

DRIVING UNDER THE INFLUENCE OF DRUGS

**Report from the
Expert Panel on
Drug Driving**

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GLOSSARY OF TERMS AND ABBREVIATIONS

ADHD

This refers to Attention Deficit and Hyperactivity Disorder, a classified as a disruptive behaviour disorder

ADME

This refers to the processes of drug absorption (A), distribution (D), metabolism (M) and excretion (E) in the body.

API

This refers to Active Pharmaceutical Ingredient and is the substance in a pharmaceutical drug that is biologically active.

Ataxia

Lack of coordination and balance

BCS

British Crime Survey

Bioavailability

The term used to describe the percentage of the administered drug which arrives unchanged in the general circulation. It is denoted by the letter 'F'

Biological fluid

A biological fluid is any fluid found in the body and may include blood, saliva, sweat or urine, which may be used to detect the presence of drugs in the body.

Binge/Bingeing

This refers to heavy episodic drinking. The Department of Health criteria for binge drinking is the consumption of ≥ 8 units at one time for males and ≥ 6 units at one time for females in a single session but normally drinking below the weekly recommended limits. Cocaine, amphetamine and metamphetamine use often occurs in binges during which time repeated dosing occurs at frequent intervals lasting a few hours to several days.

CAST

Centre for Applied Science and Technology based at the Home Office

Catecholamine

Hormone, including adrenaline, noradrenaline and dopamine, all involved as transmitter substances in brain function

CHM

The Commission for Human Medicines is an independent scientific advisory committee of the Medicines and Healthcare products Regulatory agency.

Commercial immunoassay screening test

This refers to a biochemical test that measures the presence or concentration of a drug in a solution through the use of an antibody or immunoglobulin (usually in urine and oral fluid).

Confounding factor

This refers to other factors that may independently affect the findings of a study. If the prevalence of these other factors differs between the groups being compared, they will distort the observed association between the event (e.g. road traffic accident) and exposure (e.g. drug use) under study. These distorting factors (e.g. driving conditions) are called confounding factors.

Conjugated Morphine

Morphine, when passing through the liver, becomes 'conjugated' i.e. gets converted into morphine-6-glucuronide in particular, but also other substances.

Cmax

Is the maximum concentration that a drug reaches in the general circulation following a single dose.

Crack

This is the term used for the freebase form of cocaine that can be smoked. It may also be termed rock, work, or base amongst others.

CNS

Central nervous system

CSEW

Crime Survey for England and Wales

Dopamine

One of the hormones involved as a transmitter substance in brain function.

Dose-response effect

A dose-response effect occurs when the likelihood and severity of an effect (the response) is related to the amount of exposure to the drug (the dose)

Double-blind experiment

This refers to an especially rigorous way of conducting research, in an attempt to remove subjective bias on the part of both experimental subjects and the researchers. In a double-blind experiment, neither the individuals nor the researchers know who belongs to the control group and who belongs to the experimental group. This is not revealed until after all the data have been recorded and analysed.

DRUID

This refers to the Integrated Project DRUID (Driving under the Influence of Drugs, Alcohol and Medicines) and seeks to find answers to questions concerning the use of drugs or medicines that affect people's ability to drive safely. The European Integrated

Project DRUID is a part of the 6th Framework Programme. It brings together 36 institutes from 18 European countries.

DVLA

This refers to the Driver and Vehicle Licensing Agency, which is the government agency responsible for maintaining a database of drivers and vehicles in Great Britain. The DVLA is an executive agency of the Department for Transport.

ELISA

This refers to Enzyme-linked immunosorbent assay and is a type of immunoassay test used for the identification of drugs in biological fluids.

EMCDDA

This refers to the European Monitoring Centre for Drugs and Drug Addiction that was established in 1993. It is an agency of the EU created to provide the EU and its Member States with a factual overview of European drug problems.

ESPAD

This refers to the European School Survey Project on Alcohol and Other Drugs and is a collaborative effort of independent research teams in more than forty European countries and the largest cross-national research project on adolescent substance use in the world. The overall aim with the project is to repeatedly collect comparable data on substance use among 15–16 year old students in as many European countries as possible.

First-pass metabolism

First pass metabolism occurs when a consumed drug loses the majority of its concentration before it reaches the circulatory system

Focal Point

This refers to the UK Focal Point on Drugs and is based at the Department of Health. It is the National Partner of the EMCDDA and provides information on the drug situation in England, Northern Ireland, Scotland and Wales.

Free morphine (or unconjugated morphine)

Salts of morphine e.g. morphine sulphate, in the form in which they are administered and prior to passage through the liver, where they get metabolised into water soluble substances, prior to excretion.

