar problems are encountered when 'real' driving tests such as closed-circuit driving and monitored driving on public highways are used to measure performance, especially because of motivational problems: it is a well established psychological phenomenon that when a subject is monitored, their performance improves due to increased vigilance, often to a level far above the norm (Sanders, 1986). The artificiality inherent in these studies may accordingly make the results of limited applicability.

Such 'real' on-the-road driving tests additionally often suffer from a lack of experimental control which can only exist in the laboratory, and from the previously mentioned theoretical gap between the procedures under scrutiny and actual, non-monitored driving. For example, it is generally the case that only the more automatic processes associated with driving such as lane positioning and distance negotiation can be studied since it would be unethical and dangerous to arrange for situations to be encountered with accident or crash potential. Ethical considerations also prevent the administration of high doses of drugs to subjects and therefore the results may not reflect the actual amounts used by drug abusers. Ultimately, many facets of driving behaviour are unobservable anyhow, a fact which highlights the demand for adequate theoretical models of the driving act.

1.5 Problems with Experimental Studies

Leaving aside the aforementioned problems associated with relating the experimental tasks to real-life driving, there are several other difficulties and inadequacies associated with such an approach.

One deficiency is that subjects tend to be young, healthy (and non drug-abusing) volunteers who are unlikely to be representative of the total driving population. The effects of a drug on female subjects may be confounded by hormonal changes engendered by phase of menstrual cycle, use of oral contraceptives and menopause (Dye, 1990). It also means that their post drug administration performance could be worse than the performance of real patients who take the medication in order to enhance their functioning. Other than this, there are non-trivial task measurement difficulties associated with individual differences. It can be problematic for example to quantify or operationalise such variables as mental health, motivation, fatigue and risk-taking all of which will undoubtedly effect the outcome of a task in addition to variables such as drug tolerance and physical fitness.

The influence of circadian rhythms and time of day also need to be taken into account. Even if it is possible to demonstrate the relevance of the task to actual driving, the real-life driving process is affected by other variables both environmental and vehicular as well as personal, which are virtually impossible to control for in the laboratory (Landauer, 1986). As regards the actual tasks themselves, the isolated

results from a simple task may not be useful in understanding how they are affected in a real-life situation where many competing demands may well be in operation.

Furthermore, it is generally the case that testing occurs soon or immediately after drug administration. The deficits in task performance therefore reflect the initial action of the drug when side-effects are greatest and not the long-term effects which are generally beneficial to the patient and when the side-effects have ceased. In contrast, some drugs, most notably LSD and MDMA, may have profound effects ('flashbacks') long after the drug has been eliminated from the system. Some of the stimulants including amphetamines, ecstasy and cocaine produce a sudden fatigue ('crash') after their effects have worn off. Such effects are difficult to simulate in the laboratory.

There are problems concerning the doses typically given in experimental situations. The dosage might be sub-therapeutic or even identical to the therapeutic dose, but ethical and legal problems make it difficult to administer doses greater than the recommended one, yet this prevents any understanding of the likely effects of such higher doses on the driving act. It should also be kept in mind that the same dose can have different effects in different subjects due to the individual differences already referred to. Many studies only report the effects of an acute dosage of a drug, which may be irrelevant to the vast number of individuals who have been taking drugs for a long duration.

A further problem concerns the conclusions drawn from a typical placebo-controlled investigation; if there is no difference between conditions it is not necessarily the case that the drug of interest is having no effect, and a second control using a drug known to cause impairment would need to be used.

A potentially serious problem results from the frequent use of small numbers of subjects. Hence a Type 2 error may occur, i.e. it may be concluded by an author that a drug has no impairing effects when in fact it does and this would have been determined if a greater number of subjects had been tested and a more reliable series of tests had been used. Vermeeren et al (1993) also point out that many studies suffer from a misuse of statistical tests, especially where violations of fundamental assumptions are concerned (e.g. parametric versus non-parametric tests).

A further issue which often makes it impossible to compare the effects of a drug from study to study is that data are generally not normalised or transformed to a common scale. Additionally, there are often content validity problems (the extent to which the individual tests actually represent facets of real driving). This is where relating tests to a model of driving behaviour is important, but in general this is not done. The same applies to the construct validity of tests: it is not always the case that tests measure what they are meant to measure.

Finally there is the additional problem of test-retest reliability; often authors do not state the relevant coefficient for their tests hence it is difficult to know if the same subjects would perform similarly on two or more separate occasions.

1.6 General Issues

Unlike the robust finding that there is a causal relationship between alcohol consumption and impaired driving, there is inconsistent evidence that other-drug blood levels and driving deficits are linked (Moskowitz, 1985). This is especially a problem for epidemiological studies.

The issue is further complicated by the fact that it is often impossible in field studies to separate legal from illegal drug use, although as Sherwood (1997) points out, distinct patterns often emerge when the two can be distinguished to the extent that the illicit use of drugs for sheer intoxication purposes could well be a major source of traffic accidents. In addition, it is often the case that drug traces found in crash victims are mixed with alcohol, thus making it problematic to discern the true contributing factor to the cause of the accident.

At a fundamental level, the fact that drug traces may be discovered in the body does not necessarily imply that they were producing effects in the user. This is often true of THC, the active metabolite in cannabis, which can be detected in bodily fluids for several days after initial use but which would no longer be functional. This is an important point especially as, when alcohol is not a factor, one of the most widely used drugs in field studies is cannabis.

In contrast, the observable effects of some psychoactive drugs may only be recognised once the drug blood level has returned to a very low level after initial uptake. A further complication is the multiple use of drugs which may act synergistically or antagonistically, hence rendering it difficult to quantify the contribution of each drug to behaviour. This is especially relevant to the drug habits in the new dance culture where it is common to 'mix and match'.

1.7 Models of Driving Behaviour and Effect Models

This is one of the major areas which has not been properly addressed in the vast number of studies on drugs and driving. Due to the complexity of the driving process, it is necessary to base experimental studies on a solid theoretical framework which distinguishes the various performance demands involved. Although several models exist including general information processing, processing-stage models, trait models, threat-avoidance and zero-risk models, (see Rothengatter (1997) for review), one very popular, if general model, is based on the classification system of Janssen (1979, cited in Sanders, 1986).

This assumes a hierarchical allocation of resources in which three stages are generally distinguished: the operational or control level, the tactical or manoeuvring level, and the strategic level. The strategic level includes general trip planning, route selection and risk assessment. The tactical level deals with actual vehicle manoeuvring and involves overtaking, distance between vehicles, avoidance of obstacles, and so forth. Finally the operational level includes aspects such as tracking and adjustment of speed. It is assumed that the tactical level is particularly resource-demanding in that it requires effortful processing and attention. Thus it is comparatively slow and inherently flexible. In contrast, the operational level is considered to be an automatic, routine process which is fast and relatively inflexible. Through practice, an increasing

number of driving processes are expected to operate at the lower, automatic level. It is notable that very few studies have been conducted which incorporate their performance tasks into such a model. It is consequently unclear at which levels or sublevels drugs are having their effect.

Klebensberg (1988) has suggested that one of the ways forward methodologically is the development of models for possible effect mechanisms. He postulates that four types of effect need to be differentiated: Type A effects are in the form of direct changes in the physiological conditions relating to efficiency, without however the subjects noticing and interpreting these effects (e.g. a deceleration of motor activity). Type B effects are in the form of direct changes in motivation (e.g. increase in subjective efficiency). Type C effects are secondary and in the form of indirect changes in motivation which are the result of the subjective interpretation of drug-induced changes in the physiological preconditions for achievement. Finally Type D effects are also secondary and in the form of indirect changes in achievement as a result of drug-induced changes in motivation (e.g. deterioration in the quality of achievement as a result of drug-induced euphoria).

It can be important in the assessment of a drug's effects for example to distinguish between Type A and Type D effects. In addition Klebensberg (1988) suggests that it is important to distinguish between primary effects of a drug (on the physiological level), secondary effects (on the perceptual level), and tertiary effects (on the cognitive and emotional levels). Again it is notable that very few studies relate their findings to this type of model.

1.8 Recent Proposals

In a recent report by the Institute for Human Psychopharmacology in the Netherlands (Vermeeren et al, 1993), thirteen precise methodological guidelines were proposed by an international panel of experts for experimental research on medicinal drugs affecting driving behaviour. Their recommendations are worth quoting in full as they provide an excellent comprehensive survey of the most important methodological issues described so far.

1) Regarding the problems associated with the use of young volunteers and the issue of male versus female subjects, it was proposed that:

"Subjects participating in drugs and driving studies should reflect a cross-section of the driving population and the target population of the drug for age and gender. Female subjects should provide assurance of reliable birth-control during the trial. Medical screening of female subjects should include a pregnancy test before beginning the trial. Medical screening of middle aged and elderly subjects should include additional blood and urine examinations, and resting ECGs."

2) Regarding the problems associated with the extensive use of healthy volunteers as opposed to real patients, it was proposed that:

"Healthy volunteers are generally the first choice for subjects. A healthy volunteer study should be followed up by a patient study when it is known or strongly suspected that healthy volunteers and ambulant patients would experience different drug reactions capable of influencing driving performance."

3) Where the issue of doses is concerned it was proposed that:

"Studies undertaken to demonstrate a new drug's effects on driving or skills related to driving for the first time, should involve at least two conditions with the drug's doses differing between them. The doses administered should be the lowest and highest to be given therapeutically, or in multiples of the therapeutic dose if there is only one. A drug should be tested in healthy volunteers in doses of 1x, 2x and 4x the standard therapeutic dose to establish a dose-effect curve, given evidence that the drug is well tolerated in such cases. A drug should be tested in the healthy elderly to determine its effects on driving performance or skills related to driving in sensitive patients."

4) Regarding duration of treatment it was proposed that:

"Studies of a particular drug's effect on driving and skills related to driving should generally involve multiple dosing lasting at least until the drug's plasma concentration has achieved steady-state, or until a therapeutic effect would have occurred in patients."

5) With reference to control groups or conditions it was proposed that:

"Studies undertaken to determine a drug's effects on driving or skills related to driving should generally include the following control conditions: (1) placebo, (2) an active control from the same therapeutic class or a verum (i.e. a 'standard' control, not necessarily from the same class). Studies including the use of a verum should preferably use one of the following: (1) ethanol sufficient to raise blood alcohol concentrations to 0.5 or 0.8 mg/ml., (2) diazepam 10mg."

6) Regarding sample size it was proposed that:

"The number of subjects employed in studies of drug effects on driving and skills related to driving should provide an acceptable balance between probabilities of Type 1 and Type 2 errors. The sample size in studies of drug effects on driving and skills related to driving should be determined by power calculations. In general, 18 or more subjects in a crossover design and more than 18/group in a parallel group design are deemed necessary for achieving a sufficient degree of statistical power."

7) Regarding the issues related to the experimental hypothesis it was proposed that:

"Investigators should state their hypothesis concerning a particular drug's effect on performance before applying statistical tests to the data. They should distinguish clearly between the following hypotheses: (1) the drug is assumed to have some adverse or beneficial effect on performance, (2) the drug is assumed, a priori, to have no effect that can influence performance in a practically relevant manner. Investigators aiming to demonstrate the presence of a drug effect should set the Type 1 error probability at $p < .05$. Results showing a mean drug-placebo difference with a lower p -value should be described as showing a significant drug effect. Investigators aiming to demonstrate the absence of a drug effect should set the Type 2 error probability at $p < .10$, or lower, by (a) defining a practically relevant mean drug-placebo difference, (b) performing power calculations, and (c) ensuring that the sample size is large enough to achieve that objective. Results that fail to achieve significance at the $p < .05$ level, while $p < .10$, can then be described as showing no practically relevant drug effects."

8) Concerning the selection of statistical tests it was proposed that:

"Investigators should state the reasons for the selection of statistical tests used to analyse the data. Studies determining the effects of a drug on driving performance or skills related to driving should employ the most powerful statistical test that can rightly be applied. Evidence should always be given to the effect that the tests' assumptions are not violated by the data. Investigators should indicate what measures they have taken to correct for alpha-inflation."

9) Regarding content validity it was proposed that:

"Performance test batteries applied for determining drug effects on driving should possess content validity in two dimensions. The test battery as a whole should provide measures covering: (1) a representative range of independent mental/behavioural functions relevant to driving, (2) as many independent pharmacological effects of the drug under study as possible. Studies determining a drug's effects on driving should always include a test to measure sedation or drowsiness as one of the drug's possible pharmacological effects. Investigators should always give arguments when they don't include tests to measure these pharmacological effects. Studies determining a drug's effects on driving should always include tests to determine whether the drug affects one of the following functions: divided attention or continuous perceptual-motor co-ordination. Investigators should always give arguments when they don't include tests to measure these functions. Besides the functions [previously mentioned], studies determining a drug's effects on driving should preferably include tests to measure as many as possible of the following mental/behavioural functions: (1) discrete responding, (2) speed and accuracy of decision making, (3) vigilance, (4) risk avoidance, (5) dynamic visual acuity, and (6) short-term memory."

10) Where construct validity is concerned it was proposed that:

"Individual performance tests applied to determining drug effects relevant to driving should possess construct validity in two dimensions. The test should be able to measure accurately: (1) a specified mental/behavioural response essential for driving, and (2) a specified pharmacological effect that could have an adverse effect on performance in any situation. Laboratory performance tests used in a categorisation procedure should first be validated by correlating drug induced changes in performance on the test with changes in actual driving performance."

11) Concerning test-retest reliability it was proposed that:

"Studies undertaken to be included in a drug dossier that will be used for categorisation or other legal/regulatory affairs pertaining to effects of drugs on driving or skills related to driving should possess the following: (1) either a test-retest reliability coefficient for raw scores measured in the absence of drug effects of $r =$ or $>.70$, or (2) a test-retest reliability coefficient for drug-placebo change scores of $r =$ or $>.50$ (preferable). Every reliability coefficient should be accompanied by a full description of the type of group on which it was determined."

12) Where the use of a common scale is concerned it was proposed that:

"The practical goal of standardising behavioural tests for drug screening purposes can not be achieved until the performance measures they yield are recorded on a common scale. Procedures for accomplishing this exist and should be applied by every investigator participating in research aimed at categorising the driving hazards of drugs. Investigators should know the population distribution parameters of tests

they commonly use. Investigators should share information on population distribution parameters of tests they commonly use with other investigators. This can be achieved by collecting all placebo data in a central repository, from which these data are generally available. Shifts in performance of one population standard deviation, or more, relative to placebo or baseline, should always be considered a large and relevant change in performance."

13) Finally, where simulators and on-the-road paradigms are used, the following proposal was made:

"Studies for establishing the driving hazard potential of a particular drug should proceed from conventional laboratory testing to sophisticated driving simulators and finally actual driving tests as far as they can be safely applied. The final evidence that therapeutic doses of the drug in question would be safe or hazardous to a specified degree should be based on the combined results of all tests in the programme. Tests that are to be included in a test program should be validated before their results are used for formal categorisation of drugs as presumably safe, minor, moderately or severely impairing. The most important factor in normal daily driving is the frequency of incorrect decisions, i.e. at traffic lights, when passing, merging and crossing an intersection. Simulator tests intended to determine drugs' effects on normal daily driving ability should therefore include tests of reactions to traffic signals, compliance with traffic control devices, passing manoeuvres and turning at intersections. Closed-course driving tests should involve decision making and response to changes in traffic control devices and manoeuvres involving interaction with other experimentally controlled vehicles. Over-the-road driving tests must be psychometrically sound and realistic, and include combined city and highway driving tests wherein fundamental aspects of the driver-vehicle-road interaction (e.g. road tracking, speed maintenance, car following, etc.) are objectively measured and subjectively rated by an accompanying driving expert."

1.9 Conclusion

Despite the methodological problems outlined in this section it is evident that the various approaches, when correctly executed, are the best available at the present time. Certainly there *are* many studies which fulfil most of the criteria described here and this is especially true of the more recent investigations. These studies will be discussed in this literature review.

In conclusion, any attempts to investigate the relationship between drugs and driving should answer as many of the following questions as possible (Starmer, 1985):

- 1) Does the drug have effects which may impair human skills performance?
- 2) If so, what is the nature of the toxic effects which occur?
- 3) Are these effects manifest at therapeutic dosage?
- 4) Do these effects occur in all or only certain individuals?
- 5) What conditions is the drug used to treat? (Can a case be advanced that the driver is safer with his medication than without it?)
- 6) Is the drug available only on medical prescription or can it be bought over the counter?
- 7) Is the drug used recreationally?

- 8) Does the drug interact adversely with other drugs or with alcohol?
- 9) To what extent is the drug used by the driving population?
- 10) Can the drug be detected in body fluids?
- 11) How often is the drug detected (or self-reported) in: (a) drivers apprehended by police? (b) drivers hospitalised after a crash? (c) autopsy samples from crash victims?
- 12) Is there reliable information linking plasma concentration with degree of impairment?
- 13) Is the drug representative of its class and are alternatives available?

Whilst few studies can lay claim to such comprehensive treatment of the issues involved, the foregoing does indicate the requirement for both experimental and epidemiological studies to be carried out with reference to each other. The caveats outlined here concerning methodological approaches should be kept in mind in the following section, which describes the evidence from both experimental and field studies of a relationship between a selection of widely-used drugs and driving impairment.

Chapter Two

Evidence from Experimental and Field Studies of a Relationship between Drug Use, Driving Impairment and Traffic Accidents

2.1 Introduction

In this chapter, evidence will be described from both experimental and epidemiological investigations concerning the relationship between drug use and driving impairment. Whilst the review cannot possibly cover the literally hundreds of studies which have been conducted over the years, it will concentrate on key studies and issues which have produced the most valuable data.

In general, studies have been selected which fulfil most of the methodological criteria outlined in the previous section. Where more work has been conducted on a particular drug (e.g. cannabis) than on another drug (e.g. ecstasy), this will be reflected in the number of studies referred to. Similarly, where a drug has been the subject of more experimental investigation as opposed to epidemiological analysis (e.g. antihistamine) or vice-versa (e.g. amphetamine), this will be reflected in the relative number of investigations described.

There is sometimes an overlap in the studies cited where epidemiological studies are concerned, so that the same investigation may be used to give information about the prevalence of different drugs. The review also represents a reasonably comprehensive coverage of international investigations, especially from Europe and America.

The choice of possible drugs to discuss, both licit and illicit, is extremely large. Whilst not every drug will be covered, the drugs selected for review (amphetamines (including metamphetamines), antidepressants, antihistamines, ecstasy (MDMA) and other new synthetic and diet drugs, benzodiazepines (anxiolytics and hypnotics), cannabis (THC) and methadone) are representative of both the drugs which have been the subject of the most intense research efforts as evidenced by the number of studies produced, and of the drugs which are presently of particular concern in regards to their potential deleterious effects on driving safety.

This is especially the case with ecstasy. In addition, a brief outline is given of the major findings of research on alcohol which have emerged from studies conducted over more than half the century. The other drugs will be compared to the particular case of alcohol throughout the review.

2.2 Alcohol

It is estimated that alcohol is involved in 19% of injurious accidents and 22% of fatal accidents in the European Union (Lillsund, 1998). The American National Highway Traffic Safety Administration (1994b) has estimated that 7% of all crashes and 44% of fatal crashes in 1993 involved alcohol use. That year approximately 17,500 people died and 289,000 were injured in alcohol-related traffic crashes. In 35% of all traffic

fatalities (13,984), the deaths had arisen from crashes in which at least one driver or nonoccupant had a blood alcohol content (BAC) of 0.10% or greater³.

High as these figures are, they actually represent a reduction compared to previous years. In a recent Australian study, Robertson and Drummer (1994) devised a method to examine the culpability of a driver in an accident based on the assumption that contributory drugs should be over-represented in a 'responsible-for-accident' sample. They analysed a sample of 341 driver fatalities for BAC and found alcohol to be over-represented in the culpable group ($p=.001$), with the over-representation rising rapidly as the BAC rose over 10%. This is a widely replicated finding.

Alcohol is detected in as many as 70% of single-vehicle crashes, but less so in multiple-vehicle accidents. Increased BAC's are associated with greater severity of injury. Remarkably, where involvement in traffic accidents is concerned, no drug or drug group has ever been found with a frequency that compares to that of alcohol (Simpson, 1987).

A recent review of the effects of alcohol on driving by Kerr and Hindmarch (1998) comprehensively assimilates what the current state of knowledge is. As regards measures of performance, typically measured in a laboratory setting, some of the most sensitive measures for alcohol impairment include divided attention performance (with impairment starting as low as 0.02g/dl), and tracking performance (Simpson, 1988). Another frequently used measure is that of reaction time, either simple or choice (both visual and auditory).

The general conclusion must be that alcohol slows reaction time, especially at moderate to low doses. This must be the conclusion despite some reports that modest doses (0.5 1g/kg) of alcohol have either little effect on reaction time (Fagan et al, 1987) or else actually improve it (Palva et al, 1979). As Kerr and Hindmarch (1998) point out, such contradictory results can only be expected given the widely established large degree of variation in response to alcohol both inter- and intra-individually.

Further sources of variance are produced by differing experimental measures, methods and doses used by investigators in different laboratories. This is a common source of contradiction which is endemic in a substantial amount of the literature concerning drugs and driving. It may of course be that in common with many other drugs, initial acute effects resulting from low doses produce an enhancing effect on performance, but this effect deteriorates rapidly after further consumption, especially as tasks become increasingly complex. Thus it is often seen in car driving studies (simulated or 'real') that drivers who have taken alcohol will concentrate on one aspect of the driving repertoire (e.g. staying in lane) to the detriment of other aspects which are at least equally important (e.g. speed control).

Simpson (1988), in a review of 177 studies on the issue of alcohol impairment, found that 158 had demonstrated impairment on one or several performance skills at one or more BAC's (the majority at BAC's at or below 0.07g/dl). Simulator and on-the-road

³ In this section, the measurement units described are taken directly from the original sources. In the interests of accuracy, it was thought that this would be preferable to converting the units to a common scale.

experiments have generally shown alcohol to have deleterious effects on a range of driving skills including brake reaction time, 'collision' frequency, steering responsiveness and lane control, as well as the requisite cognitive skills such as risk-taking appreciation, decision making and planning (see Kerr and Hindmarch, 1998 for review).

At or below BAC's of 0.05g/100ml, it can generally be said that driving impairments will be seen, with the effects becoming more apparent as the BAC increases. Certainly by 100 - 150g/100ml, there will be a marked loss of co-ordination and perception. 150 - 200g/100ml will be evident as drunkenness, by 200g/100ml, the 'passing out' stage occurs, and by 300g/100ml, the risk of poisoning is greatly increased. Concentrations of over 450/500g/100ml are likely to be fatal as a result of respiratory paralysis. The causal effects of alcohol on impaired driving are well established (Joscelyn and Donelson, 1978), to the extent where it has been possible to enact legislation for the use of alcohol by drivers based on a valid classification system (BAC 0.05 - 0.08% = risk curve begins to ascend; BAC > 0.08% = considerable risk increase for most drivers; BAC . 0.1% = definite increase in crash risk for all drivers; Klebelsberg, 1988). This is not the case for other drugs. In view of these figures it is unsurprising that a 'zero-limit' approach is often argued for.

It is also widely established that the impairing effects of alcohol are generally potentiated in a synergistic fashion by the presence of other drugs, although some may attenuate its effects or have little effect. In general, where sedative drugs such as some of the barbiturates and benzodiazepines are concerned, the combined effect with alcohol will produce dangerous additive effects. The addition of some, but not all antidepressants, antihistamines and stimulants will also vastly impair cognitive and psychomotor abilities beyond the single effect of the alcohol. Interestingly, such social drugs as caffeine and nicotine could neutralise the impairing effects of alcohol (Michel and Battig, 1989), although, as is often the case, there are contradictory results and more work needs to be done to clarify this issue.

2.3 Methadone

Methadone has become the drug of choice for the treatment of heroin/morphine withdrawal because it mimics many of its actions including its analgesic properties (5 - 15mg). It has a long half-life (1 to 1.5 days). Individuals on methadone maintenance programmes generally take a daily dose of 60 - 80mg (but this can vary from 30 - 120mg). Its effects are such that heroin or morphine addicts are often able to resume 'normal life', which can include driving cars. Tolerance develops to the extent that if heroin abuse is attempted again the dose is usually insufficient to surmount the methadone tolerance (Chesher, 1989).

A recent report on drugs, other than alcohol, and driving in the European Union (de Gier, 1995), stated that the incidence of known narcotic analgesic abuse among drivers in traffic accidents was in Denmark (1993 survey): 4 cases; Spain (1992 survey): 1.4% of 289 cases; UK (1995 survey): 0.05%; and Italy (1978-1989 survey): 3.5% of cases. In the UK the number of heroin addicts has increased four-fold between 1980 and 1994, and also the proportion of these on methadone maintenance has risen from approximately 50% in 1988 to 70% in 1993 (Alberry et al, 1998).

2.3.1 *Methadone Experimental Studies*

It is known that methadone can have impairing effects on subjective mood and this theoretically could lead to performance skill deficits, at least in non-tolerant subjects (Chesher, 1989). However this hypothesis is seldom supported. For example, Kelley et al (1978) tested thirty methadone-maintenance patients (mean dose 63mg) on tests of distance perception, variable reaction time, auditory threshold, attention span, digit span and time perception. They found that the cognitive, perceptual and perceptual-motor capacities of these patients remained relatively stable throughout the duration of the experiment, although there was a small, but significant impairment in the distance perception test. This however may not be true of distances greater than those tested in the laboratory.

Rothenberg et al (1980,a,b) examined the effects of acute doses of methadone (5 or 10mg) on naive subjects. They found that methadone caused specific impairments in smooth pursuit performance, depressing the gain of horizontal tracking movements. Although this is of relevance to driving, the effects may alter with increased tolerance as would be the case with methadone-maintenance individuals.

Moskowitz and Robinson (1985) investigated the effects of methadone on tracking performance, of potential relevance to driving. In one experiment, 12 patients on methadone maintenance (60 - 100mg/day) were compared to 12 ex-heroin addicts not on maintenance on both a compensatory and a pursuit tracking task. No significant differences were found between the groups: both groups exhibited normal performance. In order to control for the possibility that subjects had compensated for their performance, a further tracking task of increasing difficulty was used with two more groups. Again performance was normal in both groups.

These results suggest that methadone users should not be considered 'impaired' in their driving abilities. Note how this contrasts with the Rothenberg et al (1980,a,b) studies mentioned above. This illustrates the apparent contradictions which often appear in the literature due to differences in methodology, dosage rates, and experimental design.

In a complementary study, Robinson and Moskowitz (1985) examined methadone influence on visual functioning, concentrating on acuity, accommodation, peripheral vision and attentional allocation. Fifteen methadone-maintenance patients (60 - 80mg/day) were compared to a control group of ex-heroin addicts. Both groups were found to perform normally, even two hours later when the drug should have reached maximum effect. A second experiment tested more specific aspects of skilled performance, including visual search rate and rate of information processing. No significant differences were found in the visual search rate task or in information processing, however the methadone group did require a greater time interval to transfer information from immediate to long-term memory. This effect is however unlikely to be of significant importance in a real-life driving situation.

Interestingly, methadone has even been shown to *improve* some aspects of performance skills, for example reaction times (Gordon, 1970; Rothenberg et al, 1977), although this contrasts with other studies (e.g. Moskowitz and Robinson, 1985). Gordon (1970) in a much-cited study, found that methadone patients actually demonstrated shorter reaction times across a series of three tasks compared to

appropriate controls. They concluded that this was not due to a faster motor response but to faster information processing, stemming perhaps from increased arousal or motivation in the methadone users. Subsequently Rothenberg et al (1977) compared twelve methadone users (on 20 - 70mg/day) with a naive control group on two tasks, (a vigilance task and a reaction time task) which also included an offer of monetary reward for good performance to investigate the motivation hypothesis. Subjects were tested before and 2.25 hours after placebo, 5, or 10mg methadone. Again they found that addicts had faster reaction times and missed fewer responses than controls, even after additional doses.

In contrast control subjects demonstrated a dose-dependent slowing of reaction times following methadone administration. In the vigilance task, there were no differences found between the groups pre-drug administration but in the post-phase the addicts improved relative to the pre-phase whereas the opposite was true of control subjects. In terms of the hypotheses originally proposed by Gordon (1970), the fact that there were no pre-phase differences in the vigilance task implies that the reaction time differences cannot be attributed to attentional differences. In addition, motivation is unlikely to be the explanation for the faster reaction times in the methadone group since the monetary reward was the same for both groups. Although the precise explanation for this phenomenon remains unclear, it is likely that it reflects the differences between the tolerance of the addict group (therefore the additional doses had no effect), and the effects of methadone on the naive controls.

In Germany, it is the case that every drug addict is deemed unfit to drive, including those on methadone maintenance. In contrast the weight of experimental evidence suggests that impairments among such individuals are only slight. Accordingly, Berghaus et al (1993) set out to investigate two issues: (1) can methadone patients be considered as a homogeneous group especially with respect to additional drug consumption? and (2) what is their performance like on tasks other than vehicle handling skills, such as perception of traffic situations, risk-taking, risk cognition, complex performance tasks and personality traits?

The authors compared methadone patients with appropriate naive controls on personality and risk-taking questionnaires, and tests of short-term memory, tracking, decision and reaction behaviour, perception, sustained attention, speed estimation, peripheral attention with a simultaneous central task, and reactive loading. They found that the methadone patients differed from controls on several personality variables, including heightened sensitivity and emotionality, and a poorer degree of check on themselves and of accident avoidance. The patients also yielded poorer results on all of the psychomotor tests. Many methadone patients had to be excluded from this experiment due to their usage of other drugs, therefore the authors concluded that methadone users in Germany are not a homogeneous group – they can be separated into those who use methadone only and those who combine it with other drugs. The outcome of the testing for the remaining patients (i.e. those taking methadone only) suggests that they were indeed unfit to drive. The authors explain the discrepancy between their results and those from other studies in terms of their patient selection procedure in that other studies may have positively selected ‘better’ methadone patients (perhaps stabilised) who would be less likely to differ from controls.

Interestingly, a similar conclusion has been reached by Staak et al (1993). When they compared thirteen methadone-maintenance patients with control subjects, they found that the methadone patients were impaired on tests of tracking, short-term memory, decision and reaction time, perception, sustained attention, speed estimation, peripheral attention and reactive loading. They noted that when six very good methadone taking patients were tested, the differences dissipated but that personality parameters, as assessed by personality inventories, remained different. They conclude that, "driver fitness of the very few optimal patients depends on the amount of the personality disorders." However one problem with these studies is that the subjects may have either been undergoing detoxification *or* being maintained on methadone. This may account for the discrepancy between these results and those from other studies (Alberry et al, 1998).

Berghaus and Friedel (1994) examined ten studies of driving aptitude amongst methadone-maintenance patients and concluded that in the majority, patients did not differ from controls in measures of psychomotor performance. Again this suggests that such maintenance patients, given that they do not ingest other psychoactive drugs, should not be considered unfit to drive. A similar conclusion has been reached by Kubitzki (1992/3). They gave twenty-two methadone patients doses of methadone ranging from 14 to 120mg and compared them to controls on psychomotor tests tapping reaction time, cognitive perceptual speed and peripheral perception. He found no significant differences between the two groups.

2.3.2 Methadone Field Studies

Starmer (1986) asserts that, where body fluids have been examined for drug traces, "narcotic analgesics [including methadone] have not featured prominently," (p.265). Reviewing other epidemiological studies of traffic fatalities, he concludes that narcotic analgesics have not been found in sufficient numbers to cause concern. For example, an early study by Blomberg and Preusser (1974) found no differences between methadone patients and control drivers in terms of the frequency of their involvement in traffic accidents including those which caused injury or death.

Maddux et al (1977) compared the driving records of 104 former heroin users in Texas during one year of heroin use before admission to methadone maintenance, with their records during one year after admission while they were being maintained on methadone. Whilst they found that the number of convictions for speeding had significantly increased from the year on heroin to the year on methadone, there was no change in convictions for negligent collision, other moving violations, driving without a licence or in number of accidents. However, the frequency with which the drivers were involved in accidents was not significantly different from that of all Texas licensed drivers. The authors suggest that the increase in speeding convictions amongst methadone users may be a function of the possibility that heroin users drive more carefully in order to evade arrest. They further conclude that methadone users should not be restricted in their driving on the basis of these findings.

Nielsen et al (1989), in a review of the prevalence of analgesics and benzodiazepines in traffic accidents, noted that it was a common conclusion that methadone use is only dangerous in traffic until the user has become adjusted to a regular dosage. Similarly, Christensen et al (1990) analysed 461 records in Denmark. Of the 180 cases in which

an accident had occurred, antidepressants and benzodiazepines were represented above the mean, whereas opioids were not. They suggest therefore that opioids do not necessarily make driving dangerous (a common hypothesis), unlike the other drugs examined. This may be because of increased tolerance for opioids and a compensating increase in attention by the users.

In a U.S. National Transportation Safety Board study (1990) of 157 fatal-to-the-driver heavy truck crashes, only in one case was a driver's blood found to contain an opiate compound, and he also tested positive for chlorpheniramine, one of the antihistamines. Budd et al (1989) also found only a single case of opiate consumption in a sample of 600 fatally injured drivers in Los Angeles County and stated that this was probably a legitimate therapeutic dose. This was found to correlate well with the results from four other epidemiological studies from both the USA and Canada.

Augsburger and Rivier (1997) examined the driving records of 641 drivers suspected of driving under the influence of drugs (DUID) in Canton de Vaud. They found that methadone was present in 10% of samples. However, the majority of all cases contained two or more drugs and this was particularly true for the methadone samples.

2.3.3 Summary

In a major report from the Institute for Drugs, Safety and Behaviour in the Netherlands (Wolschrijn et al, 1991), two experts rated methadone impairment at a dose of 2.5-10mg as 'moderate'. Thus at least some degree of caution is evidently warranted where this drug is concerned. Chesher (1989) suggests that the literature warrants the following general conclusions: (i) in naive individuals, the effect of acute methadone administration is to produce a dose-dependent reduction in reaction time, in visual acuity and in information processing; (ii) with new patients on a maintenance programme it is advisable to suggest a period of up to a month during which they should not drive. Once established on the programme there is insufficient evidence to consider them as impaired where driving is concerned; (iii) in general the effects of the opioids are slight when compared to other drugs such as benzodiazepines. This may be because the opioids only act upon opioid receptor cells which are presumably not as important for motor skills as are the benzodiazepines receptor-bearing cells.

In general then the weight of the evidence reviewed suggests that methadone use does not result in sufficient driving impairments to merit *non-naïve* users being designated as 'unfit'. However, one gap in the literature on methadone, as Alberry et al (1998) note, is that no assessment of the population of methadone patients driving, and their frequency of driving, has been made.

2.4 Cannabis

The primary active ingredient of cannabis is THC (delta-9-tetrahydrocannabinol) and, depending on dose and the individual, effects can include those of stimulants, sedatives, analgesics and hallucinogens. Most often it is inhaled, with the first psychological symptoms becoming noticeable after 5 - 10 minutes. Peak effects may occur after 30 minutes and the duration of action of one cigarette can be in the region

of 2 to 3 hours. Effects are slower if the drug is orally ingested. The issues of tolerance, dependency, and side-effects are still disputed, but the most common physiological side-effects are cardiovascular and respiratory. Some have suggested a link between cannabis use and schizophrenia (WHO Report, 1996) As this section will outline, many investigators have found dose-dependent impairments in several cognitive and psychomotor skills. The case of cannabis has become even more relevant in recent times because of the proposed therapeutic effects of cannabis for conditions such as multiple sclerosis and chemotherapy sickness, however a recent report by the Royal Pharmaceutical Society of Great Britain (1998) concluded that, "the evidence for the medical efficacy of cannabis for all the putative indications is based on anecdote, case reports or relatively small studies. [However] overall, the body of evidence, although small, points to efficacy of cannabinoids and the need to encourage research," (p.9-10).

In a recent report on drugs other than alcohol and driving in the European Union (de Gier et al, 1995), it was stated that the incidence of known cannabis abuse among drivers involved in traffic accidents was, in Denmark (1993 survey): 1 case; Spain (1992 survey): 1.4% of 289 cases; UK (1995 survey): 4.0%; and Italy (1994 survey): 5.5% of 200 cases.

2.4.1 Cannabis Experimental Studies

Manno et al (1971) examined pursuit tracking performance in twelve subjects who were given four levels of THC dosage (0, 5 and 10mg). Pursuit tracking involves seeing the object being tracked as well as the tracking mechanism. They found that both high and low doses produced performance deficits at all levels of the task complexity. However, the task chosen may not necessarily be of absolute relevance to car driving. Sharma and Moskowitz (1975) used a compensatory tracking task which is probably more relevant to the actual driving process since it involves the subject trying to keep a stimulus in a particular place despite the presence of displacing movements. They found that subjects taking THC (200mcg/kg) were impaired on this task over the entire duration of the experiment. Thus it appears that cannabis, across a range of doses and durations, does impair tracking ability. This suggests that it may be attentional processes which are primarily effected.

In a simulator study conducted by Rafaelsen et al (1973) using eight subjects receiving either 70gm alcohol or 8, 12 and 16mg THC, it was found that both alcohol and THC had an effect on latency of response in stopping the 'car' when a red light occurred. The impairment was especially remarkable at the higher THC doses with alcohol producing a midway effect. However THC had no effect on gear changing (unlike alcohol). Apparently it was the perceptual aspects of the task which were primarily affected.

Kvalseth (1977) investigated simple and complex reaction time in six cannabis users at dose levels of 0, 6.5, and between 19.5 and 26.0mg (THC). The subjects had to press a button to respond to a variety of presented visual stimuli. It was found that THC had no effect on simple reaction time and there was no relationship between THC dose level and performance as the complexity and information processing demands of the task increased. This finding is fairly robust especially where simple reaction time is concerned. For example in another study of the effects of practice on

reaction time conducted by Peeke et al (1976), it was found that a practised reaction time test was virtually insensitive to THC effects whereas the unpractised version is sensitive. They suggest that it is the automatic nature of the well-practised task which renders it insensitive to THC effects, whereas it is the attentional demands of the unpractised version which is primarily impaired by the drug. This is an opinion also shared by Moskowitz (1985).

Smiley et al (1981) used a sophisticated simulator and experimental design with thirty-five subjects. They found that cannabis increased variability of velocity and position whilst negotiating curves, and of headway and lateral position while following curves. There was also a decrease in turn-offs taken in response to traffic signs and a reaction time increase to lights requiring responses. Analysis of the tracking demands of the task also revealed that cannabis caused more crashes at high doses. Similar results have been reported by Dott (1972), and are in general agreement with studies which have used real cars for testing (e.g. Attwood et al, 1980). As such the results imply that cannabis does impair car handling performance, although it should be kept in mind that such tasks inherently underestimate the true complexities of real-life driving.

Due to the common epidemiological finding that cannabis is often ingested with alcohol also present, some studies have examined the interaction between the two drugs. For example Chesher et al (1976) gave twelve subjects either a placebo alone, cannabis alone (10mg/70kg), alcohol alone (0.54gm/kg) or alcohol plus cannabis. They found that the combination of drugs produced impairments in standing steadiness, manual dexterity and perceptual speed. However the drugs taken alone had little effect. The interaction was considered to be additive. Again this is a common finding and points to the fact that ingestion of alcohol and cannabis together produces impairments which are greater than the effects of either ingested alone.

In an interesting series of studies conducted by Robbe (1995/96), the effects of cannabis on actual driving performance were examined. In the first study, on a road closed to other traffic, twenty-four subjects were given either THC 100, 200 or 300mcg/kg, or placebo. In a 22 kilometre road tracking task (beginning 30 and 90 minutes after smoking), it was found that their lateral position variability significantly increased after each dose relative to placebo in a dose-dependent manner, for up to two hours after ingestion. In the second study, (with other traffic present), sixteen subjects were given similar doses and performed a 64 kilometre tracking task both preceded and followed by car following tasks.

The results were similar to those from the first test, except that the car following was only slightly impaired. In the third and final study, (in high-density urban traffic), another group of sixteen subjects given either THC 100mcg/kg and placebo, or alcohol (mean BAC .034g/%) and placebo, it was found that the alcohol impaired performance, but this was not evident to the subjects themselves. In contrast, THC did not impair performance yet subjects considered that it had. Robbe concluded that THC in single doses up to 300mcg/kg has significant but not dramatic effects on driving performance.

Mathias (1996) cites a study by Heishman which aimed at separating the effects of alcohol from THC on the functional components of driving. He gave subjects a

cannabis cigarette (containing either 0, 1.8 or 3.6% THC) and then another one 10 minutes later. After 20 minutes it was found that subjects were impaired in their ability to stand on one leg for 30 seconds or touch their finger to their nose. Balance became much worse where the higher doses were concerned.

Pope et al (1995) reviewed the literature on cannabis and driving looking especially for evidence regarding the residual effects of the drug. They found that the data support a 'drug residue' effect on attention, psychomotor skills and short-term memory during the 12 - 24 hour period immediately after ingestion, but evidence is still lacking to support or refute a more prolonged residual effect. In addition, Schmidt et al (1995), in a review of 150 simulator and actual driving studies, found that the results in general show that cannabis doses between 1, 4 and 22.5mg produced a subjective 'high' and that driving impairments were revealed within 2 hours of ingestion. However they also note that extended effects have only been found in flying simulator tasks wherein the complexity of the tests are very high.

2.4.2 Cannabis Field Studies

Epidemiological studies of alcohol involvement in impaired driving have worked because there is an approximately 97% compliance rate with being asked to give a breath sample and because these samples are highly correlated with the degree of impairment. The same does not hold for epidemiological studies of THC however since *blood* must be sampled and there is typically only a 50-75% compliance rate (Moskowitz, 1985). Here we note again that many studies lack an appropriate control group. Also, there is little correlation between THC blood concentration and degree of impairment largely because psychomotor impairments typically occur one hour after smoking when the blood THC content is very low. Therefore a negative THC finding does not necessarily indicate that THC was not involved in an accident genesis (Moskowitz, 1985).

Reeve (1979) found that 285 (15.9%) blood samples from 1792 Californian drivers arrested for impaired driving contained THC greater than 5.0mcg/l, although 111 of these also contained alcohol. However the authors do not state how many drivers would not give a blood sample but did offer a breath or urine sample, as the law allows in California (Moskowitz, 1985). Interpretation is therefore difficult. Mason and McBay (1984) heavily criticise this study on methodological grounds and state that it is "doubtful" if it provides any useful data. Smart (1974) examined cannabis and accident probability through the use of self-report questionnaires. He found that cannabis users have almost as many accidents under its influence as they do when under the influence of alcohol. The value of this is limited however because it is difficult to show a relationship between cannabis consumption and accidents especially as this method relies on the validity of the individual's subjective recall of previous events.

Owens et al (1983) examined the blood specimens of 169 dead drivers following traffic accidents. They detected no opiate, amphetamine or phencyclidine in any specimen, but did find THC (5.9%), barbiturate (5.3%) and cocaine (0.6%), although alcohol was also present in the majority of cases. In contrast 66.9% contained ethanol. The very low number of cases of drugs other than alcohol lead the authors to conclude: "Diverting attention from the many alcohol influenced drivers to the few

who might be influenced by other drugs most probably would be counterproductive to highway safety," (p.378). This conclusion was repeated by Mason and McBay (1984). They analysed blood samples from 600 drivers killed in single-vehicle crashes in North Carolina between 1978 and 1981. They again found that ethanol detection was far greater (79.3%) than THC (7.8%), methaqualone (6.2%) and barbiturates (3.0%). These non-ethanol traces contained concentrations which were within or below therapeutic/active ranges. Other drugs were either not detected or only rarely (for example no amphetamine traces were found and traces of PCP were rare). Of those samples containing drugs, alcohol was also found, and non-alcohol multiple drug use was rare. They conclude that, "Ethanol was the only drug tested for that appears to have a significantly adverse effect on driving safety," (p.987). This highlights the difference between conclusions reached from experimental studies and those from field approaches.

McBay and Owens (1981) studied specimens from 100 North Carolina car drivers involved in single vehicle crashes. They found THC present in 9 of these, but in 6 of these, alcohol was also present. Again because no data concerning THC extent in the at-risk population was given, the results may or may not be an overrepresentation of the situation. Williams et al (1985), in a survey of 440 young Californian drivers killed at the wheel, found that 37% of the sample had THC traceable in their systems. The role of cannabis in crash responsibility could not be determined.

A similar finding occurred in a study conducted of 641 drivers conducted by Augsberger and Rivier (1996): in the majority of cases two substances were found, one of them generally being alcohol, although THC alone was detected in 109 cases. However, Warren et al (1981) had previously found that a higher percentage of drivers responsible for crashes were found among drivers in whom cannabis was present than among drug-free drivers.

In one of the few prospective studies on the subject, Soderstrom et al (1988) examined specimens from 1023 vehicular and non-vehicular accidents. They found that THC activity of 2ng/ml or more was detected in 34.7% of samples, although there was no difference between the two groups. They additionally found that use of cannabis and alcohol in combination (16.5%) was highly significant compared with cannabis alone (18.3%), alcohol alone (16.1%) or neither drug (49.1%). Alcohol was used more than other drugs by the victims of vehicular trauma.

In a U.S. National Transportation Safety Board study (1990) of 164 fatal-to-the-driver heavy truck crashes, THC was found to be in the bodies of 21 drivers (12.8%). This was identical to the number of cases involving alcohol. Nahas and Latour (1992) in a study of 120 blood and urine samples from victims of French traffic accidents, found that 14% contained cannabis, 10% benzodiazepines and 1% opiates. Again the highest frequency was for alcohol (36%). Heishman (1996) reports that from 6 to 12% of non-fatally injured drivers and 4 to 16% of fatally injured drivers had THC in their systems. Again it is noted however that most of these samples contained alcohol, hence making it difficult to single out the contribution of THC alone. In a U.S. study, Brookoff et al (1994) tested 150 samples taken from drivers stopped for reckless driving. Of these 13% contained cocaine, 33% cannabis, and 12% both drugs.

Recently, in an interim report published by the Department of the Environment in the UK (1998), it was found that in a sample of 619 road user fatalities, the drug most frequently detected was cannabis, but the usual problems apply when trying to estimate the true role of this drug in accident causation. The prevalence of cannabis however indicates that there has been a significant increase in the number of users killed in traffic accidents. The authors conclude that alcohol is still a much larger problem than that represented by drugs.

2.4.3 Summary

Whilst cannabis does not seem to significantly impair basic visual transducing or sensory transmission mechanisms, it does impair other aspects of perceptual performance such as vigilance tasks and signal detection tasks, although these are typically observed at higher doses (Moskowitz, 1985). One thing that is not often made clear is whether impairment is maintained for tolerant individuals taking low cannabis doses or whether increasing dosage has an additive impairing effect on both naive and tolerant users (Alberry, 1998).

Taking both the laboratory and epidemiological evidence together, the conclusion reached by the World Health Organisation (1996) is probably justified:

"There is sufficient consistency and coherence in the evidence from experimental studies and studies of cannabinoid levels among accident victims to conclude that there is an increased risk of motor vehicle accidents among persons who drive when intoxicated with cannabis... This risk is magnified when cannabis is combined with intoxicating doses of alcohol ..." (p.15).

In summary, the evidence points clearly to the fact that cannabis causes impairments in several psychomotor abilities especially tracking, perceptual abilities, vigilance, co-ordination and driving skills as assessed by both simulator and on-the-road methodologies. However it should be noted that most studies, for obvious reasons, have used fairly low doses of cannabis and this may not reflect the doses ingested by real cannabis users. Mathias (1996) recommends that future studies should, with safety precautions taken, use higher doses. This is of especial relevance in a time when cannabis use has increased more than any other drug amongst young people in America (1995 Monitoring the Future report cited in Mathias (1996)).

2.5 Benzodiazepines (Anxiolytics and Hypnotics)

The benzodiazepines are primarily prescribed for the relief of anxiety, sedation and sleep induction and the benefits can generally be sustained for several months. Most, if taken at night, show little residual action the following day, unlike some of the barbiturates, however these effects vary depending on the particular hypnotic used and individual tolerance.

Sometimes diazepam and chlordiazepam are given for the relief of symptoms following alcohol withdrawal. The most frequent side-effect is drowsiness, especially in the elderly. There is substantial evidence that they produce tolerance, although this is sometimes disputed. Severe withdrawal effects are rare. Since there are such a variety of benzodiazepines available there are a variety of concomitant

pharmacodynamic effects, although generally speaking peak blood plasma levels occur from 1 - 8 hours. Half-lives and durations differ depending on the particular drug used. Benzodiazepines represent the biggest share of the total world utilisation of psychotropic drugs and are the most frequently prescribed minor tranquilliser (Ellinwood and Heatherly, 1985). They are also the most frequently detected licit drugs in all driver populations (de Gier, 1998).