FSS

Forensic Science Service

GC-MS (Gas Chromatography/Mass Spectrometry)

This is an analytical technique used for the analysis and identification of chemical compounds. The GC/MS instrument consists of a gas chromatograph (GC) which separates individual chemical components of a sample, and a mass spectrometer which is used to detect and/or identify these components based on their mass.

HSCIS

This refers to the Health and Social Care Information Centre of the National Health Service in England and is a key source of social care information and provides national comparative data for secondary uses. The organisation was created on 1 April 2005 following a merger of parts of the Department of Health, parts of the NHS Information Authority, and the Prescribing Support Unit.

Half-life

This term refers to the time it takes for the concentration of a drug in blood while in the body to halve and can give an indication of for how long the effects of the drug may persist.

Hyperphagia

Excessive hunger

Hyperpyrexia

This refers to an excessively high temperature: elevated above that observed for a fever (also known as pyrexia) and has been linked to those using MDMA and ketamine.

Hypothalamic thermoregulation

This refers to the maintenance of body temperature which is a dynamic system controlled mainly by the anterior hypothalamus of the brain.

Immunoassay

This is a type of biochemical test which measures the presence or concentration of a substance in biological solutions such as blood or urine.

Intravenous injection

This refers to injection of a drug directly into the veins of the body's general circulatory system.

LOD

This refers to a laboratory's limit-of-detection. This is the lowest concentration of a drug that the analytical procedure can reliably differentiate from a concentration of zero and can be positively identified according to predetermined criteria and/or levels of statistical confidence.

LOQ

This refers to a laboratory limit-of-quantification. This is defined as the lowest measurable quantity of a drug that can be detected according to the technological limits of the equipment with an acceptable level of accuracy and precision.

Logistic regression

Logistic regression is part of a category of statistical models called generalized linear models for estimating the relationships among variables.

Metabolite

A break down product of the drug consumed

MHRA

This refers to the Medicines and Healthcare products Regulatory Agency which is an executive agency of the Department of Health.

MMT

This refers to methadone maintenance treatment and is the prescription of a fixed daily dose of the drug over a prolonged period.

Narcolepsy

This is a chronic sleep disorder which causes disruption to the normal sleep pattern, producing excessive sleepiness.

Nasal insufflation

This is the practice of inhaling substances into the body via the nose and is a common route of administration for many recreational drugs because it brings about a much faster onset of action than use by the oral route.

NDTMS

This refers to the National Drug Treatment Monitoring System, the official method of monitoring the extent and nature of structured drug and alcohol treatment in England.

NHTSA

This refers to the National Highway Traffic Safety Administration which is an agency of the Executive Branch of the U.S. government and part of the Department of Transportation having a similar role to the DVLA in the UK.

Nystagmus

This refers to uncontrolled eye movements, usually involving quick, jittery movements made by both eyes, both horizontally and vertically and which affects vision.

Opiates

Any of the opioid alkaloids found as natural products in the opium poppy.

Opioids

This term refers to drugs that include natural or synthetic substances, which relieve pain by binding to opioid receptors in the brain.

Parenterally

Administered or taken not through oral consumption and the digestive tract, but for example through injection

Pharmacokinetics

This is the science related to determining what 'the body does to a drug' that is being consumed, i.e. what happens to substances, in this case drugs, when they are consumed by a living person. This includes how the substance is absorbed, how it distributes in the body how it breaks down or changes within the body and how it is excreted.

Pharmacodynamics

This is 'what the drug does to the body', i.e. the effect that the drug has on the body of a living person. This report is particularly interested in how the drug affects the brain and central nervous system.

Placebo-controlled

A placebo is an inactive substance used as a control in an experiment. The placebo effect is the measurable, observable, or felt improvement, not attributable to the actual treatment. To eliminate the effect of positive thinking researchers often run placebo-controlled studies.

Prescription Pricing Authority

This refers to a unit within the National Health Service that provides prescribing information services for the primary care sector: to produce information for General Practitioners (GPs), Nurses, Primary Care Trusts (PCTs) and other NHS stakeholders about prescribing volumes, trends and costs.

Psychoactive

A psychoactive drug is any substance that affects the functioning of the central nervous system and in turn alters behaviour. This can be any substance whether used recreationally or prescribed.

Racemic

This refers to a compound in which two enantiomers are present (usually as an equal (1:1) mixture of dextro (D) and levo (L) isomers). Some drug molecules are chiral, and the enantiomers have different biological effects. They can be sold as one enantiomer or as a racemic mixture. For instance, a single amphetamine dose combines the neutral sulphate salts of dextroamphetamine and amphetamine, with the dextro isomer of amphetamine saccharate and D/L-amphetamine aspartate monohydrate. The prescription analgesic tramadol is also a race mate.