2.5.1 Benzodiazepine Experimental Studies

There is still a comparative paucity of material related to the illegal use of tranquillisers such as the benzodiazepines and their effect on driving skills, although work has been done experimentally with healthy volunteers. A common finding is an increased sedation and consequent lowering of anxiety after benzodiazepine ingestion. This is in turn related to impairments on psychomotor tests, but it is unclear if increased risk-taking necessarily ensues as a result. Certainly benzodiazepines are over-represented in epidemiological studies of drug-involved traffic accidents (see below).

de Gier et al (1981) compared diazepam ingestion (5mg 3x/day) to controls in a sample of twenty-two subjects, using both a real driving situation and a laboratory test battery including measures of vigilance and simple eye-hand co-ordination (thus tapping two opposing attentional states). They found that diazepam subjects were impaired in real driving and in the eye-hand co-ordination. They also found no relationship between diazepam plasma levels and the measures of performance.

Since many benzodiazepines are known to have a "hangover" effect next morning and have been shown to impair certain psychomotor tasks (depending on dose, plasma half-life and individual differences), Betts and Birtle (1982) examined the effects of temazepam (a short half-life) and flurazepam (a longer half-life). Both drugs impaired actual driving performance the next morning in subjects which is particularly surprising in the case of temazepam as it is known to cause little psychomotor impairment the morning after ingestion. However the authors note that they cannot say whether the effects would wear off or not or if the effect is dose-dependent.

Harrison and Hindmarch (1985a), compared the residual effects of four drugs (7.5mg zopiclone, 1mg lormetazepam, 0.25mg triazolam, 1mg flunitrazepam and placebo) on psychomotor performance the morning after ingestion in ten subjects. Zopiclone, triazolam and flunitrazepam caused impairments in an information-processing task one hour after initial administration. In addition, flunitrazepam impaired reaction time on the following morning in the same task.

Laurell and Tornros (1986) investigated the effects of three short-acting benzodiazepines (brotizolam (0.25mg), oxazepam (25.0mg) and triazolam (0.25mg)) together with nitrazepam (5.0mg) and placebo as controls, on measures derived from a simulated 2.5 hour monotonous driving test and a real car emergency avoidance test. Motivation was controlled by giving subjects an equal amount of money which could be reduced following poor performance. They found that in the acute phase, both brotizolam and nitrazepam effected brake reaction times in the monotonous driving test relative to placebo whereas the other two drugs did not. In the carry-over phase,

no significant differences were found between groups on the same task. In the emergency avoidance test, triazolam and nitrazepam caused impairments although the differences between groups were not significant. Where oxazepam and nitrazepam were concerned in the same test, a slight improvement was noted but again there were no significant differences between groups. Thus it would appear that these benzodiazepines at low doses have little effect on driving performance. However the authors note that results may be different for subjects belonging to high-risk categories.

de Gier et al (1986) found that lorazepam (1.0mg three times/day for two weeks) and bromazepam (1.5mg three times/day for two weeks) failed to produce impairments in either an actual driving test or laboratory tests using actual patients. These benzodiazepines have a relatively short elimination half-life compared to, for example, diazepam and chlordiazepoxide.

Differing doses of flutoprazepam (2mg and 4mg) on eighteen healthy volunteer subjects were analysed for their effects on psychomotor tasks relevant to driving by Moser (1990). Two and a half hours after ingestion, only the 4mg dose was seen to impair performances, whereas the 2mg dose resulted in only minor skill reductions.

O'Hanlon et al (1995), using patients receiving therapeutic doses of lorazepam, found that after two weeks of training on an on-the-road task, patients' lateral driving position became very variable despite reported decreases in anxiety. This may not be a realistic measure of driving impairment however. More interestingly, the authors found that half the patients could not complete the test at the end of the first week (whereas all the placebo patients could), but after a further week, only one of the lorazepam patients could not complete the test and the lateral position impairment had decreased. This study suggests that driving impairments resulting from benzodiazepine treatment may only be evident at the start of treatment programmes, and may decrease to baseline levels thereafter.

O'Hanlon et al (1995) also compared the effects of diazepam and lorazepam with benzodiazepine-like anxiolytics alpidem and suricione and a 5-HT-3 antagonist ondansetron on actual driving performance. Although ondansetron had no effect, all the others caused a "marked and persuasive" impairment which lasted throughout treatment.

Asoh et al (1995) investigated the acute effects of an anxiolytic agent, tandospirone, and diazepam on actual driving performance. Twelve subjects were given either a placebo, 30mg tandospirone, or 5mg diazepam. Whilst driving continuously for two hours at sixty miles per hour, measures of eye movement, steering wheel operation, speed variability and sleepiness were taken. Whilst diazepam increased long blinking, sleepiness measures, large steering wheel reversals and driving speed reversals, tandospirone subjects did not differ from controls. It can therefore be concluded that whilst tandospirone does not impair certain aspects of driving, diazepam causes a potentially dangerous tendency to fall asleep at the wheel. This steering impairment result for diazepam had previously been suggested by Smiley and Moskowitz (1986) using simulator technology, although the same task was unaffected by buspirone ingestion.

In an elaborate study using 145 healthy subjects, Kozena et al (1995) examined the effects of diazepam (5mg or 10mg), nitrazepam (5mg), oxazepam (10mg), medazepam (10mg) and alprazolam (0.2 or 0.5mg) on a vigilance task (discriminating sounds and a visual tracking task). They found that only diazepam (5 and 10mg), alprazolam (0.5mg) and nitrazepam (5mg) significantly impaired vigilance and required a greater effort to overcome perceived sleepiness. They further noted that diazepam had a quicker onset whereas alprazolam effects lasted longer.

2.5.2 Benzodiazepine Field Studies

Using a survey approach, Skegg (1979) found that individuals who had recently used drugs, in particular benzodiazepines, were involved in more accidents than others who had not been recent drug users. Based on a series of previous epidemiological studies, Honkanen et al (1980) suggested that the minimum increment of accident risk induced by diazepam to be approximately five times less than that of alcohol. He concluded that the evidence indicates that diazepam users in particular are over-represented in both injured and fatally injured drivers.

A Danish study of 1382 blood samples taken from drivers stopped for ethanol determination (Worm et al, 1985), revealed that 5.5% contained diazepam or desmethyldiazepam. The prevalence of diazepam was also noted by Cosbey (1986). He analysed 212 drink-driving specimens for drugs taken over a three year period. 18% of samples contained drugs, and of these the most frequent were benzodiazepines (87%), especially diazepam. He notes that diazepam is also the most common drug found in surveys conducted in many other countries including New Zealand, Australia and Norway. Again, the overall percentage of positive cases is quite low, and Cosbey suggests that this may be because the citizens of Northern Ireland are more aware of the dangers involved in driving with drugs.

A Norwegian study conducted by Gjerde et al (1988) compared re-arrest rates for fifty drunken drivers and fifty drivers with high blood drug concentrations. Of the drugged drivers, 32 had high traces of diazepam and 16 were re-arrested inside the following three years. The re-arrest rate was low for drivers using amphetamines by contrast. For alcohol, the corresponding figure was predictably higher at 20%. The high re-arrest figure for diazepam users suggests that it may be useful to administer a benzodiazepine screening test when such drivers are re-arrested for drunk-driving.

In an examination of 492 cases from a drugs and driving database maintained by the Canadian Society of Forensic scientists, Peel and Jeffrey (1990) found that there were relatively few cases of impaired driving due to drug use in Canada. They found that the most common drugs involved in impaired driving were THC, diazepam, cocaine and codeine, and they tended to be single-drug cases (no alcohol involvement). The authors admit that to ascertain the actual involvement of drugs in driving, a study of the greater population of Canadian drivers would be necessary. They attribute the low number of cases to the fact that Canadian law did not allow for drug testing of suspected motorists.

Christopherson et al (1992) examined 1514 samples from suspected drugged drivers in Norway. They found that the majority contained benzodiazepines or THC. Benzodiazepine doses above the therapeutic level and in combination with other

drugs was common. They concluded that benzodiazepines played more of a role in Norwegian traffic accidents than THC or amphetamines, although these three are the most frequently detected drugs in Norwegian drivers.

In an analysis of 2852 blood samples from accident victims, the Benzodiazepine/Driving Collaborative Group (1993) found that 8% contained benzodiazepines. When the contribution of alcohol was accounted for, no significant difference was found between the 'responsible' and 'non-responsible' groups. The authors conclude that alcohol is a much more important risk factor than benzodiazepines. In contrast, Currie et al (1995), in a study of 229 blood samples from people involved in accidents, found that there was a significantly greater representation of tricyclic antidepressants and benzodiazepines present in samples taken from 'responsible-for-accident' ($n = 48$) drivers than the corresponding not-responsible group ($n = 15$). However the sample size in this study is comparatively small, and again no estimates of causality can be made.

In a Swiss study, Ulrich (1994) examined the blood samples of 1000 drivers tested for alcohol and found benzodiazepine constituents in 42 cases (primarily valium, vegeasan, tranxilium, lexotanil and scresta). Thirty five samples also had an alcohol level above 0.08%. After further analysis it was decided that benzodiazepine concentration was very high in 4 cases, high in 7 cases, moderate in 26 cases and low in 10 cases.

In a Canadian study, Mercer and Jeffery (1995) analysed 227 blood sample records and concluded that drugs other than alcohol were related to fatal traffic accidents. Only 9% of the sample involved drugs only, and of these the most frequent were THC, cocaine and diazepam. Although the sample size is very small, the results are generally consistent with other studies.

In a Finnish study conducted by Lillsunde et al (1996), they found that benzodiazepines were the most frequently found drugs in both 1979 ($n = 298$; 6%) and 1993 ($n = 332$; 22.9%). No amphetamine traces were found in the earlier study, but by 1993 the frequency had increased to 2.7%. No data for THC were available earlier, but by 1993 the frequency was 2.4%. However these last two drugs were always in combination with others. The authors state that alcohol was responsible for impairment in the majority of cases. Although it was evident that drugs other than alcohol had increased in Finland, it was not possible in this study to determine the effects of each drug on their own.

As can be seen, the results of epidemiological studies examining benzodiazepine involvement in road crashes are generally inconsistent. This may reflect the differing effects of long- and short-half-life drugs and variations in their duration of use. To investigate this issue, Hemmelgarn et al (1997) examined the records of 5579 Canadian elderly people from 1990 to 1993 and compared them with ten control cases. They found that there was an increased rate of crash involvement within the first week of long-half-life benzodiazepine use (rate ratio 1.45) whereas the rate ratio for continuous use of longer duration up to one year was lower but still significant (1.26). In contrast to this, there was no increased risk after the initiation of treatment with short-half-life benzodiazepines (1.04) or after continued use (0.91). They conclude that, whilst there is no elevated risk for short-half-life benzodiazepines,

there is an increased risk for traffic accidents with brief or extended exposure to long-half-life benzodiazepines.

2.5.3 Summary

Where experimental results are concerned there is little consistency, even where similar doses are given before similar tasks (Friedel and Staak, 1992). Studies clearly reveal that drug-plasma level is not convincingly correlated with psychomotor/driving impairment. Factors such as acute peak levels and tolerance, chronic tolerance and individual differences need to be taken into account.

There is an argument that compared to the impairing effects of other drugs which are used as minor tranquillizers, benzodiazepines are generally safer (Ellinwood and Heatherly, 1985). However, to add a cautionary note, in a Medline search from 1980 to 1997 of the relation between benzodiazepine use and traffic accidents, Thomas (1998) concluded that using benzodiazepines approximately doubled the risk of motor vehicle accidents. In addition, the risk was higher for drivers over age sixty-five when they took longer-acting and greater quantities of the drug.

Table 1: Ratings for acute effects

Drug	Dosage (mg)	Impairment Rating
Alprazolam	0.25 / 0.5	minor
	1.0	moderate/not severe
Bromazepam	1.5	minor
	3.0/6.0	moderate/not severe
	12.0	severe
Brotizolam	0.125/0.25	not severe
Chlordiazepoxide	5.0/10.0/20.0-25.0	moderate/not severe
Diazepam	2.0/5.0	moderate
	10.0/20.0	not severe/severe
Flunitrazepam	0.5/2.0	severe
Flurazepam	15.0/30.0	severe
Lorazepam	0.5/1.0	not severe
	2.5/5.0	severe
Lormetazepam	0.5/1.0	moderate/not severe
	2.0	severe
Medazepam	5.0/10.0	minor/moderate
	15.0	severe
Nitrazepam	2.5/5.0	moderate/not severe
	10.0	severe
Oxazepam	10.0/20.0	moderate/not severe
	30.0/50.0	severe
Temazepam	5.0/10.0	moderate
	20.0/30.0	severe
Triazolam	0.125/0.25	moderate/not severe
	0.5	severe

Table 2: Ratings for residual effects

Drug	Dosage (mg)	Time (hrs)	Impairment Rating
Brotizolam	0.125/0.25/0.5	22	minor/none
Diazepam	10.0/15.0/20.0	12	not severe
		22	moderate/not severe
Flunitrazepam	0.5/1.0/2.5	12	not severe
		22	moderate/not severe
Flurazepam	15.0	12	not severe
		22	moderate/not severe
		22	moderate/not severe
		12	severe
Lorazepam	1.0	22	moderate/not severe
		12	minor
		22	moderate/not severe
		12	severe
Lormetazepam	0.5/2.0	22	moderate/not severe
		12	none/minor
		22	minor/moderate
		12	minor
Nitrazepam	2.5/5.0	22	minor/moderate
		12	not severe
		22	moderate/not severe
		12	not severe
Oxazepam	10.0	22	moderate/not severe
		12	minor
		22	none
		22	minor
	20.0	22	minor
		12	moderate/not severe
		22	none/minor
		12	moderate/not severe
Temazepam	10.0/30.0	22	minor
		12	minor
		22	none/minor
		12	minor
Triazolam	0.125/0.25	12	minor
		22	none
		12	moderate/not severe
		22	moderate/not severe

Sherwood (1997) tentatively concludes that some benzodiazepines tranquillisers may impair driving skills in the first few weeks of treatment, but that these effects may dissipate with continued use.

In a major report from the Institute for Drugs, Safety and Behaviour in the Netherlands (Wolschrijn et al, 1991), the mean impairment ratings shown in Tables 1 and 2 were given for most of the benzodiazepines referred to in this review (refer to reference for ratings on all other benzodiazepines).

2.6 Antihistamines

Antihistamines are generally prescribed for the treatment of allergic states such as hay fever and sometimes as hypnotics. There are two main types: H1-receptor antagonists and H2-receptor antagonists. Generally the older antihistamines produce sedative effects and consequent impairments on some cognitive and psychomotor tests. These effects result from the drugs' impairment of central nervous function which in turn are a consequence of their ability to cross the blood-brain barrier. However the newer drugs (e.g. astemizole and terfenadine) tend to be largely free of these effects and tend to act on peripheral rather than central receptors. Users of antihistamines, especially when they are bought over-the-counter, are generally free to engage in everyday activities, including the operation of machinery and driving. In 1988, an estimated 30 million Americans spent more than \$500 million for single-entity antihistamine (Meltzer, 1990).

2.6.1 Antihistamine Experimental Studies

Nicholson (1979) compared the effects of sustained release formulations of antihistamines which are less likely to cause daytime sedation if used overnight. Using female subjects, they found that triprolidine hydrochloride (2.5mg) had an immediate effect on visuomotor co-ordination persisting for 3 hours, whereas a 10mg sustained release form reduced performance only between 1.5 and 5 hours. Brompheniramine maleate (4mg) was found to decrease performance between 1.5 and 3 hours, but the sustained release form (12mg) resulted in impairments only around 1.5 hours. For both drugs, recovery appeared within a few hours.

Nicholson and Stone (1982b) and Nicholson et al (1982) also found that terfenadine (60mg) and astemizole (10 and 20mg) caused no impairments on psychomotor tasks such as dynamic visual acuity, but again triprolidine was found to impair performance. Nicholson and Stone (1983b) also examined the effects of mequitazine, an H-1 histamine receptor antagonist widely used for treating allergic states, on measures of visuomotor co-ordination, dynamic visual acuity and digit symbol substitution. Mequitazine, ingested at its therapeutic dose of 5mg, produced minimal effects, although there were a few impairments found with a 10mg dose some hours following ingestion.

Betts et al (1984) in a controlled placebo study examined the effects of two antihistamine drugs (centrally active triprolidine and peripherally active terfenadine) on an actual driving task using female subjects. They found that only triprolidine significantly impaired performance. They therefore concluded that antihistamine-using drivers should avoid those drugs which act centrally. However Bhatti (1989) found that terfenadine could impair driving-related psychomotor tasks in a dose-related fashion in that only doses of 240mg caused impairment and not doses of 60mg or 120mg. This probably reflects the methodological differences between the two studies.

de Gier et al (1986) tested twelve healthy male subjects on an actual driving test and psychomotor tests both before (day one) and after (day eleven) ingesting a placebo or astemizole (10mg three times per day for ten days). The driving test was approximately 60km long and lasted for approximately 90 minutes. Behavioural and

cognitive skills were rated on a scale from 'satisfactory' to 'insufficient'. Psychomotor tasks consisted of two attentional tasks, one highly demanding and the other not. They found that the groups did not significantly differ from each other on the day eleven driving tests. The laboratory tests revealed a slight improvement for the astemizole subjects, but this was not significant. The authors concluded that the subchronic use of astemizole in a dosage regimen of 10mg t.i.d. for seven days followed by 10mg daily for three days has no impairing effect on either car driving or psychomotor performance.

O'Hanlon (1988) found that terfenadine (a non-sedating antihistamine) did not adversely effect vehicle weaving compared to placebo controls. Neither terfenadine or loratadine (also non-sedating) potentiated the adverse effects of alcohol on the driving measures. Similar results have been found for cetirizine: Gengo and Manning (1990) examined the central effects of cetirizine on psychomotor performance. They found that cetirizine (20mg) induced minimal changes in mental performance tests.

Brookhuis et al (1993) investigated the effects of a relatively recent antihistamine, ebastine (given in doses of 10, 20 and 30mg), versus a control drug, triprolidine (10mg) on car driving performance in actual traffic using fifteen subjects. It was found that ebastine caused no changes in performance at any dosage either on day one or five of the test. In contrast, triprolidine (at 10mg) significantly increased the degree of weaving and the delay in following speed manoeuvres of a leading car compared to a placebo condition. Thus ebastine may be relatively safe for driving in doses up to 30mg whilst triprolidine is likely to cause impairment.

In a review of studies comparing the effects on actual driving of both 'sedating' antihistamines (triprolidine, diphenhydramine and clemastine) and 'non-sedating' antihistamines (terfenadine, loratadine, cetirizine, acrivastine, mizolastine and ebastine), O'Hanlon and Ramaekers (1995) found an array of results which suggest that some of the newer drugs both enhance and impair performance depending on dose. The effects of mizolastine (10mg) and cetirizine (10mg) were also examined by Patat et al (1995) in conjunction with alcohol (BAC 0.7g/l) in eighteen male volunteers. The alcohol was found to impair both actual and simulated driving in addition to tests of divided attention and adaptive tracking even after 5.5 hours. The other drugs did not impair driving ability or arousal but did impair the divided attention task after 6 hours. Additionally, after 7.5 hours, mizolastine impaired tracking speed performance and cetirizine impaired the same task from 1.30 to 7.50 hours after initial administration. The authors also did not find an adverse interaction between the antihistamines and alcohol.

2.6.2 Antihistamine Field Studies

Starmer (1985) states that antihistamines are seldom suggested as causative factors in traffic crashes (although this may be due to lack of reportage). Certainly it is the case that there are very few field studies which indicate traces of the drug in accident victims. Teo (1975) found that 25% of Australians tested positive for alcohol and of these, 5.4% reported that they had used antihistamines. In a Canadian study, Cimbura et al (1980) found antihistamines present in 2.1% of samples taken from Ontario drivers, although most of these were in combination with other drugs.

In a U.S. National Transportation Safety Board study (1990) of 168 fatal-to-the-driver heavy truck crashes, antihistamine was found to be in the body of only one driver. This lack of risk associated with antihistamine use was also reported by Ray et al (1992). They conducted a retrospective cohort study of Tennessee drivers aged 65 -84 and calculated crash risk for four groups of psychoactive drugs including antihistamines. They found that increased risk was not associated with antihistamine use, but was with benzodiazepine use and cyclic antidepressants. These results could not be attributed to the confounding effects of alcohol use or driving frequency.

2.6.3 Summary

Peripherally active as opposed to centrally active antihistamines are less likely to cause impairing sedative effects (Nicholson and Stone, 1986). Some antihistamines which are slow to cross the blood brain barrier and thus produce tolerance without central effects, such as astemizole, and especially terfenadine, are likely to be of little detrimental effect on skilled performance. Meltzer (1990) concluded that the centrally active first generation agents commonly cause greater performance decrements as compared with the newer, non-sedating second generation antihistamines. Since antihistamines vary in the extent of their impairing effects it is important that doctors and users try to use the less toxic and impairing versions available. Therefore the use of antihistamines is not necessarily likely to result in impaired driving performance. This conclusion is supported by the very few epidemiological studies which find traces of antihistamines in blood samples from traffic accident victims.

In a major report from the Institute for Drugs, Safety and Behaviour in the Netherlands (Wolschrijn et al, 1991), the mean impairment ratings shown in Table 3 were given for most of the antihistamines referred to in this review (refer to reference for ratings on all other antihistamines).

Table 3: Impairment ratings for various antihistamines

Drug	Dosage	Impairment Rating
Astemizole	10.0/30.0	none
Acrivastine	4.0/8.0	none
Brompheniramine	4.0/8.0	insufficient evidence
	12.0	moderate/not severe
Cetirizine	10.0	none
	20.0	minor
Ebastine	-	no impairment
Loratadine	10.0/20.0	none
Mequitazine	5.0	none
	10.0	moderate/not severe
Terfenadine	60.0/120.0	none
	240.0	minor
Tripolidine	2.5/5.0	not severe/severe

2.7 Antidepressants

Antidepressants are prescribed to selectively treat the symptoms of depression although they may also be used to treat some phobias and obsessive-compulsive disorders. They can be separated into tricyclic antidepressants, monoamine oxidase (MAO) inhibitors and the newer 'second-generation' antidepressants. Tricyclic antidepressants reach peak plasma levels in 30 - 60 minutes, although it can take 5 - 10 days for plasma levels to stabilise and the main therapeutic effect may not be apparent for 1 - 4 weeks.

Although there are great variations, they generally have long half-lives. MAO inhibitors reach peak blood levels in about 60 minutes and most of this is excreted within 24 hours. Despite this they have a long effect latency and therapeutic effects may be felt in about 10 days after regular doses. Doses are generally given in groups of 20 - 30mg twice a day. They can have very toxic side-effects however, including high blood pressure. They do not cause dependency or withdrawal effects. The newer second-generation antidepressants tend not to have the bad side-effects of the other drugs. Well known types are fluvoxamine, bupropion and fluoxetine (Prozac).

The other main advantage of some of these drugs is the fact that they can begin to have therapeutic effects in a very short time. In general, antidepressants do not have a euphoric effect, therefore they are comparatively less likely to be abused. In addition, the majority of antidepressant users are middle aged women, who tend to have a low incidence of traffic accident involvement (Linnoila and Seppala, 1985).

2.7.1 Antidepressant Experimental Studies

Louwerens et al (1983) examined the acute effects of oxaprotiline (25mg t.i.d.), mianserin (10mg t.i.d.), amitriptyline (25mg t.i.d.), doxepin (25mg t.i.d.) and placebo on twenty healthy male subjects driving a car over a 100km circuit in normal traffic. They found that amitriptyline and mianserin impaired control on lateral position and speed. Doxepin also slightly impaired lateral position, but not speed control. Oxaprotiline caused no impairments. Thus the results suggest that amitriptyline and mianserin in particular impair driving performance. Further evidence for this was the fact that half the tests in the amitriptyline condition had to be terminated early due to an objective decision that to continue would be dangerous.

In general the results compare favourably with earlier studies demonstrating impairments resulting from these tricyclics. In addition, Brookhuis et al (1986) confirmed these results for the same drugs, doses and conditions using EEG energy-density spectra technology. They found that mianserin, amitriptyline and doxepin increased the amplitude of theta, or of both alpha and theta activity, whereas oxaprotiline did not differ from placebo on this measure. However the authors admit that their use of healthy subjects tested on the first day of treatment might not be generalisable to real patients who are on a longer course of medication and consequently may not show impairments to such a degree.

In two experiments, Gerhard and Hobi (1984) investigated the effects of certain antidepressants on the psychomotor abilities of actual depressive patients. In the first experiment, twenty patients were used who were on treatment regimes of either

maprotiline (150mg/day), lithium, dibenzepine (720mg/day) or two antidepressants in sequence, and compared with a control group of 32 healthy subjects. The tasks were a choice reaction test and a simple/divided attention test. Tests were administered on day one and again about two months later (day 2). They found that on the choice reaction time test the patients were significantly worse than controls on both days, but both patients and controls showed improvements across trials on each separate day, but no improvements were demonstrated for either group between the two days.

In the divided attention test, the differences between groups were barely significant, but there was a slight improvement between the two days in addition to an improvement across trials on both days, as before. In experiment two, seven male anxious-inhibited depressive inpatients being treated with amitriptyline were compared to seven healthy controls on the two tasks. Trial one was administered on day 1, trial 2 a week later, and trial 3 during maintenance dosage just before or after patients were discharged.

Both controls and patients showed some improvement across trials on the divided attention test (although less remarkably for the patients), and in the choice reaction time test the subjects showed a significant deficit by trial three compared to controls. Overall however, taking both experiments into consideration, patients did demonstrate an improvement in performance, although they were worse than controls in all tests. The authors conclude that the deficits were slight and as such do not render patients 'unfit' to drive. The degree of intra-individual variability amongst patients suggests that performance evaluation may be better using individuals as opposed to groups.

Linnoila and Seppala (1985), in a review of the relevant literature, have found that studies which use healthy volunteers as subjects and have used only single doses have tended to show that the more sedative drugs produce more impairments. In addition, there is some evidence that in the acute phase, antidepressant dosage positively correlates with degree of impairment. Ranking drugs in order of impairing effects with the most impairing at the start, the authors found that the following list applies: Amitriptyline, Imipramine, Mianserin, Viloxazine, followed by least impairing drugs such as: Amoxapine, Desipramine, Doxepin, Nomifensine, Nortriptyline and Zimelidine. Where chronic doses are used in healthy subjects, some degree of tolerance to impairing effects becomes noticeable in the literature for most of these drugs, although the adverse effects of lithium can still be detected (Judd, 1979).

Using real patients, Seppala and Linnoila (1980) have found that skills impaired by depression improve with continued use of antidepressants. In fact impairment of skills and sedative effects only lasted the first several days of treatment. This also includes the case of lithium (Linnoila and Seppala, 1985).

Gerhard and Hobi (1986) note that impairments in psychomotor performance have been noted after single doses of nortriptyline, imipramine and viloxazine, although the less sedating drugs like viloxazine, like doxepine, provoke less impairment on some tasks, notably attention, vigilance and learning, than the more sedating drugs such as amitriptyline.

Hindmarch, Harrison and Shillingford (1988) examined the effects of lofepramine (70mg), lofepramine (140mg), nomifensine (100mg), amitriptyline (50mg) and

placebo (all given at weekly intervals) on the psychomotor performance of ten healthy females. Amitriptyline, the positive control, resulted in the expected sedative effects. However lofepramine (70mg and 140mg) and nomifensine (100mg) were generally free from impairing effects.

Ramaekers et al (1992) tested seventeen healthy subjects taking either moclobemide or mianserin over eight days on psychomotor tests. They found that whereas moclobemide was free of impairing effects, mianserin treatment caused impairments on most measures included tracking and driving-related abilities. The authors attributed the deficits primarily to the sedative effects of the mianserin.

Herberg (1994) compared the effects of paroxetine (1 x 20mg/day) with doxepine (2 x 50mg/day) and placebo, all administered over a three week period. After twenty days, ethanol was given (0.05% BAC). Sixty male and female subjects were given seven tests of visual orientation, forced concentration, simple reaction time, choice reaction time, reaction under stress, vigilance and motor co-ordination. It was found that paroxetine did not impair performance whereas doxepine resulted in impaired vigilance, motor co-ordination, concentration and simple reaction time.

Robbe and O'Hanlon (1995) examined acute and subchronic effects of paroxetine (20 and 40mg), amitriptyline (75mg/day - the active control) and placebo on actual driving and psychomotor performance in sixteen healthy subjects. Whilst amitriptyline had its expected sedative and impairing effects (although these were gone by day 8), paroxetine 20mg (therapeutic dose) was free of effects. Paroxetine (40mg) did not effect road tracking but did impair some other psychomotor tests persistently. They noted however that some dose-related side effects (e.g. nausea and delayed ejaculation) were reported by subjects during paroxetine treatment only.

Vanlaar et al (1992) used two groups of twelve anxious outpatients receiving buspirone (5mg three times/day for first week, 20mg/day thereafter) or diazepam (5mg three times/day for duration). The driving test took place over a 100km stretch of road and subjects were required to maintain constant speed and steady lateral position. Whilst both drugs were equally effective in reducing anxiety symptoms, only diazepam impaired lateral position control in the first three weeks, but not in the fourth week, and speed control was effected only in the first week. This suggests that impairments diminish as treatment duration lengthens.

Vanlaar et al (1995) also examined the effects on actual driving performance of a relatively new antidepressant, nefazodone (100 and 200mg twice daily), the tricyclic imipramine (50mg twice daily) and placebo using twenty-four healthy subjects. They found that imipramine (the reference drug) impaired lateral driving position after a single dose but this effect diminished after repeated dosing. Minor impairments were also noted on psychomotor tests on day 1 and day 7. In contrast, single doses of nefazodone (both dosages) did not impair driving (in fact there was some enhancement) and had no or little effect on psychomotor performance. After repeated dosing, nefazodone (200mg only) produced slight impairment of lateral position control and dose-related impairments of cognitive and memory functions were found. Neither drug appeared to cause daytime sleepiness.

2.7.2 *Antidepressant Field Studies*

Excluding the previously mentioned problems associated with epidemiological studies, it is the case that few studies show that antidepressants are detected in accident victims more than would be expected (Linnoila and Seppala, 1985). Jick et al (1981), in an examination of 244 people hospitalised for traffic injuries, found that antidepressant use was similar in 'responsible' drivers and non-responsible drivers and passengers. It was only slightly higher in these groups than in the wider driving population. The authors suggest that the results are due to the fact that people take the warnings on medicine bottles seriously.

Alvarez et al (1992) analysed questionnaires from 675 Spanish drivers and found that 3.4% were taking tranquillisers. Ray et al (1992) conducted a retrospective study of older drivers in Tennessee. They found that increased risk was confined to benzodiazepines (relative risk = 1.5) and cyclic antidepressants (relative risk = 2.2). For both these drugs, relative risk increased with dose, especially with high doses (2.4 for greater-than-or-equal-to 20mg diazepam and 5.5 for 125mg amitriptyline). Further analysis also revealed that these results were not confounded by the presence of alcohol. Ray et al (1992) also showed that patients taking amitriptyline 125mg/day are six times more likely to be involved in a road traffic accident than patients taking other drugs.

Currie et al (1995) analysed 229 blood samples from 'responsible-for-accident' and non-responsible drivers. They found that there was a higher incidence of tricyclic antidepressants and benzodiazepines amongst the responsible group compared with the non-responsible group. A similarly high prevalence was found by Deveau et al (1996). They conducted a prospective study of 103 fatally injured drivers and pedestrians in France. Of the 29% of fatalities studied, half contained antidepressants. In contrast, Logan and Schilke (1996), in an analysis of blood/urine samples from fatally injured drivers in Washington State found that whilst antidepressants were not greatly represented, there was a trend for them to be associated with a higher BAC, and they were more prevalent amongst the 45+ age group.

2.7.3 *Summary*

Although some studies indicate that antidepressants may impair performance in healthy subjects taking the drugs for a week or more, there still remains the fact that real patients' performance may actually improve as the result of the drugs relieving their depressive symptoms.

Little is known about the effects of depression *per se* on driving abilities. Antidepressants can have both beneficial and detrimental effects on psychomotor performance. If possible, the newer, less sedating drugs should be used in preference to older drugs such as amitriptyline. Although these newer drugs are very effective in treating symptoms, they generally do not speed up recovery from the root depression which is the reason they were prescribed in the first place (it may be two weeks before an improvement is observable). Additionally, there is little research available on the newer, less sedative antidepressants in relation to their effects (other than sedation) on psychomotor performance. The side effects of the most popular antidepressant, fluoxetine, such as nausea and insomnia, can themselves effect driving (Sherwood,

1997). Where alcohol is combined with antidepressants, especially the more sedative ones, the worst impairments are generally seen in the initial phase of treatment and diminish after prolonged treatment. Still alcohol is a bigger problem, and the effects of severe, untreated depression on driving capacities may be worse than the effects of antidepressants.

In a major report from the Institute for Drugs, Safety and Behaviour in the Netherlands (Wolschrijn et al, 1991), the mean impairment ratings shown in Table 4 were given for most of the antidepressants referred to in this review (refer to reference for ratings on all other antidepressants).

Table 4: Impairment ratings for various antidepressants.

Drug	Dosage	Impairment Rating
Amitriptyline	12.5/25.0/50.0/75.0	not severe/severe
Bupropion	100.0	minor
Butriptyline	25.0	minor
Dibenzipine	80.0	none
Doxepin	25.0/50.0	not severe/severe
Fluoxetine	20.0/40.0/60.0	none/minor
Imipramine	25.0	minor
	50.0	not severe
	75.0	severe
Maprotiline	25.0	minor
	75.0	moderate
Mianserin	10.0/20.0	moderate/not severe
Nortriptyline	10.0/50.0	minor
	75.0	moderate/not severe
Paroxetine	30.0	none
Viloxazine	100.0	none

2.8 Amphetamines

Generally amphetamines may only be prescribed in certain countries for the treatment of narcolepsy, some eating disorders and attention deficit disorder in children. However it is a widely abused drug largely because of its euphoric effects. Effects may begin after 30 minutes and peak within 2 to 3 hours; a full dose has usually dissipated after 72 hours. Increased mental alertness and physical energy may result from 5-25mg doses. Higher doses can cause impairments of cognitive and psychomotor abilities. There is substantial evidence that tolerance develops especially to the euphoric effects of amphetamine. Psychosis may result from regular daily doses of 60 - 300mg. In a recent report on drugs other than alcohol and driving in the European Union (de Gier et al, 1995), it was stated that the incidence of known amphetamine abuse among drivers involved in traffic accidents was, in Denmark

(1993 survey): 3 cases (no total given); Spain (1992 survey): 1.0% of 289 cases; UK (1995 survey): 1.0%; and Italy (1994 survey): 1.0% of 200 cases.

2.8.1 Amphetamine Experimental Studies

Sometimes amphetamines are reported to result in psychomotor enhancement rather than impairment (e.g. Hurst, 1987). However such studies generally use low doses of stimulants. Earlier Laties and Weiss (1967) had confirmed that the main enhancing effects of amphetamine resulted from a restoration of baseline performance in subjects who were fatigued. They also noted enhancing effects of the drug on measures of motor co-ordination and control, monitoring, vigilance and physical endurance at low doses. In 1962 Hurst had investigated the effects of amphetamine on risk-taking and found that increased risk resulted from doses of 10 -15mg. A further study (Hurst et al, 1967) revealed that the enhanced self-perception that is an effect of the drug also corresponded with greater risk-taking. Thus it would appear that the so-called positive effects of amphetamine could be the very reason for increased likelihood of impairment.

Pickworth et al (1997) examined the effects on eight subjects of THC (1.3 and 3.9%), ethanol (0.3 and 1.0 g/kg), hydromorphone (1 and 3mg), pentobarbital (150 and 450mg) and amphetamine (10 and 30mg - within the therapeutic range). Participants were then tested on several psychomotor tasks including reaction time, card-sorting and search tasks. They found that alcohol impaired all tasks, THC impaired only one measure out of fourteen, and amphetamine had little effect at all. This supports the idea that amphetamine produces little change in performance in unimpaired individuals. The authors admit however that the motor and cognitive demands of their tests may not accurately reflect those of real-life driving.

There are only a few studies of ethanol-amphetamine interactions which have been reported, and the results are generally contradictory (Perez-Reyes et al, 1992). These authors used twelve subjects familiar with the recreational use of alcohol and amphetamines, and gave them either a placebo, 0.85g/kg ethanol, 0.09 or 0.18mg/kg dextroamphetamine. They were then tested on a test of reaction time, attention, memory, decision making and information processing. They found that ethanol impaired performance especially where accuracy and reaction time were concerned, and that this impairment was attenuated by dextroamphetamine in a dose-response fashion, although the dextroamphetamine per se did not improve performance on the tasks.

2.8.2 Amphetamine Field Studies

In epidemiological studies examining drugs and driving, amphetamine is rarely found (see for example Mason and McBay, 1984). This has sometimes led to the conclusion that it is of little significance where impaired driving is concerned. For example, Hurst (1987) concluded that therapeutic doses of amphetamine are no threat to traffic safety and may actually improve performance. In contrast, Smart (1969) had found a high rate of traffic accidents among amphetamine abusers.

Hurst (1976, 1987) in reviews of the field evidence, concluded that there was insufficient evidence to specifically implicate amphetamine use in traffic accidents, largely due to a lack of controlled studies. Lund et al (1988) found that only 2% of U.S. drivers voluntarily tested had taken methamphetamine, although the refusal rate was 12%. Crouch et al (1993) found a higher incidence (7%) in samples taken from fatally injured truck drivers.

In a U.S. National Transportation Safety Board study (1990) of 164 fatal-to-the-driver heavy truck crashes, amphetamine was found to be in the bodies of 12 drivers (7.3%). A higher prevalence was found by Gjerde et al (1992). They examined the incidence of amphetamine in 380 suspected drugged drivers in Norway, where the drug is amongst the most commonly abused. As elsewhere, it is rarely used medically other than for the treatment of childhood hyperkinesia and narcolepsy where the dose given is 2.5-30mg daily. The authors found that 92% of the drivers had blood amphetamine levels greater than the therapeutic dose and 79% had other drugs present in addition to amphetamine. In 248 cases, clinical tests of impairment revealed that 84% of drivers were impaired (in the 49 cases where amphetamine was the only drug found, 78% were impaired). The authors concluded that amphetamine abuse may therefore lead to irregular or dangerous driving resulting in traffic accidents.

Drummer (1995) found that out of 1052 samples from fatally injured drivers, amphetamines (and related stimulants) were found in 35 cases. However, because of the very high incidence of alcohol involved in all cases, the author concluded that drugs were only responsible in a small proportion of cases compared to alcohol. Kriger et al (1995), in a German Roadside Survey from 1992 to 1994 of 2234 drivers, found that amphetamines were present in 0.6% of cases. This is a useful result since the results were adjusted to reflect a representative driving population. As a cautionary note, however, Pidetcha et al (1995) have found that quite different numbers of positive samples can be detected depending on the exact type of immunoassay screening technique which is used.

In a Norwegian study, Christopherson et al (1995/96) found that amphetamines were present in 4.1% of the samples tested (n = 394). However alcohol was found in 62.9%, benzodiazepines in 13.7%, cannabis in 7.5% and opiates in 4.3%. Overall the authors conclude that drivers taking any of these drugs, including amphetamine run a considerable risk of being involved in an accident.

Rohrich et al (1995) noted that there had been a significant increase in amphetamine-positive cases amongst drivers in Greater Frankfurt between 1987 (0.49%) and 1993 (9.40%). They further noted that in 80% of cases amphetamine had been consumed in combination with cannabis, with additional use of tranquillisers and occasionally cocaine. Since only impaired drivers had been screened in this sample, the number of undetected cases must remain unknown.

Logan (1996) examined the records of 28 drivers arrested or killed in accidents and who had tested positive for methamphetamine. Most of the arrests resulted from accidents in which the driver was responsible. Although methamphetamine-alcohol combinations were uncommon, use of cannabis was traced in approximately a third of the cases. The main driving impairments were: drifting out of lanes, erratic driving, weaving, speeding, drifting off the road and high speed collisions. Logan suggests

that some of the impairments may have been caused by methamphetamine withdrawal which can cause impaired judgement and increased risk-taking. He concludes that usage of amphetamines at any dosage is likely to render the user unsafe on the roads. In an additional study, Logan and Schwilke (1996) found that amphetamines accounted for 2% of samples taken from fatally injured drivers in Washington State.

Pelisser et al (1996) compared drug use (including amphetamines) in young adults involved in road accidents and a control group. Interestingly they found no significant differences between the two groups. Augsberger and Rivier (1997) found only 4% of samples from 641 suspected drivers in Canton de Vaud contained amphetamine, and most samples were combined with alcohol. A small amphetamine prevalence was also found by Marquet et al (1998). They compared drug levels in urine samples of injured drivers (n = 296) in France with a comparable group of non-accident victims (n = 278). Amphetamines were found in 1.4% of drivers and 2.5% of controls. They concluded that, unlike suggestions from other studies in other countries, amphetamine use did not appear to be a significant problem in the context of driving safety.

Recently Logan et al (1998) investigated 146 accident reports in which methamphetamine had been found in the drivers. Of these cases, 52 were drug-caused and in 92 the drug was not directly responsible for the accident. In these 92, the median concentration level was 0.42mg/l (range 0.05 - 9.30mg/l) and 90% of these had concentrations under 2.20mg/l. The highest concentrations were in the accidental/undetermined drug-caused deaths. In the methamphetamine related traffic deaths, blood concentrations ranged from 0.05 - 2.60mg/l (median 0.35mg/l). This means that most of the methamphetamine deaths occurred with blood concentrations greater than 0.5mg/l, but could occur with levels as low as 0.05mg/l, although other drugs or disease were contributory factors.

2.8.3 Summary

Sherwood (1997) concludes that at lower doses amphetamines have few effects on cognitive functioning, but at higher doses risk-taking increases and responses become inappropriate. Therefore whilst there may be subjective positive effects associated with amphetamine use, these same effects especially at higher doses, could result in personality changes leading to an increased likelihood of impaired driving.

Only a few studies have directly examined alcohol-amphetamine interactions and the results are often contradictory. In general, high doses of amphetamine are likely to increase the impairing effects of alcohol. In a major report from the Institute for Drugs, Safety and Behaviour in the Netherlands (Wolschrijn et al, 1991), three experts rated amphetamine and dextroamphetamine (5 and 10mg) as likely to cause 'moderate/no severe' impairment.

2.9 Ecstasy and Other Synthetic Drugs

Where these drugs are concerned there is little experimental and field evidence available regarding their effects on the driving act. Therefore studies must be examined which have investigated prevalence in various other populations or which

have looked at the effects of the drugs on cognition, and extrapolate from these to the likely effects on driving. This section will correspondingly not have separate sections on experimental and field studies.

2.9.1 Ecstasy

Ecstasy has been the most prominent designer drug of the eighties and nineties largely due to its popularity on the dance and 'rave' scene. Its technical name is MDMA (3,4-methylenedioxymethamphetamine), one of the MDA family of hallucinogenic amphetamines which also include MMDA, MBDB and MEDA. Most MDMA use is oral with initial doses ranging from 20 - 180mg and supplementary doses of about 40mg. Effects begin after 20 - 60 minutes. Pills may contain toxic ingredients such as atropine, although more commonly flunitrazepam, caffeine, ephedrine and quinine. The best known effects are subjective feelings of positive mood/self-image and intimacy with others. Such effects may last for a week. Sometimes hallucinogenic experiences are encountered similar to LSD. Side-effects may include tension, tremor, nausea, insomnia and reduced appetite. 'Flashbacks' are also possible.

At very high doses the drug is potentially lethal and indeed there have been several high-profile deaths reported in the media, although whether these can be attributed to the direct action of the drug itself, to dehydration, or even to *excessive* fluid intake, is still a matter of debate (UK Parliamentary Office of Science and Technology, 1996). Tolerance develops to MDMA, but no physical dependence. It was originally developed as an appetite suppressant and has also been put to, largely unofficial, psychotherapeutic use. The popularity of the drug has resulted in the establishment of many underground laboratories manufacturing other designer synthetic drugs, most of which are substituted phenethylamines and often based on 'recipes' from 'PIHKAL' ('Phenethylamines I Have Known And Loved') by Dr. Alexander and Ann Shulgin, which is widely available through the Internet. (See section on new synthetic drugs).

To date, no studies have directly examined MDMA effects on driving performance, although there are a few which have looked at cognitive and perceptual effects, which may have relevance to driving. For example, DuPont and Verebey (1993) examined the effects of MDE or placebo on fourteen normal subjects. They found that subjects who had taken MDE displayed a general stimulation with increased psychomotor drive. One subject developed a toxic psychosis, one displayed dysphoric reaction and one suffered from anxious episodes for several days following the test.

Moeller and Hartung (1997) cite a controlled clinical study by Helmlin et al (1996) of two subjects taking MDMA. The applied dose was 1.5mg/kg body weight, which is notable because this is also the approximate dose ingested by a consumer at a 'rave' disco. A delay in breakdown of MDMA can occur and this is very relevant where participation in road traffic is concerned. It is possible thus that an acute influencing effect is still evident many hours after the original ingestion.

Curran and Travill (1997) investigated the acute and residual effects of MDMA on twelve MDMA users and twelve subjects who reported that they had only consumed alcohol. Measures were taken of participants' mood and cognitive function. On day 1, MDMA users reported an elevated mood, but this had significantly decreased to the extent of clinical depression in some users by day 5. The alcohol group showed less

pronounced changes with the lowest mood rating occurring on day 2. The MDMA group also evidenced significant impairments on an attentional/working memory task compared with alcohol users. These results have obvious ramifications for driving behaviour.

Parrott et al (1998) administered a battery of psychomotor tests to three groups of subjects: ten regular MDMA users, ten novice MDMA users who had tried ecstasy one to nine times, and ten control subjects who had no experience of the drug. All tests were given on a drug-free day. Results indicated that the three groups did not differ on measures of simple reaction time, choice reaction time and number vigilance, but that both MDMA groups were impaired relative to controls on immediate word recall and delayed word recall. These findings are consistent with other work indicating memory decrements in ecstasy users.

Creighton et al (1991) found 3 cases of flashbacks and 1 case of recurrent psychosis following MDMA consumption. In a case more specifically related to driving, Hooft and Can de Voorde (1994) cited the single case of a fatal car accident involving a 26 year old man who tested positive for MDMA (0.63mg/l), although alcohol was also involved as well as amphetamines.

Moeller and Hartung (1997) in studies carried out in 1995 and 1996 were able to prove the presence of ecstasy and related substances in impaired drivers in 30 cases. The presence of MDMA was demonstrated in 18 cases and MDEA in 17 cases (the latter alone in 5 cases). In all of the other cases there was a combination of these substances, sometimes with amphetamine. MDA was found in 23 cases. They noted that THC was also found in 25 of the 30 drivers with ecstasy in their blood.

Giroud et al (1997) examined the extent of use of MDMA in Switzerland where ecstasy and other phenylethylamines are used extensively at 'raves' and where there has been an increasing number of MDMA-related deaths. Qualitative analysis of street samples indicated that only some of them contained MDMA or related phenylethylamines (MDA, MDEA, MBDB and 2c-B). Most of them were mixed with caffeine and an excipient. Also detected were amphetamine cut with caffeine, stimulants and LSD. Quantitative analysis revealed large fluctuations in the amount of active substance(s) per tablet. Forensic analysis of blood samples from people suspected of driving whilst under the influence of psychoactive drugs determined that there were significant levels of MDMA, MDEA and MDA. However the variable composition of tablets indicates that unpredictable types and amounts of drugs may be taken by MDMA abusers. They conclude that there is major concern that traffic accidents may be caused by MDMA users, especially when combined with other drug types.

In an interim report published by the Department of the Environment in the UK (1998), it was found that a sample of 619 road user fatalities contained virtually no amphetamine users including ecstasy users. In contrast, the drug most frequently detected was cannabis, but the usual problems apply when trying to estimate the true role of this drug in accident causation. The authors conclude that alcohol is still a much larger problem than that represented by drugs.

Windhaber et al (1998) describe the case of a young female who developed panic disorder after multiple ingestion of MDMA. This was successfully treated with Paroxetine (a serotonin re-uptake inhibitor) after 3 months of treatment. It is such unpredictable side-effects which make ecstasy a potential danger amongst drivers. Interestingly, a recent report from the Ministry of the Interior, Paris (1997) estimated that 'ecstasy-related traffic offences' accounted for 3% of drug-related traffic offences in France.

2.9.2 GHB

Gamma-hydroxybutyric acid (GHB) is a naturally occurring transmitter in the mammalian brain, related to sleep regulation and possibly to energy balance. GHB was first introduced in clinical anaesthetic practice more than 35 years ago. Although GHB can induce a reliable state of sedation and anaesthesia without depressing either respiratory or cardio-circulatory parameters or liver and kidney function, the drug was nearly displaced from clinical practice because of its prolonged duration of action (Kleinschmidt and Mertzlufft, 1995).

In addition to its use as an anaesthetic, GHB may be useful in the treatment of alcohol and opiate withdrawal syndrome, has been investigated as a tool for inducing absence seizures, and for treatment of narcolepsy. Since 1990 GHB has been abused in the United States for euphoric, sedative and anabolic effects. Coma and seizures have been reported following its abuse. Adverse effects of GHB may include prolonged abuse, seizure activity and a withdrawal syndrome (Galloway et al, 1997). This withdrawal syndrome includes insomnia, anxiety and tremor; symptoms resolve in 3-12 days. GHB is not detected with common drug screens. The compound is easily available since it can be produced simply in the home.

GHB has been illicitly marketed by body builders as a growth hormone releaser. Steele and Watson (1995) report two cases from Kansas City where the patients presented in, or developed profound coma. They conclude that physicians should suspect GHB poisoning in patients who present with unexplained seizures and/or coma, particularly if they are body builders, health food fanatics or dieters.

Li et al (1998) described seven patients presenting with combination substance abuse involving GHB. All patients presented with acute delirium and transient but severe respiratory depression. With supportive care, including intubation and mechanical ventilation in four cases, normal mentation and respiratory function returned within 2 to 6 hours. None of these patients had documented seizures, and none of the four patients who received naloxone intervention had a reversal response. This clinical observation supports previous experimental work in GHB-intoxicated human subjects demonstrating neither epileptiform changes on electroencephalography nor reversal with naloxone. In one patient they observed a peculiar state of violent aggression despite near or total apnea.

Hernandez et al (1998) have described what may be the first psychiatric hospitalisation due to GHB-induced delirium reported in the medical literature. A patient presented with a chief complaint of feeling suicidal and a 1-year history of GHB use. Chin et al (1998) assembled a retrospective series of all cases of GHB ingestion seen in an urban public-hospital emergency department and entered in a

computerised database from 1993 to 1996. They concluded that patients who overdosed on GHB presented with a markedly decreased level of consciousness. Patients typically regain consciousness spontaneously within 5 hours of the ingestion. Similar findings have been reported by Williams et al (1998). They found that profound unconsciousness occurred in all cases (six) and despite full (and often rapid) recovery all patients required medical intervention. Adverse effects occurred both when GHB was used alone or in combination with other illicit drugs and alcohol.

In a case more specifically related to driving, Stephens and Baselt (1994) reported the case of a driver who was found asleep behind the steering wheel of his car, and the vehicle was at rest in a traffic lane with the engine running. His manifestations included horizontal and vertical gaze nystagmus, muscle flaccidity, and severe ataxia. He admitted ingesting a white powder, which he identified as an amino acid, about 1 hour prior to discovery by police. A urine specimen collected approximately 1 hour after the traffic stop contained 1975 mg/L of GHB. They tentatively concluded that GHB may cause impairment of the psychomotor skills required for safe operation of a motor vehicle.

2.9.3 Ketamine

The intravenous anaesthetic ketamine is widely used in sub-anaesthetic doses as a potent analgesic in emergency and disaster medicine. Among the different sites of action, N-methyl-D-aspartate (NMDA)-receptor antagonism is considered to be the most important neuropharmacological mechanism of ketamine. Following intravenous administration, a rapid onset of action is seen within 1 minute, lasting for about 10 minutes. The most important adverse effects are hallucinations and excessive increases in blood pressure and heart rate.

These reactions can be attenuated or avoided by combining of ketamine with sedative or hypnotic drugs like midazolam and/or propofol (Adams and Werner, 1997). Former studies suggested that ketamine is a proconvulsive agent; however, recent studies have demonstrated anticonvulsive and even neuroprotective properties (Detsch and Kochs, 1997). Subanaesthetic doses of ketamine can produce psychedelic effects in healthy volunteers (Bowdle et al, 1998). A standard recreational dose of ketamine is typically 1/8 g, usually taken intranasally, with effects lasting for approximately one hour. It is one of the drugs consumed regularly amongst members of the new dance culture.

Hersack (1994) in a review of the literature, found that after 25 years of clinical experience with ketamine, fewer than 10 cases documented the occurrence of delayed psychological effects potentially attributable to that drug. In most cases, the delayed effects were temporary, resolving within 3 weeks. Further, there were no long-term psychological effects clearly attributable to ketamine. Hersack notes that several controlled studies investigating the risk of long-term psychological effects due to ketamine fail to document that the risk of permanent psychological changes from ketamine is any greater than that from any other anaesthetic. The author concludes that there is no evidence in the literature that ketamine presents a higher risk compared to other anaesthetics for causing long-term psychological effects that result in a patient not being able to return to his or her occupation.

In contrast Krystal et al (1994) tested 19 healthy subjects following ingestion of ketamine hydrochloride (0.1 mg/kg), or ketamine hydrochloride (0.5 mg/kg). Ketamine (1) produced behaviours similar to the positive and negative symptoms of schizophrenia; (2) elicited alterations in perception; (3) impaired performance on tests of vigilance, verbal fluency, and the Wisconsin Card Sorting Test (a test of frontal lobe function); (4) evoked symptoms similar to dissociative states; and (5) preferentially disrupted delayed word recall, sparing immediate recall and postdistraction recall. These data indicate that NMDA antagonists produce a broad range of symptoms, behaviours, and cognitive deficits that resemble aspects of endogenous psychoses, particularly schizophrenia and dissociative states.

Pfenniger et al (1994) evaluated ketamine's analgesic and psychotropic effects in subanaesthetic doses given to 16 healthy volunteers. Subjects received ketamine racemate (1 mg/kg) and S(+)-ketamine (0.5 mg/kg) i.m. with 1-week intervals between injections. Analgesia (electric pain stimulation of the median nerve), long-term memory, anterograde amnesia (recognition of simple pictures), motor co-ordination (Trieger test), immediate recall (short test of general intelligence) and concentration capacity (test: recognition of a preselected symbol among several symbols) were measured over a 60-minute period and mean arterial pressure, heart rate, and ketamine plasma levels in venous blood samples were determined. Within 15 minutes, both agents induced a measurable degree of analgesia. Ketamine racemate did not exert measurable effects on long-term memory, whereas anterograde amnesia was observed in 46% and 54% of the study subjects after 15 and 30 minutes, respectively. However, after S(+)-ketamine, only 8% of the volunteers demonstrated anterograde amnesia. Immediate recall also declined in both groups whereas concentration capacity worsened after ketamine racemate and significantly less, after S(+)-ketamine.

Malhotra et al (1997) found that, following ketamine ingestion, schizophrenics experienced a brief-ketamine-induced exacerbation of positive and negative symptoms with further decrements in recall and recognition memory. They also displayed greater ketamine-induced impairments in free recall than normals. Qualitative differences included auditory hallucinations and paranoia in patients but not in normals. These data indicate that ketamine is associated with exacerbation of core psychotic and cognitive symptoms in schizophrenia. Moreover, ketamine may differentially affect cognition in schizophrenics in comparison to normal controls.

Adler et al (1998) administered ketamine (0.12 mg/kg bolus and 0.65 mg/kg/hour) to 10 healthy volunteers to characterise the formal thought disorder and specific memory dysfunction associated with ketamine. Thought disorder was evaluated with the Scale for the Assessment of Thought, Language and Communication. Cognitive testing involved working and semantic memory tasks. They found that ketamine produced a formal thought disorder, as well as impairments in working and semantic memory. The degree of ketamine-induced thought disorder significantly correlated with ketamine-induced decreases in working memory and did not correlate with ketamine-induced impairments in semantic memory.

Finally, in a further study by Krystal et al (1998) in normal volunteers, it was demonstrated that ketamine produced behaviours similar to the positive and negative symptoms of schizophrenia as assessed by the Brief Psychiatric Rating Scale (BPRS).

It also evoked perceptual alterations as measured by the Clinician-Administered Dissociative States Scale (CADSS) and impaired performance on the Wisconsin Card Sorting Test and other tests sensitive to frontal cortical impairment.

2.9.4 PCP

Phencyclidine (PCP) or "angel dust" is a dissociative anaesthetic agent with notoriety as an abuse substance. A derivative of the anaesthetic ketamine, PCP is the predominant member of the arylhexylamine class of 'designer drugs' (Buchanan and Brown, 1988). States of florid psychosis lasting for days can follow a brief encounter with PCP (Isaacs et al, 1986).

Pradhan (1984) summarised the observations of many investigators which showed that the acute effects of PCP following several routes of administration were shown to be dose-related. High doses of PCP produce disturbing manifestations including psychosis, numbness, light-headedness, vertigo, ataxia, and nystagmus due to acute intoxication. Furthermore, some subjects became irritable, argumentative or negative under the conditions of social stress and demanding tasks. In addition to a variety of central actions, PCP has also been shown to affect cardiovascular function, heat storage, and exercise performance. It can also induce, although rarely, psychotic episodes in psychotic and pre-psychotic personalities.

Tolerance, but not physical dependence, develops to the effects of PCP. Psychological dependence as indicated by craving for the drug has however been reported. The elicitation of violent or psychotic behaviour by phencyclidine is well documented. There are indications, however, that behavioural responses to PCP may differ among PCP users as a function of background or personality characteristics, (McCardle and Fishbein, 1989). PCP is generally less abused in Europe in comparison to the U.S.A.

Graeven et al (1981) analysed a sample of 200 phencyclidine users from an area with a 10-year history of extensive PCP use. Three types of users were studied: heavy chronic, light chronic, and recreational users. Results showed that heavy chronic users were more likely than recreational users to feel energised by PCP, and to experience negative ideations (thoughts about suicide and death). When age was controlled for, heavy chronic users were also more likely to experience violent effects. Analysis of moods over time showed some similar patterns between heavy chronic and recreational users, as well as some striking differences. Overall, heavy chronic users reported greater mood elevations while high on PCP, and a more dramatic drop in mood after the high wore off, than recreational users.

Gorelick and Wilkins (1989) screened 155 consecutive admissions to a voluntary, 4-6 week substance abuse inpatient rehabilitation programme. They found a 13% prevalence of PCP abuse and a 23% prevalence of nonabusive PCP use, as defined by DSM-III criteria. A majority of both abusers (80%) and users (97%) also abused other drugs, including alcohol (57%), opiates (29%), marijuana (29%), and stimulants (18%). Six patients still had PCP detected after 4 weeks of hospitalisation, without evidence of PCP reuse. These findings suggest that PCP abuse and use are common among unselected patients seeking substance abuse inpatient treatment.

Poklis et al (1990) conducted a survey of 104 deaths involving PCP occurring from 1981 through 1986 in Missouri. Four males died from fatal PCP intoxication. PCP was detected in an additional 100 deaths. In 50% of deaths where PCP was detected, other drugs were co-administered: ethanol (35%) and cocaine (20%) being the most common mixtures. A dramatic continuous increase in PCP abuse from 1984 through 1986 was demonstrated by drug abuse indicator data: treatment admissions, emergency room episodes, police exhibits, and driving under the influence of PCP arrests. Increased abuse of PCP in Missouri has been associated with increased medical emergencies and violence against persons.

Cosgrove and Newell (1991) administered a battery of 12 neuropsychological tests on two occasions to 15 chronic PCP users who reduced or eliminated use of PCP over a 4-week period. A comparison sample of 15 non-PCP drug users who did not differ in age, sex, education, and ethnic composition also were tested at the two time periods. Impairment, initially higher for PCP users, decreased significantly after reduction in use of PCP. A nonsignificant increase in impairment was found for non-PCP drug users. Analysis of each variable revealed that substantial improvement occurred on the acquisition, recall, and delayed recall scores of the Randt Memory Test. Improvement also was noted for some individuals on Trails B and Digit Symbol tests.

Previous studies indicate that PCP users have different characteristics from other drug users and that female PCP use is more common than use among males. Furthermore, there is evidence that those who respond to PCP with violence may differ from those who do not. Fishbein (1996) found that female PCP using subjects reported more dysphoria and aggressiveness when not using PCP, while male subjects were more likely to report aggressive behaviour and dysphoria under the influence.

Where screening is concerned, Nakahara et al (1997) have reported the simultaneous detection in hair of phencyclidine (PCP) and its two major metabolites, 1-(1-phenylcyclohexyl)-4-hydroxypiperidine (PCHP) and trans-1-(1-phenyl-4-hydroxycyclohexyl)-4'-hydroxypiperidine (t-PCPdiol). However the recent consensus is that hair analysis in general is a poor screening method (see following section on drug testing).

2.9.5 Fentanyl

Fentanyl, like methadone, is sometimes used as a heroin substitute but is primarily used as an anaesthetic during major surgery. At therapeutic doses the drug is safe and can produce a euphoric effect, but at high doses respiratory arrest can occur. Like many of the newer synthetic drugs, there exist many fentanyl analogues as a result of diffuse underground laboratory activity.

Ghoneim et al (1975) gave 10 healthy male subjects diazepam (10 or 20 mg), fentanyl (0.1 or 0.2 mg) or a placebo intravenously at weekly intervals. They were tested on a battery of psychological and electroencephalographic tests at 0.5, 2, 6, and 8 hours following injection. Fentanyl had little effect on memory while diazepam reduced the ability to learn without increasing forgetting of material already acquired. By the second hour post injection, only the low dose of fentanyl had no residual effect. Recovery was complete by the sixth hour for all treatments according to the psychological tests except for the lagging effect of high doses of diazepam on

memory. The electroencephalographic effects of diazepam persisted beyond the end of the testing sessions while those of the high dose of fentanyl recovered by the eighth hour.

Thus in the dosages tested, diazepam had more intense and prolonged effects than fentanyl. Interestingly, however, the opposite dichotomy was found in a driving study conducted by Stevenson et al (1986). They compared the effect of fentanyl (100 micrograms), diazepam (7.5 mg), and placebo on the driving ability of young volunteers as measured by the tachometer. Speed and accuracy were impaired at 30 and 120 minutes by both drugs, and by fentanyl more than diazepam.

Sold et al (1983) tested seven subjects on a quasi continuous word recognition task i.e. after a preload list of 150 words played on a tape they had to indicate if the following words (grouped into 10 blocks of 100 words each) were new ones or had occurred already. Interposed were measurements of reaction time to a visual stimulus, and of concentration and short-time memory. During the experiment, unknown to the test person, diazepam 10 mg/70 kg, flunitrazepam 1 mg/70 kg, fentanyl 0.15 mg/70 kg or placebo were infused over 3 minutes. The results clearly indicated that only the benzodiazepines specifically impaired memory function, the effect of flunitrazepam being more pronounced and longer in duration.

Zacny et al (1992) examined in thirteen healthy volunteers the subjective and psychomotor-impairing effects of intravenous fentanyl (0-100 micrograms/70 kg). A randomised, placebo-controlled, crossover design was used in which subjects were injected with 0, 25 (N = 6), 50 and 100 micrograms/70 kg fentanyl in a double-blind fashion. Subjects completed several questionnaires commonly used in abuse liability testing studies before drug injection and at periodic intervals for up to 3 hours after drug injection. Subjects also completed several psychomotor tests at these times. Some aspects of psychomotor functioning (e.g., eye-hand co-ordination) were impaired by fentanyl. Fentanyl produced dose-related increases in ratings of "high" and "sedated," but also tended to produce dysphoria and somatic symptomatology.

Veselis et al (1994) administered fentanyl or placebo to nine healthy volunteers by continuous i.v. infusion, targeting plasma concentrations of 1, 1.5, and 2.5 ng/mL in succession. A battery of memory and psychomotor tasks was administered at each plasma concentration of fentanyl, and at two points in the recovery phase while drug levels were decreasing. At increasing plasma concentrations of fentanyl, they found the following effects on memory (in comparison with placebo): a progressive decline in verbal learning; decreased delayed recognition of words presented at different test times; and decreased spontaneous recall of pictures shown during infusion. Fentanyl at concentrations above 2.5 ng/mL caused a performance decrement of 15%-30% relative to baseline on all the psychomotor tests administered. Plasma concentrations less than 2.25 ng/mL had negligible effects on performance with the exception of the critical flicker fusion frequency, which decreased by 5 Hz at plasma concentrations between 1.5 and 2.25 ng/mL. Visual analogue scale (VAS) measures of mental and physical sedation were significantly affected by fentanyl, but euphoria was not demonstrable. All subjects receiving fentanyl experienced severe nausea and four of six had one or more episodes of emesis.

Thapar et al (1995) compared impairment caused by different sedative/analgesic combinations commonly used in ambulatory settings to that of alcohol at BACs higher than or equal to 0.10%. Impairment was measured via subjective (mood) and objective (psychomotor performance) assays. Twelve healthy volunteers were exposed to five drug conditions across 5 weeks. Each of the following drug conditions were adjusted for body weight (per 70 kg): fentanyl 50 micrograms and propofol 35 mg (FP), fentanyl 50 micrograms and midazolam 2 mg (FM), fentanyl 50 micrograms, midazolam 2 mg, and propofol 35 mg (FMP), alcohol 56 g (orally administered), and placebo. With the exception of alcohol, the other drugs were administered via the intravenous route. Psychomotor impairment caused by alcohol at 15 minutes postingestion was used as a benchmark with which impairment caused by other sedative/analgesic combinations was compared. All the study drug combinations produced impairment (i.e., impairment greater than that seen with placebo), similar to that observed with alcohol at a BAC of 0.11%.

2.9.6 Ephedrine and Phentermine

There has been little study of the abuse liability of ephedrine, a naturally occurring drug used in medicine for thousands of years and currently sold as a "legal" stimulant (Chait, 1994). Most studies show that, as a stimulant, ephedrine does not improve performance. More recently, ephedrine has been purported to be effective as a fat burner and used by athletes to maintain or improve muscle mass. Although research on individuals with obesity supports the use of ephedrine for fat loss, no studies have been done on athletes (Clarkson and Thompson, 1997). Clinically it is also used for treatment of asthma, allergic disorders and narcolepsy. Phentermine is also used to treat obesity and may have useful effects in the treatment of drug abuse. Phentermine is an anorexigenic drug with catecholaminergic action and may be used in moderate or severe obesity (BMI > 30 kg/m²) after a complete clinical assessment and in the context of an integral medical treatment.

In a randomised, placebo-controlled, double blind study by Toubro et al (1993), 180 obese patients were treated by diet (4.2 MJ/day) and either an ephedrine/caffeine combination (20mg/200mg), ephedrine (20mg), caffeine (200mg) or placebo 3 times a day for 24 weeks. They conclude that the ephedrine/caffeine combination is effective in improving and maintaining weight and that the side effects are minor and transient and no withdrawal symptoms have been found.

Chait (1994) measured the reinforcing and subjective effects of ephedrine in a group of 27 adults with no history of drug dependence. A discrete-trial choice procedure was used to assess the reinforcing effects of a single oral dose of ephedrine selected to produce a moderate subjective response in each subject (range: 37.5-75 mg). Of the 27 subjects, 5 chose ephedrine on either 2 or 3 out of a possible 3 occasions; overall, ephedrine was chosen on 17% of occasions. In the group as a whole, ephedrine had no effect on ratings of drug liking, but did increase ratings of "high" and scores on the MBG ("euphoria") scale of the Addiction Research Centre Inventory. Ephedrine also increased scores on a number of mood scales reflecting CNS stimulation and anxiety. Ephedrine choice was positively associated with current use of marijuana and lower levels of baseline anxiety and hunger, as well as with lower scores on two scales measuring dimensions of the personality trait of harm avoidance. Males and females

differed in their response to ephedrine; males chose ephedrine more frequently than females and showed a more positive mood response to the drug.

Kuitunen et al (1984) tested the physical and mental effects of a single oral dose of ephedrine (ephedrine HCl 30 or 40 mg), fenfluramine (fenfluramine HCl 15 or 20 mg), phentermine (7.5 or 11.25 mg) and prolintane (prolintane HCl 10 or 20 mg). Each group consisted of 16-43 healthy volunteer medical students. Memory, learning and concentration ability were evaluated with sign recording and digit span tests. In the digit span test no changes were obtained. In the sign recording test (for 3 min), phentermine increased significantly the recording score at both 1.5 hour and 2.5 hr and prolintane at 2.5 hour after drug administration. The results suggest that in the doses given, which are commonly used in medical practice, ephedrine has the most pronounced cardiovascular effects, while phentermine and prolintane seem to be most active in the performance of some mental tasks.

Brauer et al (1996) tested the effects on 14 healthy subjects of d-amphetamine (10 and 20 mg), phentermine (30 mg), fenfluramine (40 and 80 mg), phentermine (30 mg) with fenfluramine (40 mg), phentermine (30 mg) with fenfluramine (80 mg), and placebo. Phentermine produced effects that were similar to those of d-amphetamine, whereas fenfluramine produced different and apparently aversive effects (e.g., it increased measures of anxiety and confusion). Phentermine reduced the apparently aversive effects of fenfluramine when the two drugs were given together. These results suggest that the combination of phentermine and fenfluramine would have a low potential for abuse.

2.9.7 Summary

It is evident from the comparatively sparse literature on MDMA and driving that much more research is required in order to increase understanding of the impairing effects of this drug. In particular, most medical research has concentrated on the short-term effects of MDMA and little is known of its consequences following long-term usage.

Only a few countries have the technology to isolate new synthetic drugs from other substances in blood or urine samples and so data is lacking. For the present, the well-established side-effects and widely-publicised MDMA-related deaths are suggestive that the drug is far from free of impairing effects.

This is exacerbated by the fact that ecstasy tablets are often comprised of numerous, potentially toxic constituents, the combined effects of which are largely unknown; a problem which also arises from the fact that polydrug use is common amongst the dance culture.

The contents of tablets keep changing in order to evade arrest as defined by the 1971 United Nations Convention on Psychotropic Substances (it generally takes two or three years for new drugs to be added to the list). All precursors and other ingredients are available freely within the EU. Similarly, there is very little evidence concerning the specific effects of GHB, ketamine, PCP, fentanyl and abused diet drugs on driving abilities and in field studies they have not been frequently detected.

Given the known side-effects of these drugs however and especially given the perception- and cognition-altering effects of some of them, notably PCP and fentanyl, it is likely that they constitute a danger where driving is concerned.

At present, much more experimental work needs to be carried out in order to elucidate the effects of all these drugs on mental and psychomotor performance.

Chapter Three

Description of Drug Testing Procedures in Context of Driving in EU, Issues Raised by Testing, and Assessment of the Criteria that are Used or Proposed in Relation to the Scientific Evidence

3.1 The Existing Situation in European Union Countries

Parts of the following descriptions of drug-testing legislation in EU countries are based on work conducted by Dr Johan de Gier for the Institute for Human Psychopharmacology in The Netherlands in 1993. Since only eight countries were included in that study (Belgium, Denmark, France, Germany, Italy, Spain, The Netherlands and the United Kingdom), the present summary will also outline the situation in the remaining seven countries that are currently in the EU. All of the EU member states, including those originally covered by de Gier, were contacted for information on their drug-testing procedures. The information given below reflects the level of detail submitted by contacts in each of these countries.

3.1.1 Belgium

There are no specific criteria relating to different drugs (licit or illicit) or the extent of use in Belgium. Drivers can be penalised for driving under the influence of drugs as if alcohol had been used above the legal limit. However no indication is given of how to define the influence of drugs.

Police may hold a person to have laboratory specimens of their blood taken if there is cause to suspect that they have committed an offence. Police can use a urine test on the roadside, but a blood test has to be used to determine the presence of drugs other than alcohol.

Court decisions to convict a person of DUI are not influenced by police reports but by the findings of blood sample analyses carried out by experts. As de Gier (1993) noted, it is not clear how an offender is required to prove that he is no longer abusing drugs; this depends on the decision of the medical adviser.

Package inserts produced by pharmaceutical companies must contain specific warnings about the effects on driving or operating machinery, as required by EU legislation.

Belgium is currently considering a 'project of law' which covers several illicit drugs including ecstasy and cannabis; it is unclear whether this law will pursue a zero limit or an impairment approach (Kruger et al, 1999).

3.1.2 Denmark

As is the case in most EU countries, police may hold a person to give bodily specimens if there is reason to suspect that they have committed an offence. It is not clear under what circumstances the police will in fact do this.

In common with several EU countries, a driving licence may be refused to any person who is *addicted* to drugs, or who is a known alcohol abuser.

Doctors have a strong influence on monitoring fitness to drive and are guided by governmental guidelines (although they do not cover the use of prescribed or illicit drugs).

Since 1983, all Scandinavian countries have a package label warning, a red triangle, which is portrayed on all 'especially hazardous' drugs.

3.1.3 Austria

In Austria, an individual driver can be tested for the presence of psychotropic drugs other than alcohol only if there is sufficient behavioural reason to do so.

Where alcohol is concerned, every individual can be tested. Blood samples can only be screened for alcohol; only with the donor's permission can tests be conducted to detect other drugs.

As well as not allowing forcible blood testing, there is no urine testing under Austrian law.

3.1.4 France

Police may hold a person to apply breath alcohol analysis if there is strong reason to suspect him of having committed an offence. If more than drunkenness is suspected, the person may be taken for a medical examination in a psychiatric hospital, although it is not clear under what circumstances the police will decide to do this.

Doctors decide on the need to have blood or urine samples taken. If a serious accident or offence has been committed, a 'Prefet' may order an examination by a Medical Commission.

A driving licence may be refused to any person who is *addicted* to drugs, or who is a known alcohol abuser. A booklet was published in 1991 for drivers' information and contains a list of all drugs available in France that could impair driving performance.

3.1.5 Sweden

Swedish police have the authority to stop any driver at any time and anywhere and request a breath sample as a screening test for the detection of alcohol. Drivers cannot refuse to provide a sample. If they do not give a breath sample, a blood sample will be taken anyway. As for other drugs, blood samples can only be taken in those cases where the police have reasonable suspicion that the driver is under the influence of a substance which is impairing driving performance.

Sweden is likely to produce new legislation within six months which will probably include a zero tolerance limit for illegal drugs.

3.1.6 Germany

Police may require a driver to give specimens if there is cause to suspect them of DUI. Experts may indicate positive evidence of the presence of given medicinal drugs in the blood to be the cause of the violation in a court situation, but this is considered to be a rare event in the experience of the German authorities (de Gier, 1993).

Since August 1988, blood samples containing cannabis, heroin, morphine, cocaine, amphetamines and their analogues can result in a driver being arrested for a regulatory offence. Tests can be carried out even without the driver having committed an offence. Germany has adopted a 'zero-tolerance' policy for drugged driving. Doctors must inform patients about the potential impairing effects of medication.

3.1.7 Spain

Spain has no specific legislation related to driving and drug abuse. Instead police and the civil guard may require a driver to give specimens if a driver appears to be endangering him/herself or other road users or if there is cause to suspect them of DUI. Experts may indicate positive evidence of the presence of given medicinal drugs in the blood to be the cause of the violation in a court situation, but this is considered to be a rare event in the experience of the Spanish authorities (de Gier, 1993).

A driving licence may be refused to a known addict.

Package inserts alert drivers to the possible impairing effects of medicines.

3.1.8 Italy

Police have powers similar to those in countries already mentioned. Urine samples can be screened for the presence of both licit and illicit drugs if there is clear reason to suspect a driver. Driving licences may be refused to any known addict or habitual alcohol abuser. There is no official list of drugs maintained by health authorities that could be used to require additional patient warning activities on the part of doctors and pharmacists (de Gier, 1993).

3.1.9 Netherlands

Police have powers similar to those in countries already mentioned. de Gier (1993) found that the Forensic Laboratory receives about 250 requests for blood sample analyses every year, one third for illicit drugs and two thirds for medicinal drugs.

Published guidelines outline conditions in which a person is unfit to drive where medicinal drugs are concerned. However, the system does not take into account the differences between differing drugs and doses.

After a general information campaign on the influence of drugs on driving, a questionnaire study revealed that 70 % of patients who were using a labelled drug still had not changed their behaviour towards driving (de Gier, 1993).

A graded level warning system for drugs which impair driving performance has been proposed by Dutch scientists.

3.1.10 Ireland

Members of the Garda Síochána or Irish police force may stop a driver suspected of DUI under the 1994 Traffic Act if there is sufficient cause to do so. They may then be taken to a Garda station and required to give a blood or urine sample if intoxicants other than alcohol (that is drugs) are suspected.

In accordance with Road Traffic Legislation, the Medical Bureau of Road Safety arranges for the determination of the presence of drugs in the sample and this arrangement involves analyses being carried out by the State Laboratory.

Medical evidence, although helpful in a court of law, is not essential in deciding whether or not a driver was unfit to drive as a result of drug ingestion.

General package inserts inform the public as to the likely impairing effects of medication.

3.1.11 United Kingdom

Police have powers similar to those in countries previously mentioned. Several roadside screening devices have been tested in the UK.

General package inserts inform the public as to the likely impairing effects of medication although no official list of drugs is maintained by health authorities that could be used to require additional patient warning activities by physicians and pharmacists. There are no specific leaflets on drugs and driving for patient information.

The warning on drug labels affixed by pharmacists are not considered as being very effective, since patients don't see pharmacists as health care providers who can advise them. de Gier (1993) found that the implementation of a European warning system would be considered an important contribution to traffic safety and public health in the UK.

3.1.12 Portugal

Police have powers similar to those in countries already mentioned. Although it is illegal in Portugal to drive whilst under the influence of narcotics, stimulants or illicit substances, there are no drug testing procedures in use outside of standard sobriety tests for alcohol consumption.

3.1.13 Luxembourg

Police have powers similar to those in countries previously mentioned. As things stand at present, Luxembourg does not have any drug testing procedures. However, if a driver has been stopped by police for erratic or unsafe driving they must submit themselves for a medical examination if asked to do so.

3.1.14 Greece

As in other EU countries, drivers suspected of DUI may be required to give a blood and/or urine sample for toxicological analysis. The central Anti-Drug Co-ordination Unit has recently suggested the implementation of drug testing procedures based on urine and blood analyses after fatal accidents. This proposal was made in the framework of the development of the Early Warning System in Greece and is under consideration by the Ministry of Public Order.

3.1.15 Finland

There are no legal limits for drugs and driving in Finland. A driver can be convicted for the intake of drugs if he/she is intoxicated to the extent that he/she may be dangerous to traffic safety. In order to identify drunken drivers in Finland, the police are authorised by law to submit drivers to the breath test even without any suspicion. If necessary, a blood and/or urine sample can be taken even against the will of the driver. A standardised roadside sobriety test is not yet in use in Finland.

Alcohol and drug determinations of suspected driving under the influence of alcohol and/or drugs are centred in the National Public Health Institute (KTL) in Finland. Drug analysis is performed at the request of the police. Blood samples of all cases are analysed for ethanol. The urine samples in the suspected drug cases are screened for other drugs usually only if the alcohol concentration is below 1.2 %. If a urine sample is not available, drug screening in blood is performed. After screening for the drugs in urine, blood concentrations are measured in order to evaluate the effects of the drug on driving ability.

Drugs that have potentially harmful effects on driving ability have warning labels on their packages.

3.1.16 Summary

Countries in the European Union have no laws defining illegal blood limits of illicit drugs or medicines. At present there is insufficient evidence to define safe levels where drugs other than alcohol are concerned. However it is common in the Union to withhold driving licences from individuals dependent on licit or illicit drugs which compromise driving abilities (Patel, 1995).

All EU Member States have legal provisions for prohibiting (DUI of) psychotropic substances in addition to alcohol in their Traffic Codes. However there are no specific criteria related to the different types of drugs (licit or illicit) or the extent of usage.

There are substantial differences between countries in applying sample analysis for the determination of drug abuse and it is often unclear under what circumstances police officers will require a driver to give a sample. Blood sample analyses are conclusive in a court's decision on DUI in Belgium, the UK, Germany and Spain. In Denmark, The Netherlands, Germany and Italy urine samples may be taken when blood sampling is deemed unacceptable on medical grounds and in Italy urine samples must be taken in the presence of a doctor. Police in France may hold a driver for medical examination in a psychiatric hospital.

de Gier (1993) concluded that, as regards identifying and checking driving under the influence of illicit or medicinal drugs, there is little police enforcement compared to that applied to alcohol related road safety problems in the EU. It is probable that EU licensing authorities would require more conclusive experimental and field data on increased accident risk before more effective methods for identifying drug-impaired driving could be legislated for. This would also be necessary before standardised dosage and duration instructions could be drawn up.

de Gier (1993) also concluded that, since government campaigns are mainly focused on alcohol and driving, and seldom mention the detrimental effects of medicinal and illicit drugs upon driving, one can expect a minimal awareness of the problem of drugs and driving among the driving public. Therefore, where medicinal drugs are concerned, people must rely on general package inserts. Although a uniform EU warning symbol may be useful, it may also come to be ignored, as suggested by reaction to a similar warning system in The Netherlands. The European Union's Committee for Proprietary and Medicinal Products has in fact enforced, albeit slowly, a three-tier warning system for identifying the possible impairing effects of drugs. In general, in the case of prescribed drugs, the medical profession could be involved to a greater extent in spreading awareness about the role of drugs in driving impairment.

3.2 Existing and Proposed Methods of Testing

Generally, without the aid of actual sample-measuring tests, police officers have to rely on standard field sobriety tests (SFSTs) based on breath tests or blood tests for alcohol. These tests do have a good track record, but suffer from a fundamental lack of speed in administration and processing. In some parts of the USA police are trained as Drug Recognition Experts (DREs) and can evaluate an individual for drug consumption based on a series of behavioural tests (Crandon, 1997).

Such tests involve (1) an initial breath test; (2) an interview; (3) a preliminary examination including having the person standing on one leg for 30 seconds, walking and turning tests, divided attention tests and a horizontal/vertical gaze nystagmus test; (4) dark room examination (including checks on pupil response); (5) vital signs examinations (blood pressure, temperature, etc.); (6) muscle rigidity examination; (7) examination of injection sites; (8) suspects' statements; (9) opinions of the evaluator are recorded; and (10) a toxicological examination for scientific confirmation. Ideally, the last step could be administered on-the-road with results produced on a time scale similar to or better than the initial breathalyser test, although the issue of 'fitness-to-drive' would still have to be addressed. Such schemes are also under test in Germany and in Scotland.

Standard laboratory drug testing of biological fluids generally consists of immunoassay screening followed by gas chromatographic-mass spectrometric (GC/MS) confirmation conducted on a urine sample (Kintz et al, 1998). Newer methods using sweat or saliva samples are potentially preferable because they are virtually non-invasive, fast, and easy to execute by non-scientists (e.g. police officers). For them to be able to compete with standard laboratory techniques, such tests must have a high sensitivity and a high specificity in order to avoid false positive and negative results. Sherwood (1997) points out that at present in the UK, an initial test for alcohol only costs approximately £15, whereas a subsequent laboratory analysis for drugs costs around £350. A further necessity for the newer techniques is therefore that they are cost-effective.

At present there are no roadside drug tests in regular usage, although several tests are now available including Triage, Ezscreen, Accupinch, Mach IV, Verdict, Biosign and I.D. Block (see Crouch et al, 1998)⁴. Drugwipe devices (Securetec, Ottobrun, Germany) have been developed which take a sweat specimen from the forehead, or armpit, and can be used with saliva also (drug traces are revealed by colour changes on the strip). The chemical test box uses antibodies to detect substances, and results are presented within approximately five minutes. If positive, drivers can be taken to a police station to give a blood or urine sample for confirmatory purposes. At present, a different device is required for different drugs, but the wipe can test for cannabis, amphetamines, MDMA, methadone, benzodiazepines, cocaine, barbiturates and opiates. There are also saliva-testing or "lollipop" technologies (Cozart Bioscience LTD, Oxfordshire) which give digital readouts from colour changes and these also can detect cannabis, amphetamines, MDMA, cocaine benzodiazepines and opiates. There is ongoing work concerned with establishing the sensitivity and specificity of many of these tests.

'Drugwipe' has been experimentally tested by Kintz et al (1998). They tested six subjects after oral ingestion of 60mg codeine. They found that, with the exception of one female subject, Drugwipe exposed the codeine in the sweat samples. However the saliva Drugwipe caused too many 'false negatives' for the authors to consider it reliable. The authors could not explain the non-detection in the female subject, or the poor saliva testing results, but suggest that the volume taken of saliva may not have been great enough, some interfering substances may have been present, or the sampling time (10 seconds) was too short. Overall however, the results for the sweat Drugwipe were promising.

An earlier use of saliva testing was conducted by Peel et al (1984). Fifty six saliva samples from 445 suspected drivers were analysed for the presence of cannabinoids, volatiles and benzodiazepines using the enzyme multiple immunoassay technique (EMIT) and confirmed by GC/MS. The authors concluded that the use of saliva was a potentially versatile non-invasive technique. More recently, the EMIT ETS system has been used to successfully screen for drugs using blood samples (Lillisunde et al, 1996). They suggest that this method can be used when urine samples are unavailable, although urine is preferred since drug concentrations are usually higher and can be detected for longer in urine. However the use of blood samples may be more

⁴ Most of the tests referred to in this section are new or under development. We did not have access to exact information regarding the sensitivity or specificity of these tests.

important with respect to the evaluation of driving performance related to the drug. Although the system is laboratory based, the through-time is about 50 samples per day, given three technicians working on the samples.

A recent development which uses only three drops of urine for drug testing is the Syva Rapid Test assay (Behring Diagnostics GmbH, Frankfurt). The test is a small hand-held device which displays easy-to-read results in five minutes. Negative outcomes are indicated when lines appear in both the test and control windows (a line in the control window only indicates a positive result). This test can detect THC, methamphetamine, opiates, amphetamines, phencyclidine, barbiturates, benzodiazepines, methadone and tricyclic antidepressants. It is currently available in the UK and Ireland, and will be available in Scandinavia, Spain and the U.S.A. as well as other countries (Labmedica, 1997). The simplicity of this procedure reduces the likelihood of human error.

Several other urine sampling 'on the spot' tests have been developed. For example, Syva and Roche have individual tests for amphetamines, opiates and cannabinoids. Merck/BDH have a 7-substance screen in just the one test, and Tepnol Diagnostics have developed a test wherein individual test sticks join together into the required combination. However these still fall short of the breathalyser tests since they require a flat surface to work on, require several minutes to process substances, the reagents which are used often must be kept cooled and good light is necessary to determine colour/pattern changes (UK Parliamentary report, 1996). They can be used for initial screening purposes however, and compared to laboratory techniques they are much cheaper (£5 - £30).

Buchan et al (1998) evaluated the accuracy, efficiency and cost-effectiveness of four on-site multi-analyte drug testing devices. 303 urine samples were tested with Triage (Biosite Diagnostics, U.S.A.), Abu-sign (Princeton BioMeditech, U.S.A.), OnTrack (Roche Diagnostic Systems, U.S.A.), and TesTcup (Roche Diagnostic Systems, U.S.A.) and confirmed by GC/MS testing. Overall the authors concluded that all the tests worked well, however the Abu-sign and TesTcup devices were superior, largely because they eliminate the need for reagent mixing/handling. In contrast the OnTrack was the most cumbersome. For cannabis, Abu-sign showed 100% sensitivity whereas OnTrack showed the least sensitivity at 82.9%. The situation was similar for cocaine, but all tests showed 100% sensitivity for opiates. All kits also showed excellent specificity and performed well on negative predictive value measures (i.e. the probability that a negative result is a true negative). The highest false-negative rate was only 8% (TesTcup).

OnTrack TesTcup and Abuscreen OnTrack were also tested by Crouch et al (1998) and compared to standard laboratory results (Abuscreen Online and GC/MS analysis). They found that TesTcup had virtually a 100% agreement with the laboratory tests when testing negative samples. For samples containing opiates and benzodiazepines the agreement rates were 100% and 98% respectively. Less agreement was found for THC however. OnTrack also had a 100% agreement when testing negative samples and samples containing opiates, although agreement was 91% for benzodiazepines. Again the least agreement was for samples containing THC. It was concluded that both on-site tests were effective and produced results comparable to laboratory tests.

Although some techniques have been examined which test hair samples, the consensus of opinion indicates that they are not reliably effective due to the inconsistent relationship between results and recent drug ingestion.

3.3 Issues Involved in Testing for Drug Use

Typically, Road Traffic Acts state that it is an offence to be in charge of a motor vehicle while "unfit to drive through drink or drugs." Although the acts give limits for alcohol, no limits are given for drugs. This obviously makes it difficult for police forces to arrest individuals suspected of driving whilst under the influence of drugs. Even if this is possible, in order for a conviction to be established, expensive and complex forensic evidence has to be produced. This in turn makes the police hesitant to arrest in the first place. Unlike the case with alcohol, it is often difficult to tell by external behaviour alone that an individual has been taking drugs. Indeed they may appear coherent and confident. This may be true even in the case of hallucinogenic drugs.

The subtle indications of drug use such as dilated pupils or increased heart rate may be especially difficult to spot by the untrained observer. Again, unlike the case with alcohol, it is difficult to establish a relationship between dose and effect. Due to the variable action of many drugs, the impairment obvious to a police officer may not be evident at all by the time a drug test is conducted. Unfortunately, it is virtually impossible to decide on a 'legal limit' for drugs, as some have suggested, since risk curves cannot be reliably calculated. It may therefore be more practical to carry out behavioural impairment tests. There is the additional problem that any legislation would have to legislate for drugs which can be used both legally and illegally.

One possible solution to this is to give police forces expert training in roadside behavioural evaluation of suspects. Such a scheme has been established in the United States (UK Parliamentary Office, 1996), and is relatively inexpensive to set up. Another approach to the problem is to establish roadside drug testing in a similar manner as the prevalent breathalyser tests, only using immunological assays, some of which were described above. This in itself suffers from several practical and logistical constraints, most notably that privacy needs to be ensured in order for the requisite urine sample to be given and thus some type of portable toilet/laboratory is necessary. However, the scheme is inexpensive compared to the cost of sending samples for professional analysis.

Evidently the ideal would be the development and use of techniques which can deal in real-time with non-invasive samples. It should be emphasised however, that merely demonstrating the existence of a drug trace in the body is not sufficient proof of being unfit to drive or that the drug was responsible for impaired psychomotor behaviour. Only if unfitness was proved, for example via a standard field sobriety test, could a conviction be secured.

3.3.1 Mandatory drug testing

It has been suggested on occasion that mandatory drug testing should occur for employees or individuals whose potential drug abuse could affect public safety, including highway safety. However this concept has sometimes been criticised for

amounting to little more than a "witch hunt" by those whom it may affect, who claim that it is not only intrusive, but also unnecessary and ineffective (Sutherland, 1992).

Such a situation has arisen in Canada in the multinational Imperial Oil Limited where it is compulsory for all new employees to have a urine sample screened. This scheme was attacked by the Canadian Civil Liberties Association under the Ontario Human Rights Code. The main criticism apart from the inherent privacy infringements was the possibility that workers taking legal prescription medicines could be discriminated against.

Sutherland (1992) also notes that the scheme may have ruled out the possibility of recovery for drug addicts and may have consequently caused a resumption of addictive behaviour. As the strategy stands, employees are screened for alcohol, cannabis, cocaine, amphetamines, opiates and phencyclidine hydrochloride; all urinalyses are confirmed by gas chromatography/mass spectrometry.

British Rail, London Buses, London Underground, BP, Shell and Texaco all have drug and alcohol testing procedures. The Confederation of British Industry (CBI) estimates that 8% of its members have formal drug-testing policies (Parliamentary Office of Science and Technology, 1996). The International Transport and Workers Federation (ITF) believes that the "targeting of transport workers is the result of a widespread, but totally unproven, belief that drug and/or alcohol abuse is a major factor in transport accidents" (Bargaining Report, 1993). In addition to the infringement of 'civil liberties' involved, they also believe that testing can only reveal whether the individual has consumed a substance not whether they are a habitual consumer or addict. There are evident concerns that victimisation, scapegoating and harassment may ensue.

Types of testing include:

- (1) Voluntary testing – despite the positive aspects of this, it still needs to be ensured that no negative consequences follow a refusal.
- (2) Pre-employment screening – it needs to be ensured that discrimination does not occur and that medicine users and non-addicts can still be employed.
- (3) Random testing (one-off probe or regular intervals) – reasonable grounds for this need to be established.
- (4) Regular testing (of whole groups in 'safety sensitive' positions).
- (5) 'For-cause' testing (of suspected individuals) – again, just cause must be established to prevent harassment, and the judgement should be based on more than one individual's assessment.
- (6) Post-accident testing.
- (7) Post-treatment testing – it is often suggested that random testing will not deter those dependent on drugs and that drug-related health promotion activities are preferable, especially activities such as performance appraisal which is more consistent with industrial relations practice (Bargaining Report, 1993).

3.3.2 Warning Labels

A recent Automobile Association report (Sherwood, 1997) notes that in the case of prescribed medication, where warnings on bottles and so forth are concerned, there is usually little acknowledgement that impairing side-effects generally wear off. However given the 'small-print' nature of most warnings it is likely that users may ignore them, or if it is stronger, may not take the medicine and thus unwittingly become a road hazard. There should perhaps be a differentiation between warnings for immediate effects and warnings for longer term effects.

Some countries use a warning symbol on bottles, but there is a risk that if this were widely used it would become ignored. Given that there are many 'newer' drugs which have less impairing side-effects, doctors should perhaps prescribe these in preference to the older drugs, although the newer ones may be more expensive (to produce and/or use). If an individual has taken medicinal drugs and subsequently committed a crime (such as DUID), the drugs may actually exonerate them from the crime. In addition, a pre-existing condition such as epilepsy may have played a role. Issues such as the instructions the person was given by their GP/pharmacist, the bottle instructions and the dosage are important because the person may have committed the crime unwittingly - or may have combined drugs, or taken them at the wrong time or dosage. However, Samuels (1987) admits that drugs can never really be a defence.

3.4 The Possibility of Registering New Drugs

Where registration for new drugs intended for future patient use is concerned, O'Hanlon et al (1986) have noted that it is important that *some* type of drug test is implemented because the effect of having nothing is to potentially cause loss of life, whereas the cost of having some type of test is likely to be counted in monetary terms only. The results of a test or battery of tests could be used in several ways: (1) To completely prohibit driving for the drugs' users (either for a specific time period measured from the time of last ingestion, or at the beginning of a regular administration period, or both); (2) To restrict the type of driving (e.g. night driving) during all or part of the drugs' use; (3) To issue specific warnings regarding the potential impairing effects of the drug by doctors or pharmacists; and (4) To require drug manufacturers to give explicit warning information on their products.

O'Hanlon et al (1986) further suggest that one test developed by the Traffic Research Centre may be a useful start. It consists of an actual driving test which is taken after ingestion of a drug, in which subjects have to maintain a constant speed (95km/hour) and steady lateral position between lanes on a 100km circuit in normal traffic. The main test measurement is the standard deviation of lateral position (SDLP), although whether this is a valid indicator of driving ability has been disputed. The authors admit that the test could not be applied during preliminary stages of drug screening, but may be useful until such a time as highly effective on-the-road tests can be used.

3.5 Towards a Unified Approach

Each country in the European Union has a different approach to drug testing. Based on a survey of 270 European laboratories, the Toxicology Experts Working Group

drew up a list of recommendations to try and establish uniformity amongst the different countries (de la Torre et al, 1997).

As regards sample handling and chain of custody it was proposed that (a) Sample collection procedures should ensure privacy for the donor; (b) A split sample is preferable (A and B aliquots) to permit dual analysis; (c) Although it is preferable for only the one laboratory to carry out all of the necessary tests, it is permissible to exchange samples between co-ordinated laboratories provided that chain of custody procedures are strictly adhered to; (d) All stages of analysis, including transportation, must be well-documented; (e) Chain of custody procedures must be audited; and (f) Samples not complying with the above regulations should be rejected. If all these proposals were put into practice, the preservation of the sample's integrity, test validity, and the maintenance of confidentiality should be ensured.

Regarding cut-off values it was proposed that (a) Cut-off values should be formally stated. This should limit the current confusion which exists regarding cut-off values for the identification of specific substances; (b) The following cut-off values were recommended for Workplace Drug Testing: Opiates 300mcg/l (confirmation, total morphine, 200mcg/l); Cocaine metabolites 300 mcg/l (confirmation, benzoylecgonine, 150mcg/l); Amphetamines 300 mcg/l (confirmation, amphetamine, 200mcg/l; methamphetamine, 200mcg/l; MDMA, 200mcg/l; MDA, 200mcg/l; MDEA, 200mcg/l); Cannabinoids 50mcg/l (confirmation, THC, 15mcg/l).

Concerning analytical methodology, it was proposed that (a) Validated immunoassays should be used for initial screening purposes; (b) Chromatographic methods coupled to mass spectrometry should be used for the subsequent identification of specific substances; (c) the quantification of drugs in biological fluids was recommended, and when mass spectrometry is used, isotopically labelled internal standards are preferable; (d) reference materials must be available in all laboratories (the survey had shown that this improved the performance of laboratories); (e) European regulations should facilitate the availability of drugs especially as low-concentration solutions; and (f) an organisation should be established with responsibility for providing reference materials, for holding test samples for educational and training purposes, and for devising methods of obtaining compounds not commercially available as reference substances.

The survey found that there were clear misunderstandings about terms such as 'cut-off' and the setting up of chromatographic techniques. To counter this, the following proposals were made regarding the educational requirements of all laboratory personnel, including directors: (a) minimum educational requirements for all relevant personnel should be defined; (b) educational updating should be required for all personnel; and (c) interpretation of results should be handled by the testing laboratory.

The survey also found that not enough laboratories were taking part in some form of External Quality Assessment Programme on Drugs of Abuse Testing (EQAPDAT) or Proficiency Testing Programmes (PTPs). These are important for laboratories to be accredited. Accordingly it was proposed that (a) laboratories should be accredited to EN45001 ISO Guide 25; (b) the other recommendations outlined above should form the basis for tailoring the EN45001 specifically for European drug testing; (c)

laboratories should take part in a EQAPDAT; and (d) existing EQAPDATs should collaborate on the establishment of homogeneous operation criteria.

Proposals for workplace testing also concur with several of these points (Bargaining Report, 1993):

- (1) Written consent must be obtained.
- (2) Blood and urine samples should be acquired in the presence of an independent witness.
- (3) Chain of custody procedures should be adhered to avoid contamination of, or interference with, the samples.
- (4) Split samples should be used to increase reliability.
- (5) Testing should be carried out by independent experts who can interpret the results. In addition, only government-certified laboratories should be used.
- (6) GC/MS should be used for initial *and* confirmatory screening.
- (7) Results should be interpreted to discriminate between medicinal use and illicit use.
- (8) A medical review officer should be used to arbitrate where a result is challenged.
- (9) Police should only be involved when a serious case has occurred.
- (10) All records should be confidential but available to the person concerned.

APPENDIX: Expert Workshop – Programme

The Health Research Board
in collaboration with the
Transport Policy Research Institute UCD

Study involving a
*Literature Review on the Relation between
Drug Use, Impaired Driving and Traffic Accidents*
on behalf of the EMCDDA, Lisbon

Workshop involving Invited Irish-based Experts
Dublin, 10 November 1998

AGENDA

- 1 Welcome by the Director of the Health Research Board
Dr Ruth Barrington
- 2 Chairman's Introduction
Professor Jim Crowley, UCD
- 3 Background to the Project
Ros Moran, HRB
- 4 Brief *Tour de Table*
- 5 Introduction to Work Package #1 (Methodological Issues)
Colin Gemmell
- 6 Discussion on Work Package #1
- 7 Work Packages #2 (Experimental/Laboratory Evidence) and #3 (Field Studies
of the relationship between Drug Use/Abuse and Traffic Accidents)
Colin Gemmell
- 8 Discussion on Work Packages #1 and #2
- 9 Work Package #4 (Procedures for Testing incl Legal and other Issues)
Colin Gemmell
- 10 General Discussion
All Participants
- 11 Summary and Conclusion

REFERENCES

- ADAMS, H. AND WERNER, C. (1997). From the racemate to the eutomer: (S)-ketamine. Renaissance of a substance? Anaesthetist. 46:12 1026-42.
- ADLER, C. M., GOLDBERG, T.E., MALHOTRA, A.K., PICKAR, D. AND BREIRER, A. (1998). Effects of ketamine on thought disorder, working memory, and semantic memory in healthy volunteers. Biol Psychiatry. 1 43:11 811-6.
- ALBERRY, I. P., GOSSOP, M. AND STRANG, J. (1998). Illicit drugs and driving: a review of epidemiological, behavioural and psychological correlates. Journal of Substance Misuse. 3, 140-149.
- ALVAREZ, F. J., PRADA, R. AND DEL RIO, C. (1992). Drugs and alcohol consumption amongst Spanish drivers. Forensic Science International. 53, 221-225.
- ALVAREZ, F. J., PRADA, R., DEL RIO, M.C. (1992). Patterns of drug consumption among Spanish drivers. Therapie. 47, 1, 63-6.
- ALVAREZ, F.J. AND DEL RIO, M.C. (1996). Drugs and Driving. The Lancet, 347, p.282.
- ASOH, T., UCHIUMI, M. AND MURASAKI, M (1995). The effects of tandospirone and diazepam on actual driving performance. Proceedings of the 13th International Conference on Alcohol, Drugs and Traffic Safety (T'95) NHMRC Road Accident Research Unit, The University of Adelaide, Australia, 5005.
- ATTWOOD, D., WILLIAMS, R., McBURNEY, L. AND FRECKER, R. (1981). Cannabis, alcohol and driving: effects on selected closed-course tasks. In: Alcohol, drugs and traffic safety, 3. (L.Goldberg, Ed.) Almqvist and Wiksell Int. Sweden. 938-953.
- AUGSBURGER, M. AND RIVIER, L. (1996). Incidence of interactions between drugs in 641 drivers suspected of DUID. Proceedings of the 34th TIAFT Meeting Interlaken/Switzerland, August 11-15.
- AUGSBURGER, M. AND RIVIER, L (1997). Drugs and alcohol among suspected impaired drivers in Canton de Vaud. Forensic Science International. 85 i2, 95-104.
- BARGAINING REPORT (1993). Alcohol and Drug Testing. Bargaining Report, 134, 12-14.
- BENZODIAZEPINES / DRIVING COLLABORATIVE GROUP, (1993). Are benzodiazepines a risk factor for road accidents? Drug and Alcohol Dependence. 33, 19-22.
- BERGHAUS, G. AND FRIEDEL, B. (1994). Methadon-substitution und Fahreignung (Methadone substitution and driving aptitude). Neue Zeitschrift Fuer BVerkehrsrecht. 7, 10, 377-381.

BERGHAUS, G. STAAK, M., GLAZINSKI, R., HOHER, K., JOO, S. AND FRIEDEL, B. (1993). Complementary empirical study on the driver fitness of methadone substitution patients. Alcohol, Drugs and Traffic Safety, methadone; psychomotor; experimental. T92, 120-126.

BETTS, T. AND BIRTLE, J. (1982). Effect of two hypnotic drugs on actual driving performance next morning. British Medical Journal. 285, 6345, 852.

BETTS, T., MARKMAN, D., DEBENHAM, S., MORTIBOY, D. AND McKEVITT, T. (1984). Effects of two antihistamine drugs on actual driving performance. Br Med J (Clin Res Ed). 288(6413), 281-2.

BHATTI, J. H., I (1989). The effects of terfenadine with and without alcohol on an aspect of car driving performance. Clin Exp Allergy. 19(6), 609-11.

BLOMBERG, R. AND PREUSSER, D.F. (1974). Narcotic use and driving behaviour. Acc. Anal. and Prev. 6, 21-32.

BOWDLE, T. A., RADANT, A.D., COWLEY, D.S., KHARASCH, E.D., STRASSMAN, R.J. AND ROY-BYRNE, P.P. (1998). Psychedelic effects of ketamine in healthy volunteers: relationship to steady-state plasma concentrations. Anesthesiology. 88:1 82-8.

BRAUER, L. H., JOHANSON, C.E., SCHUSTER, C.R., ROTHMAN, R.B. and deWIT, H. (1996). Evaluation of phentermine and fenfluramine, alone and in combination, in normal, healthy volunteers. Neuropsychopharmacology. 14:4 233-41.

BROOKHUIS, K. A., LOUWERENS, J.W. AND O'HANLON, J.F. (1986). EEG energy-density spectra and driving performance under the influence of some antidepressant drugs. In: 'Drugs and Driving', O'Hanlon, J.F. and de Gier, J.J. (Eds.) London: Taylor and Francis. pp.213-220.

BROOKHUIS, K. A., DE VRIES, G. AND DE WAARD, D. (1993). Acute and subchronic effects of the H₁-histamine receptor antagonist ebastine in 10, 20 and 30 mg dose, and triprolidine 10 mg on car driving performance. British Journal of Clinical Pharmacology. 36, 1, 67-70.

BROOKOFF, D., COOK, C.S., WILLIAMS, C. AND MANN, C.S. (1994). Testing reckless drivers for cocaine and marijuana. New England Journal of Medicine. 331, 8, 518-522.

BUCHAN, B. J., WALSH, J.M. AND LEAVERTON, P.E. (1998). Evaluation of the accuracy of on-site multi-analyte drug testing devices in the determination of the prevalence of illicit drugs in drivers. Journal of Forensic Sciences. 43, 2, 395-399.

BUCHANAN, J.F AND BROWN, C.R. (1988). 'Designer drugs'. A problem in clinical toxicology. Med Toxicol Adverse Drug Exp. 3(1), 1-17

BUDD, R. D., MUTO, J.J. AND WONG, J.K. (1989). Drugs of abuse found in fatally injured drivers in Los Angeles County. Drug and Alcohol Dependence. 23, 153-158.

CHAIT, L. D. (1994). Factors influencing the reinforcing and subjective effects of ephedrine in humans. Psychopharmacology. 113:3-4 381-7.

CHESHER, G. B., FRANKS, H.M., HENSLEY, V.R., HENSLEY, W.J., JACKSON, D.M., STARMER, G.A. AND TEO, R.K.C. (1976). The interaction of ethanol and Δ^9 tetrahydrocannabinol in man: effects on perceptual, cognitive and motor functions. Medical Journal of Australia. 2, 159-163.

CHESHER, G. B. (1989). Understanding the opioid analgesics and their effects on skills performance. Alcohol, Drugs and Driving. 5, 111-38.

CHIN, R. L., SPORER, K.A., CULLISON, B., DYER, J.E. AND WU, T.D. (1998). Clinical course of gamma-hydroxybutyrate overdose. Ann Emerg Med. 31:6 716-22.

CHRISTENSEN, L. Q., NIELSEN, L.M., NIELSEN, S. L. (1990). Traffic accidents and drivers suspected for drug influence. Forensic Science International. 45, 273-280.

CHRISTOPHERSEN, A. S., GJERDE, H. AND MORLAND, J. (1993). Benzodiazepines, THC and drugged driving in Norway. In: H.D. Utzelmann., G. Berghaus. and G. Kroj (Eds.) Proceedings in Alcohol, Drugs and Traffic Safety. T92 Cologne. p.1082-1087.

CHRISTOPHERSEN, A. S., BEYLICH, K.M., BJARNEBOE, A., FOSSER, S., GLAD, A., MARLAND, J. (1995/6). Prevalence of alcohol and drugs in blood samples from Norwegian drivers involved in road traffic accidents. Proceedings of the 13th International Conference on Alcohol, Drugs and Traffic Safety (T'95) NHMRC Road Accident Research Unit, The University of Adelaide, Australia. 5005.

CIMBURA, G., WARREN., R.A. AND BENNETT, R. (1980). Drugs detected in fatally injured drivers and pedestrians in the province of Ontario. Traffic Injury Research Foundation of Canada.

CLARKSON, P.M. AND THOMPSON, H.S. (1997). Drugs and Sport. Research findings and limitations. Sports Med. 24(6), 366-84.

COSBEY, S. H. (1986). Drugs and the impaired driver in Northern Ireland: An analytical survey. Forensic Science International. 32, 245-258.

COSGROVE, J. AND NEWEL, T.G. (1991). Recovery of neuropsychological functions during reduction in use of phencyclidine. J. Clin. Psychol, 47(1). 159-69.

CRANDON, L. (1997). Signs of Drugs. Police Review. 19 September.

CREIGHTON, F. J., BLACK, D.L. AND HYDE, C.E. (1991). 'Ecstasy' psychosis and flashbacks. Brit. J. Psychiat. 159, 713-715.

CROUCH, D., BIRKY, M.M., GUST, S.W. ROLLINS, D.E., WALSH, J.M., MOULDEN, J.V., QUINLAN, K.E. AND BECKEL, R.W. (1993). The prevalence of drugs and alcohol in fatally injured truck drivers. Journal of Forensic Sciences. 38, 6, 1342-1353.

CROUCH, D. J., CHEEVER, M.L., ANDRENYAK, D.M., KUNTZ, D.J. AND LOUGHMILLER, D.L. (1998). A Comparison of ONTRAK TESTCUP, Abuscreen ONTRAK, Abuscreen ONLINE, and GC/MS Urinalysis Test Results. Journal of Forensic Science. 43, 1, 35-40.

CURRAN, H. V. AND TRAVILL, R.A. (1997). Mood and cognitive effects of +/- 3,4-methylenedioxymethamphetamine (MDMA,'ecstasy'): week-end 'high' followed by mid-week low. Addiction. 92, 7, 821-31.

CURRIE, D., HASHEMI, K., FOTHERGILL, J., FINDLAY, A., HARRIS, A. AND HINDMARCH, I. (1995). The use of anti-depressants and benzodiazepines in the perpetrators and victims of accidents. Occupational Medicine. 45, 6, 323-325.

DE GIER, J. J., HART, B.J., NELEMANS, F.A. AND BERGMAN, H. (1981). Psychomotor performance and real driving performance of outpatients receiving diazepam. Psychopharmacology. 73, 340-344.

DE GIER, J. J., UIJPENS, L. AND NELEMANS, F.A. (1986). The effects of astemizole on actual car driving and psychomotor performance. In: 'Drugs and Driving', O'Hanlon, J.F. and de Gier, J.J. (Eds.). London: Taylor and Francis. pp.271-282.

DE GIER, J. J., 'T HART, B.J. AND NELEMANS, F.A. (1986). The effects of lorazepam and bromazepam on actual driving psychomotor performance of patients. In: 'Drugs and Driving', O'Hanlon, J.F. and de Gier, J.J. (Eds.). London: Taylor and Francis. pp.137-152.

DE GIER, J. J. (1993). Driving licences and known use of licit or illicit drugs. Study conducted with support of the Directorate General for Transport of the Commission of the European Communities. The Institute for Human Psychopharmacology, The Netherlands.

DE GIER, J. J. (1995) Drugs other than alcohol and driving in the European Union. Study conducted with support of the Directorate General for Transport of the Commission of the European Communities. The Institute for Human Psychopharmacology, The Netherlands.

DE GIER, J. J., VERMEEREN, A. (1995/6). Methodological guidelines for experimental research on medicinal drugs affecting driving performance: What happened after Padua and Cologne? Proceedings of the 13th International Conference on Alcohol, Drugs and Traffic Safety (T'95) NHMRC Road Accident Research Unit, The University of Adelaide, Australia, 5005

DE LA TORRE, R., SEGURA, J., DE ZEEUW, R. AND WILLIAMS, J. (1997). Recommendations for the Reliable Detection of Illicit Drugs in Urine in the European Union, with Special Attention to the Workplace. Annals of Clinical Biochemistry, 34, 339-344.

DEPARTMENT OF ENVIRONMENT, (UK) (1998). Report on incidence of drugs in road accident victims: interim results of survey, January 1998. Road Safety Division, Department of Environment, Transport and the Regions.

DETSCH, O. AND KOCHS, E. (1997). Effects of ketamine on CNS-function. Anaesthesist. 46 Suppl 1: S20-9.

DEVEAUX, M., PRANGERE, T., MARSON, J-C., GOLDSTEIN, P. AND GOSSET, D. (1996). The incidence of psychotropic drugs, opiates, and alcohol in fatally injured drivers: A prospective study in northern France. Journal of Analytical Toxicology. 20, 74.

DOTT, A. B. (1972). Effect of marihuana on risk acceptance in a simulated passing task. Public Health Service Report ICRD, RR-71-3, Washington DC.

DRUMMER, O. H. (1995/6). Drugs and accident risk in fatally-injured drivers. Proceedings of the 13th International Conference on Alcohol, Drugs and Traffic Safety (T'95) NHMRC Road Accident Research Unit, The University of Adelaide, Australia, 5005.

DYE, L. (1990). Measuring the effects of psychotropic drugs during the menstrual cycle: a methodological review. In: Hindmarch, I. and Stonier, P. (Eds.). Human Psychopharmacology: Methods and Measures (Vol.2). Chichester: Wiley and sons Ltd.

ELLINWOOD, E. H. Jr. AND HEATHERLY, D.G. (1985). Benzodiazepines, the popular minor tranquilizers: dynamics of effect on driving skills. Accid Anal Prev. 17(4), 283-90.

ENGLISH, S. (1997). 'Lollipop' may Lick Problem of Drivers on Drugs. The Times, October 9.

FAGAN, D., TIPLADY, B. AND SCOTT, D.B. (1987). Effects of ethanol on psychomotor performance. British Journal of Anaesthesia. 59, 961-965.

FISHBEIN, D. H. (1996). Female PCP-using jail detainees: proneness to violence and gender differences. Addict Behav. 21:2 155-72.

FRIEDEL, B. AND STAAK, M. (1992). Benzodiazepines and driving. Reviews in contemporary pharmacotherapy. 3, 415-474.

GENGO, F. AND MANNING M., C (1990). A review of the effects of antihistamines on mental processes related to automobile driving. J Allergy Clin Immunol. 86(6 Pt 2), 1034-9.

GERHARD, U. AND HOBI, V (1984). Cognitive-psychomotor functions with regard to fitness for driving of psychiatric patients treated with neuroleptics and antidepressants. Neuropsychobiology. 12(1), 39-47.

- GHONEIM, M. M., MEWALDT, S.P. and THATCHER, J.W. (1975). The effect of diazepam and fentanyl on mental, psychomotor and electroencephalographic functions and their rate of recovery. Psychopharmacologia. 14 44:1 61-6.
- GIROUD, C., AUGSBURGER, M., SADEGHIPOUR, F., VARESEO, E., VEUTHEY, J.L. AND RIVIER, L. (1997). Ecstasy - the status in French - speaking Switzerland. Schweiz Rundsch Med Prax. 86, 13, 510-23.
- GJERDE, H., BJORNEBOE, A., BJONEBOE, G.E. A.A., BUGGE, A, DEVRON, C.A, AND MORLAND, J. (1988). A three-year prospective study of rearrests for driving under the influence of alcohol or drugs. Accident Analysis and Prevention. 20, 1, 53-57.
- GJERDE, H., CHRISTOPHERSEN, A.S. AND MORLAND, J. (1992). Amphetamine and drugged driving. Journal of Traffic Medicine. 20, 1, 21-26.
- GORDON, N. B. (1970). Reaction times of methadone treated ex-heroin addicts. Psychopharmacologia. 16, 337-344.
- GORELICK, D. A. AND WILKINS, J.N. (1989). Inpatient treatment of PCP abusers and users. Am J Drug Alcohol Abuse. 15:1 1-12.
- GRAEVEN, D. B., SHARP, J.G. AND GLATT, S. (1981). Acute effects of phencyclidine (PCP) on chronic and recreational users. Am J Drug Alcohol Abuse. 8:1 39-50.
- HARRISON, C. SUBHAN, Z. AND HINDMARCH, I (1985a). Residual effects of zopiclone and benzodiazepine hypnotics on psychomotor performance related to car driving. Drugs Exp Clin Res. 11(12), 823-9.
- HEMMELGARN, B., SUISSA, S., HUANG, A., BOIVIN, J.F. AND PINARD, G. (1997). Benzodiazepine use and the risk of motor vehicle crash in the elderly. JAMA. 278, 1, 27-31.
- HERBERG, K. W. (1994). Antidepressives and traffic safety. Fortschr Neurol Psychiatr. 62 Suppl 1, 24-8.
- HERNANDEZ, M., McDANIEL, C.H., COSTANZA, C.D. AND HERNANDEZ, O.J. (1998). GHB-induced delirium: a case report and review of the literature of gamma hydroxybutyric acid. Am J Drug Alcohol Abuse. 24:1 179-83.
- HERSACK, R. A. (1994). Ketamine's psychological effects do not contraindicate its use based on a patient's occupation. Aviat Space Environ Med. 65:11 1041-6.
- HILDEGARD, G. AND BERGHAUS, G. (1998). Impairment of driving ability by medicines - metaanalysis of epidemiological studies. Proceedings of the International Congress "Road Safety in Europe".
- HINDMARCH, I. G., AC (1980). The effects of clobazam and lorazepam on aspects of psychomotor performance and car handling ability. Br J Clin Pharmacol. 10(2), 145-50.

HINDMARCH, I. HARRISON, C; SHILLINGFORD, C.A. (1988). An investigation of the effects of lofepramine, nomifensine, amitensine, amitriptyline and placebo on aspects of memory and psychomotor performance related to car driving. Int Clin Psychopharmacol. 3(2), 157-65.

HONKANEN, R., ERTAMA, L., LINNOILA, M., ALAHA, A., LUKKARI, I., KARLSSON, M., IVILUOTO, O., AND PURO, M. (1980). Role of drugs in traffic accidents. British Medical Journal. 281, 1309-1313.

HURST, P. M. (1962). The effects of d-amphetamine on risk-taking. Psychopharmacology. 3, 283-290.

HURST, P. M., WEIDNER, M.F. AND RADLOW, R. (1967). The effects of amphetamines upon judgements and decisions. Psychopharmacologia. 11(5), 397-404.

HURST, P. M. (1976). Amphetamines and driving behaviour. Accident Analysis and Behaviour. 8, 9-13.

HURST, P. M. (1987). Amphetamines and driving. Alcohol, Drugs and Driving. 3, 13-17.

IRVING, A. (1988). A proposed Investigation into Drug Impairment Testing Methodology. Int. Clin Psychopharmacol. 3, Supp 1, 99-109.

JANSSEN, W. H. (1979). Routeplanning en geleiding: een literatuurstudie. Rapport IZF 1979-C13. Institute for Perception TNO, Soesterberg.

JICK, H., HUNTER, J.R., DINAN, B.J., MADSEN, S. AND STERGACHIS, A. (1981). Sedating drugs and automobile accidents leading to hospitalization. American Journal of Public Health. 71, 12, 1399-1400.

JUDD, L. L. (1979). Effect of lithium on mood, cognition and personality function in normal subjects. Arch. Gen. Psychiatry. 36, 860-865.

JUDD, L. L. (1985). The effect of antipsychotic drugs on driving and driving related psychomotor functions. Accid Anal Prev. 17(4), 319-22.

KELLEY, D., WELCH, R. AND McNELLEY, W. (1978). Methadone maintenance: An assessment of potential fluctuations in behavior between doses. International Journal of the Addictions. 13, 1061.

KERR, J. S. HINDMARCH, I (1998). The Effects of Alcohol Alone or in Combination with Other Drugs on Information Processing, Task Performance and Subjective Responses. Human Psychopharmacology. 13, 1-9.

KINTZ, P., CIRIMELE, V. AND LUDES. (1998). Codeine Testing in Sweat and Saliva with the Drugwipe. International Journal of Legal Medicine, 111, 82-84.

KLEBELSBERG, D. (1988). Drugs and Traffic Safety, some basic reflections. IATSS Research. 12(1), 24-32.

KLEINSCHMIDT, S. AND MERTZLUFTT, F. (1995). Gamma-hydroxybutyric acid-significance for anesthesia and intensive care medicine? Anesthesiol Intensivmed Notfallmed Schmerzther. 30:7 393-402.

KOZENA, L., FRANTIK, E. AND HORVATH, M. (1995). Vigilance impairment after a single dose of benzodiazepines. Psychopharmacology. 119, 1, 39-45.

KRIGER, H. P., SCHULZ, E. AND MAGERL, H.J. (1995/6). The German Roadside Survey 1992-1994. Saliva Analyses from an Unselected Driver Population: Licit and Illicit Drugs. Proceedings of the 13th International Conference on Alcohol, Drugs and Traffic Safety (T'95) NHMRC Road Accident Research Unit, The University of Adelaide, Australia, 5005.

KRUGER, H.P., PERRINE, M.W.B., HUESSY, F.B. AND METTKE, M. (1999). Illicit drugs in road traffic (Appendix). Council of Europe (Pompidou Group). P-PG/Circrout (98)5.

KRYSTAL, J. H., KARPER, L.P., SEIBYL, J.P., FREEMAN, G.K., DELANEY, R., BREMNER, J.D., HENINGER, G.R., BOWERS, M.B. Jr. AND CHARNEY, D.S. (1994). Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry. 51:3 199-214.

KRYSTAL, J. H., KARPER, L.P., BENNETT, A., D'SOUSA, D.C., ABIDARGHAM, A., MORRISSEY, K., ABI-SAAB, D., AND J. D. BREMNER, BOWERS, M.B. Jr., SUCKOW, R.F., STETSON, P., HENINGER, G.R. AND CHARNEY, D.S. (1998). Interactive effects of subanesthetic ketamine and subhypnotic lorazepam in humans. Psychopharmacology. 135:3 213-29.

KUBITZKI, J. H. (1992/3). Driving behaviour and personality in methadone patients. Proceedings of the 14th International Conference on Alcohol, Drugs and Traffic Safety, Annecy. 1, 391-397.

KUITENEN, T., KIRKKLINEN, S. AND YLITALO, P. (1984). Comparison of the acute physical and mental effects of ephedrine, fenfluramine, phentermine and prolintane. Methods Find Exp Clin Pharmacol. 6:5 265-70.

KVALSETH, T. O. (1977). Effects of marijuana on human reaction time and motor control. Perceptual and Motor Skills. 45, 935-39.

LABMEDICA (1997). Simple, Rapid Test for Drugs of Abuse Introduced. Labmedica, 14, 5.

LANDAUER, A. A. (1986). Drugs and driving: historical perspectives, methodological principles and current problems. In: 'Drugs and Driving', O'Hanlon, J.F. and de Gier, J.J. (Eds.). London: Taylor and Francis. pp.17-28.

LATIES, V. G. A. Weiss, B. (1967). Performance enhancement by the amphetamines: A new appraisal. Neuropsychopharmacology. Proceedings of the 5th international congress of the Collegium Internationale Neuro-psycho-pharmacologium. Washington DC 1966. Ed. H. Brill. International Congress Series no. 129. Exerpta Medical Foundation, NY.

LAURELL, H. AND TORNROS, J. (1986). The carry-over effects of triazolam compared with nitrazepam and placebo in acute emergency driving situations and in monotonous simulated driving. Acta Pharmacol Toxicol. 58(3), 182-6.

LI, J., STOKES, S. AND WOECKENER, A. (1998). A tale of novel intoxication: a review of the effects of gamma-hydroxybutyric acid with recommendations for management. Ann Emerg Med. 31:6 729-36.

LILLSUNDE, P., MICHELSON, L., FORSSTROM, T., KORTE, T., SCHULTZ, E., ARINIEMI, K., PORTMAN, M., SIHVONEN, M-J. AND SEPPALA, T. (1996). Comprehensive drug screening in blood for detecting abused drugs or drugs potentially hazardous for traffic safety. Forensic Science International. 77, 3, 191-210.

LILLSUNDE, P. (1998). Commentary: Alcohol/drug users and traffic accidents - A review of epidemiological studies. Journal of Traffic Medicine. 26, 1-2, 5-10.

LINNOILA, M. AND SEPPALA, T. (1985). Anti-depressants and driving. Accident Analysis and Prevention. 17, 4, 297-301.

LOGAN, B. K. AND SCHWILKE, E.W. (1996). Drug and alcohol use in fatally injured drivers in Washington State. Journal of Forensic Sciences. 41, 3, 505-510.

LOGAN, B. K. (1996). Methamphetamine and driving impairment. Journal of Forensic Sciences. 41, 457-464.

LOGAN, B. K., FLIGNER, C.L. AND HADDIX, T. (1998). Cause and manner of death in fatalities involving methamphetamine. Journal of Forensic Science. 43, 1, 28-34.

LOUWERENS, J. W., BROOHUIS, K.J. AND O'HANLON, J.F. (1983). Antidepressant effects upon actual driving performance. Traffic Research Center, University of Groningen, The Netherlands, Tech. Rep. VK 83-05.

LUND, A. K., PREUSSER, D.F., BLOMBERG, R.D. AND WILLIAMS, A.F. (1988). Drug use by tractor-trailer drivers. Journal of Forensic Sciences. 33, 3, 648-661.

MADDUX, J. F., WILLIAMS, T.R. AND ZIEGLER, J.A. (1977). Driving records before and during methadone maintenance. Am J Drug Alcohol Abuse. 4, 1, 91-100.

MALHOTRA, A. K., PINALS, D.A., ADLER, C.M., ELMAN, I., CLIFTON, A., PICKAR, D. AND BREIER, A. (1997). Ketamine-induced exacerbation of psychotic

symptoms and cognitive impairment in neuroleptic-free schizophrenics. Neuropsychopharmacology. 17:3 141-50.

MANNO, J. E., IPLINGER, G.F., SCHULZ, N. AND FORNEY, R.B. (1971). The influence of alcohol and marihuana on motor and mental performance. Clin. Pharmacol. Therapeut. 12, 202-211.

MARQUET, P., DELPLA, P.A., KERGUEN, S., BREMOND, J., FACY, F., GARNIER, M., GUERY, B., LHERMITTE, M., MATHE'E, D., PELISSIER, A.L., RENAUDEAU, C., VEST, P. AND SEGUELA, J.P. (1998). Prevalence of drugs of abuse in urine of drivers involved in road accidents in France: a collaborative study. Journal of Forensic Science. 43, 4, 806-11.

MASON, A. P. AND MCBAY, A.J. (1984). Ethanol, marijuana and other drug use in 600 drivers killed in single vehicle crashes in North Carolina, 1978-1981. Journal of Forensic Sciences. 29, 4, 987-1026.

MATHIAS. (1996). Marijuana impairs driving-related skills and workplace performance. NIDA Notes. 11(1), p.6 and 8.

MATTILA, M. J., VANAKOSKI, J., KALSKA, H. AND SEPPALA, T. (1998). Effects of alcohol, zolpidem and some other sedatives and hypnotics on human performance and memory. Pharmacol Biochem Behav. 59, 4, 917-23.

MCBAY, A. J., OWENS, S.M. (1981). Marijuana and driving. National Institute on Drug Abuse (NIDA) National Institute on Drug Abuse (NIDA) Res Mongr. 34, 257-63.

McCARDLE, L. AND FISHBEIN, D.H. (1989). The self-reported effects of PCP on human aggression. Addict Behav. 14:4 465-72.

MELTZER, E. O. (1990). Performance effects of antihistamines. J Allergy Clin Immunol. 86, 4 Pt 2, 613-9.

MERCER, G. W., JEFFERY, W.K. (1995). Alcohol, drugs and impairment in fatal traffic accidents in British Columbia. Accident Analysis and Prevention. 27, 3, 335-343.

MICHEL, C. H. AND BATTIG, K. (1989). Separate and combined psychological effects of cigarette smoking and alcohol consumption. Psychopharmacology. 97, 65-73.

MINISTERE DE L'INTERIEUR (1998) Usage et trafic de stupefiants - Statistiques 1997. OCRTIS, Paris.

MOELLER, M. R. AND HARTUNG, M. (1997). Ecstasy and related substances - serum levels in impaired drivers. Journal of Analytical Toxicology. 21, p.591.

MOSER, L. (1990). Effect of flutoprazepam on skills essential for driving motor vehicles. Arzneimittelforschung. 40, 5, 533-5.

MOSKOWITZ, H., ROBINSON, C.D. (1985). Methadone maintenance and tracking performance. Alcohol, Drugs and Traffic Safety. 995-1004, U.S. Department of Transport, Washington.

MOSKOWITZ, H. (1985). Marihuana and Driving. Accident Analysis and Prevention. 17, 4, 323-45.

NAHAS, G. G. AND LATOUR, C. (1992). Detection of cannabis and other drugs in 120 victims of road accidents. Proceedings of the Second International Symposium organised by the National Academy of Medicine, with assistance of the City of Paris.

NAKAHARA, Y., TAKAHASHI, K., STIMAMINE, M. AND TAKEDA, Y. (1991). Hair analysis for drug abuse. 1. determination of methamphetamine and amphetamine in hair by stable isotope dilution gas chromatography/mass spectrometry method. Journal of Forensic Science. 36, 1, 70-78.

NATIONAL HIGHWAY TRAFFIC SAFETY ADMINISTRATION. (1993). Impact of the drug evaluation and classification program on enforcement and adjudication. Traffic Tech NHTSA Technology Transfer Series, Washington: National Highway Traffic Safety Administration. 58.

NATIONAL HIGHWAY TRAFFIC SAFETY ADMINISTRATION. (1994b). Traffic safety facts 1993: alcohol. U.S. Department of Transportation, National Center for Statistics and Analysis.

NATIONAL SAFETY COUNCIL. (1994). Accident Facts. 1994 Edition. Itasca, IL: the Council.

NATIONAL TRANSPORTATION SAFETY BOARD (USA), (1990). Safety study: fatigue, alcohol, other drugs, and medical factors in fatal-to-the-driver heavy truck crashes (volume 1). PB90-917002 NTSB/SS-90/91

NICHOLSON, A. N. (1979). Effect of the antihistamines, brompheniramine maleate and triprolidine hydrochloride, on performance in man. British Journal of Clinical Pharmacology. 8, 321.

NICHOLSON, A. N., SMITH, P.A. AND SPENCER, M.B. (1982). Antihistamines and visual function: studies on dynamic visual acuity and the pupillary response to light. British Journal of Clinical Pharmacology. 14, 683.

NICHOLSON, A. N. AND STONE, B.M. (1982b). Performance studies with the H1-histamine receptor antagonists, astemizole and terfenadine. British Journal of Clinical Pharmacology. 13, 199.

NIELSEN, S. CHRISTENSEN, L.Q. AND NIELSEN, L.M. (1989). Analgesics, benzodiazepines and traffic. Ugeskr Laeger. 151(28), 1822-5.

O'HANLON, J. F. AND DE GIER, J.J. (1986). Drugs and Driving. London: Taylor and Francis.

O'HANLON, J. F. (1988). Experimental methods for determining the influence of drugs on driving: solutions in search of the problem. Proceedings of the T86 10th International Conference. Amsterdam. Elsevier Publications B.V. 9-12, Sept 1986, Noordizj, P.C., Roszbach, R., de Gier, J.J. Neuteboom, W., Zweiptenning (Eds). Excerpta Medica.

O'HANLON, J. F. (1988). Antihistamines and driving safety. Cutis. 42(4A), 10-3.

O'HANLON, J.F., BROOKHUIS, K.A., LOUWERENS, J.W. AND VOLKERTS, E.R. (1986). Performance testing as part of drug registration. In: O'HANLON, J. F. AND DE GIER, J.J. (1986). Drugs and Driving. London: Taylor and Francis.

O'HANLON, J. F. AND RAMAEKERS, J.G (1995). Antihistamine effects on actual driving performance in a standard test: a summary of Dutch experience, 1989-94. Allergy. 50, 3, 234-42.

O'HANLON, J. F., VERMEEREN, A., UITERWIJK, M.M., VAN VEGGEL, L.M. AND SWIJGMAN, H.F. (1995). Anxiolytics' effects on the actual driving performance of patients and healthy volunteers in a standardised test. An integration of three studies. Neuropsychobiology. 31, 2, 81-8.

OWENS, S. M., McBAY, A.J. AND COOK, C.E. (1983). The use of marihuana, ethanol, and other drugs among drivers illed in single-vehicle accidents. Journal of Forensic Sciences. 28(2), 372-79.

PALVA, E. S., LINNOILA, M., SAARIO, I. AND MATTILQA, M.J. (1979). Acute and subacute effects of diazepam on psychomotor sills: interaction with alcohol. Acta Pharmacologia Toxicologia. 44, 217.

PARLIAMENTARY OFFICE OF SCIENCE AND TECHNOLOGY (UK). (1996). Common Illegal Drugs and their Effects. (Report).

PARROTT, A. C., LEES, A., GARNHAM, N.J., JONES, M. AND WESNES,. (1998). Cognitive performance in recreational users of MDMA of 'ecstasy': evidence for memory deficits. Journal of Psychopharmacology. 12, 1, 79-83.

PATAT, A., STUBBS, D., DUNMORE, C., ULLIAC, N., SEXTON, B., ZIELENIUK, I., IRVING, A. AND JONES, W. (1995). Lack of interaction between two anti-histamines, mizolastine and cetirizine, and ethanol in psychomotor and driving performance in healthy subjects. European Journal of Clinical Pharmacology. 48, 2, 143-50.

PATEL, T. (1995). Just say 'Non' to Drugged Driving. New Scientist, November 11, p.12.

PEEKE, S. C., JONES, R.T. AND STONE, G.C. (1976). Effects of practice on marihuana-induced changes in reaction time. Psychopharmacology. 48, 159-163.

PEEL, H. W., PERRIGO, B.J. AND MIKAEL, N.Z. (1984). Detection of drugs in saliva of impaired drivers. Journal of Forensic Sciences. 29, 1, 185-189.

PEEL, H. W. AND JEFFREY, W.K. (1990). A report on the incidence of drugs and driving in Canada. Canadian Society of Forensic Science Journal. 23, 2&3.

PELISSER, A. L., L'EONETTI, G., KERGUELEN, S., BREMOND, J., BOTTA, A., CIANFARANI, F. AND GARNIER, M. (1996). Urinary screening of drugs of abuse among drivers involved in road accidents. Ann Biol Clin. 54, 10-11, 365-71.

PEREZ-REYES, M., WHITE, W.R., MCDONALD, S.A. AND HICKS, R.E. (1992). Interaction between ethanol and dextroamphetamine: effects on psychomotor performance. Alcoholism: Clinical and Experimental Research. 16, 1, 75-81.

PFENNINGER, E., BAIER, C., CLAUS, S. AND HEGE, G. (1994). Psychometric changes as well as analgesic action and cardiovascular adverse effects of ketamine racemate versus s-(+)-ketamine in subanesthetic doses. Anaesthesist. 43 Suppl 2: S68-75.

PICKWORTH, W. B., ROHRER, M.S. AND FANT, R.V. (1997). Effects of abused drugs on psychomotor performance. Experimental and Clinical Psychopharmacology. 5, 3, 235-241.

PIDETCHA, P., CONGPUONG, P., PUTRIPRAWAN, T., REKAKANAKUL, R., SUWANTON, L. AND TANTRARONGROJ, S. (1995). Screening for urinary amphetamine in truck drivers and drug addicts. J Med Assoc Thai. 78, 10, 554-8.

POKLIS, A., GRAHAM, M., MAGINN, D., BRANCH, C.A. AND GANTNER, G.E. (1990). Phencyclidine and violent deaths in St. Louis, Missouri: a survey of medical examiners' cases from 1977 through 1986. Am J Drug Alcohol Abuse. 16:3-4 265-74.

POPE, H. G., GRUBER, A.J. AND YURGELUNTODD, D. (1995). The residual neuropsychological effects of cannabis- the current status of research. Drug and Alcohol Dependence. 38, 1, 25-34.

PRADHAN, S.N. (1984). Phencyclidine (PCP): some human studies. Neurosci. Biobehav. Rev. 8(4), 493-501.

RAFAELSEN, O. J., BECH, P., CHRISTIANSEN, J., CHRISTRUP, H., NYBOE, J. AND RAFAELSEN, L. (1973). Cannabis and alcohol: effects on simulated car driving. Science. 179, 76, 920-3.

RAMAEKERS, J. G., SWIJGMAN, H.F. AND OHANLON, J.F. (1992). Effects of Moclobemide and Mianserin on Highway Driving, Psychometric Performance and Subjective Parameters, Relative to Placebo. Psychopharmacology. 106, S, S62-S67.

RAY, W. A., GURWITZ, J., DECKER, M.D. AND KENNEDY, D.L. (1992). Medications and the safety of the older driver: is there a basis for concern? Human Factors. 34, 1, 33-47.

- REEVE, V. C. (1979). Incidents of marihuana in a California impaired driver population. California State Department of Justice, Sacramento, CA.
- ROBBE, H. W. AND O'HANLON, J.F. (1995). Acute and subchronic effects of paroxetine 20 and 40 mg on actual driving, psychomotor performance and subjective assessments in healthy volunteers. European Neuropsychopharmacology. 5, 1, 35-42.
- ROBBE, H. W. J. (1995/6). Marijuana's effects on actual driving performance. Proceedings of the 13th International Conference on Alcohol, Drugs and Traffic Safety (T'95) NHMRC Road Accident Research Unit, The University of Adelaide, Australia, 5005.
- ROBERTSON, M. D. AND DRUMMER, O.H. (1994). Responsibility analysis - A methodology to study the effects of drugs in driving. Accident Analysis and Prevention, 26, 2, 243-247.
- ROBINSON, C. D. AND MOSKOWITZ, H. (1985). Methadone maintenance treatment and aspects of skilled performance. Alcohol, Drugs and Traffic Safety, U.S. Department of Transport, Washington. 1145-1157.
- ROHRICH, J., SCHMIDT, K. AND BRATZKE, H. (1995). Detection of amphetamine derivatives in chemical toxicological studies 1987-1993 in the greater Frankfurt area. Blutalkohol. 32, 1, 42-9.
- ROTHENBERG, S., SCHOTTENFELD, S., MEYER, R.E. AND KRAUSS, K. (1977). Performance differences between addicts and non-addicts. Psychopharmacology. 52, 299-306.
- ROTHENBERG, S., SCHOTTENFELD, S., GROSS, K. AND SELKOE, D. (1980a). Specific oculomotor deficit after acute methadone, 1. Saccadic eye movements. Psychopharmacology. 67, 221-227.
- ROTHENBERG, S., SCHOTTENFELD, S., SELKOE, D. AND GROSS, K. (1980b). Specific oculomotor deficit after acute methadone, 2. Smooth pursuit movements. Psychopharmacology. 52, 299-306.
- ROTHENGATTER, T. (1997). Psychological Aspects of Road User Behaviour. Applied Psychology: An International Review. 46 (3), 223 - 234.
- ROYAL PHARMACEUTICAL SOCIETY OF GREAT BRITAIN, (1998). Cannabis.
- SAMUELS, A. (1987). Iatrogenic Crime: Medicinal Therapy, Prescribed Drugs, and Criminal Behaviour. Medical Science and Law, 27, 4, 302-303.
- SANDERS, A. F. (1986). Drugs, driving and the measurement of human performance. In: 'Drugs and Driving', O'Hanlon, J.F. and de Gier, J.J. (Eds.). London: Taylor and Francis. pp.3-16.

SCHMIDT, P., SCHEER, N. AND BERGHAUS, G. (1995). Marijuana use and driving - simulated and actual driving tests for determination of the influence of Marijuana - Literature review. Kriminalistik. 49, 4, 241-246.

SEPPALA, T. AND LINNOILA, M. (1980). Effects of zimeldine and other antidepressants on skilled performance: A comprehensive review. Acta Psychiatria Scandanavica. 68, (S 308), 135-140.

SHARMA, S. AND MOSKOWITZ, H. (1975). Marihuana effects on a critical tracking task. In: Proceedings, 81st Annual Conference, APA. 1035-1036.

SHERWOOD, N. (1998). A critical review of the effects of drugs other than alcohol on driving. Automobile Association (UK) Report. (Unpublished).

SIMPSON, H. M. (1987). Epidemiological and laboratory studies on alcohol, drugs and traffic safety. Alcohol, Drugs and Traffic Safety. Proceedings of the T86 10th International Conference. Amsterdam. Elsevier Publications B.V. 9-12, Sept 1986, Noordizj, P.C., Roszbach, R., de Gier, J.J. Neuteboom, W., Zweiptenning (Eds). Excerpta Medica.

SIVAK, M. (1997). Recent psychological literature on driving behaviour: what, where, and by whom? Applied Psychology: an International Review. 46, (3), 303 - 310.

SKEGG, D. C. G. (1979). Minor tranquillisers and road accidents. British Medical Journal. 1, 917-919.

SMART, R. G., SCHMIDT, W. AND BATEMAN, K. (1969). Psychoactive drugs and traffic accidents. J. Safety Res. 1, 67-73.

SMART, R. B. (1974). Marihuana and driving risk among college students. Journal of Safety Research. 6, 155-291.

SMILEY, A. M., MOSKOWITZ, H. AND ZIEDMAN, K. (1981). Driving simulator studies of marihuana alone and in combination with alcohol. In: Proceedings of the 25th Conference of the American Association for Automotive Medicine. 285-291.

SMILEY, AND MOSKOWITZ, H (1986). Effects of long-term administration of buspirone and diazepam on driver steering control. Am J Med. 80(3B), 22-9.

SODERSTROM, C. A., TRIFILLIS, A.L., SHANKAR, B.S., CLARK, W.E. AND COWLEY, R.A. (1988). Marijuana and Alcohol Use Among 1023 Trauma Patients. Archives of Surgery. 123, 733-737.

SOLD, M., LINDNER, H. AND WEIS, K.H. (1983). Effect of fentanyl, diazepam and flunitrazepam on memory function. A pharmacopsychologic study. Anaesthesist. 32:11 519-24.

STAAK, M., BERGHAUS, G., GLAZINSKI, R., HOHER, K., JOO, S. AND FRIEDEL, B. (1993). Empirical studies of automobile driving fitness of patients treated with methadone-substitution. Blutalkohol. 30, 6, 321-33.

STARMER, G. (1985). Antihistamines and highway safety. Accident Analysis and Prevention. 17(4), 311-7.

STARMER, G. A. (1986). A review of the effects of analgesics on driving performance. In: 'Drugs and Driving', O'Hanlon, J.F. and de Gier, J.J. (Eds.) London: Taylor and Francis. pp.251-269.

STEELE, M,T, AND WATSON, W.A. (1995). Acute poisoning from gamma hydroxybutyrate (GHB). Mo Med. 92:7 354-7

STEPHENS, B. G.AND BASELT, R.C. (1984). Driving under the influence of GHB. Journal of Analytical Toxicology. 18(6), 357-8.

STEVENSON, G. P., PATHRIA, M.N., LAMPING, DL., BUCK, L. AND ROSENBLOOM, D. (1986). Driving ability after intravenous fentanyl or diazepam. A controlled double-blind study. Invest Radiol. 21(9), 717-9.

SUTHERLAND, R. (1992). Mandatory drug testing: Boon for public safety or launch of a witch-hunt? Canadian Medical Journal. 146, 7, 1215-1220.

TEO, R. K. C. (1975). Alcohol, drugs and traffic accident risk. Traffic accident research unit, N.S.W. Department of Motor Transport, Sydney.

THAPAR, P., ZACNY, J.P., CHOI, M. AND APFELBAUM, J.L. (1995). Objective and subjective impairment from often-used sedative/analgesic combinations in ambulatory surgery, using alcohol as a benchmark. Anesth Analg. 80:6 1092-8.

THOMAS, R. E. (1998). Benzodiazepine use and motor vehicle accidents - systematic review of reported association. Canadian Family Physician. 44, p.799.

TOUBRO, S., ASTRUP, A.V., BREUM, L. AND QUADE, F. (1993). Safety and efficacy of long-term treatment with ephedrine, caffeine and an ephedrine/caffeine mixture. Int J Obes Relat Metab Disord. 17 Suppl 1: S69-72.

TUNBRIDGE, R. (1998). Drugging and driving. In: G.B. Grayson (Ed.) Behavioural Research in Road Safety VIII. Crowthorne, Transport Research Laboratory, 43-48.

ULRICH, L. (1994). Benzodiazepines in blood samples of alcohol intoxicated drivers. Blutalkohol. 31(3), 165-77.

VANLAAR, M. W., VOLKERTS, E.R., AND VANWILLIGENBURG, A.P.P. (1992). Therapeutic effects and effects on actual driving performance of chronically administered buspirone and diazepam in anxious outpatients. Journal of Clinical Psychopharmacology. 12, 2, 86-95.

VANLAAR, M. W., VANWILLIGENBURG, A.P.P. AND VOLKERTS, E.R. (1995). Acute and Subchronic effects of nefazodone and imipramine on highway driving, cognitive functions, and daytime sleepiness in healthy adult and elderly subjects. Journal of Clinical Psychopharmacology. 15, 1, 30-40.

VERMEEREN, A., DE GIER, J.J. AND O'HANLON, J.F. (1993). Methodological guidelines for experimental research on medicinal drugs affecting driving performance an international expert survey. Institute for Human Psychopharmacology, The Netherlands.

VESELIS, R. A., REINSEL, R.A., FESHCHENKO, V.A., WRONSKI, M., DNISTRIAN, A., DUTCHERS, S. and WILSON, R. (1994). Impaired memory and behavioral performance with fentanyl at low plasma concentrations. Anesth Analg. 79:5 952-60.

WARREN, R., SIMPSIN, H., HILCHIE, J., CIMBURA, G., LUCAS, D. AND BENNETT, R. (1981). Drugs detected in fatally injured drivers in the province of Ontario. In: Alcohol, drugs and traffic safety. (L. Goldberg, Ed.) Almqvist and Wiksell Int. Sweden.

WILLIAMS, A. F., PEAT, M.A., CROUCH, D.J., WELLS, J.K. AND FINKLE, B.S. (1985). Drugs in fatally injured young male drivers. Public Health Reports. 100, 1, 19-24.

WILLIAMS, H., TAYLOR, R. AND ROBERTS, M. (1998). Gamma-hydroxybutyrate (GHB): a new drug of misuse. Ir Med J. 91:2 56-7.

WINDHABER, J., MAIERHOFER, D. AND DANTENDORFER, . (1998). Panic order induced by large doses of 3,4-methylenedioxymethamphetamine resolved by paroxetine. J. Clin. Psychopharmacol. 18(1), 95-6.

WOLSCHRIJN, H., DE GIER, J.J., DE SMET, P.A.G.M. (1991). Drugs and Driving: a new categorization system for drugs affecting psychomotor performance. Maastricht: Institute for Drugs, Safety and Behaviour, University of Limburg.

WORLD HEALTH ORGANISATION, (1997). Cannabis: a health perspective and research agenda. WHO MSA/PSA/97 4.

WORM, K., CHRISTENSEN, H. AND STEENTOFT, A. (1985). Diazepam in blood of Danish drivers: Occurrence as shown by gas-liquid chromatographic assay following radioreceptor screening. Forensic Science Society. 25, 407-413.

ZACNY, J. P., LICHTOR, J.L., ZARAGOZA, J.G. AND deWIT, H. (1992). Subjective and behavioral responses to intravenous fentanyl in healthy volunteers. Psychopharmacology. 107:2-3 319-26.