ROSITA-2 project

This refers to a project co-funded by the European Commission in 2003-2005 to evaluate the usability and analytical reliability of the onsite oral fluid (saliva) drug testing devices.

RRCGB

This refers to Reported Road Casualties Great Britain formerly Road Casualties Great Britain (RCGB) and before that Road Accidents Great Britain (RAGB) and is the official statistical publication of the Department for Transport (DfT).

RTA

Road Traffic Accident

SCJS

This refers to the Scottish Crime and Justice Survey (previously the Scottish Crime and Victimization Survey, SCVS).

Somnolence

Sleepiness

Standardized Incidence Ratio (SIR)

A mathematical expression that compares results in a given population (e.g. drivers) with the general population

Steady-state

This refers to when the rate of administration of a drug equals the rate of elimination (where each is one dose per dosing interval) and occurs after continuous, repetitive dosing of a medicine.

Subcutaneous injection

This refers to injection into the lower layers of the skin

Sublingual

Under the tongue

TIAFT

The International Association of Forensic Toxicologists

TRL

This refers to the Transport Research Laboratory a centre for transport research, providing consultancy and advice across a wide range of transport related issues. The TRL was established in 1933 by the government as the Road Research Laboratory (RRL), it was privatised in 1996.

Unconjugated morphine

(see Free Morphine)

UNODC

This refers to United Nations Office on Drugs and Crime which provides information on drug control and crime prevention. Specific topics include drug abuse and driving and crime prevention. <http://www.unodc.org/>

Window of detection

This refers to the period of time after administration that a drug and/or its metabolites remain detectable in body fluids.

BACKGROUND

Sir Peter North's review of drink and drug driving law in Great Britain which reported in 2010 confirmed that there is a significant drug driving problem. He carried out a thorough analysis of the problems regarding drug driving and set out a road map for action which included the recommendation to create a new offence. The Government accepted the recommendation and in the 2011 Department for Transport (DfT) Strategic Framework for Road Safety, the Government committed to explore the case for introducing an additional offence of driving with a specified controlled drug in the body, without the need for proving impairment. The proposed new offence would be a strict liability offence, in the same way as the offence of driving with more than the prescribed amount of alcohol in the body.

In spring 2012, the Department for Transport convened an expert Panel to provide technical advice related to a new offence on drug driving. The Crime and Courts Bill, which was introduced into Parliament in May 2012 makes provision for a new offence of driving, attempting to drive or being in charge of a motor vehicle¹ with a specified controlled drug in the body above the level specified for that drug. It also includes a power for the Secretary of State in relation to England and Wales, and Scottish ministers in relation to Scotland, to specify the controlled drugs and the limit for each in regulations. The Panel's advice will specifically inform these regulations.

The introduction of the new offence reflects increasing evidence that drug driving is a significant road safety problem, and that the existing offence (in section 4 of the Road Traffic Act 1988) is insufficient to deal with it effectively. Impairment by drugs was recorded as a contributory factor in about 3% of fatal road accidents in Great Britain in 2011, with 54 deaths resulting from these incidents. This compares to 9% or 156 fatal road incidents, with 166 deaths, which have impairment by drink reported as a contributory factor.² Some evidence suggests drug driving is a much bigger road safety problem than reported and may be a factor in 200 road deaths per year.³Contributory

¹Driving, attempting to drive or being in charge of a motor vehicle can include e.g. driving or attempting to drive cars, buses or lorries or riding or attempting to ride a motorbike

² Department for Transport, Reported Road Casualties in Great Britain, 2011 Annual Report.

³ Report of the Review of Drink and Drug Driving Law, Sir Peter North, June 2010; Department for Transport, Impact Assessment for the new offence of driving with a specified controlled drug

factors are recorded by police officers attending the scene of an accident. The factors are largely subjective, reflecting the opinion of the reporting officer, and are not necessarily the result of extensive investigation. Contributory factor data are likely to underestimate the true scale of the issue. Based on coroners and breath test data, the provisional estimate for the number of people killed in drink drive accidents was 280 in 2011 (15 per cent of all road fatalities).

Box 1: Extract from the Panel's Terms of Reference

1. To discern which compounds from the following list should form part of the statutory instrument related to a specific offence of driving whilst under the influence of drugs:
 - a. Amphetamine-type;
 - b. Benzodiazepines and hypnotics;
 - c. Cannabinoids (natural and synthetic);
 - d. Cocaine (including salt and crystalline forms);
 - e. Hallucinogens;
 - f. Opioids (natural and synthetic);
 - g. Other substances if the group considers they have a similar and significant presence in the population
 2. To consider different sources of evidence to help to establish the degree of risk associated with specific drugs in relation to road safety
 3. To establish whether it is possible to identify for average members of the adult population concentrations of the drugs identified (1a – 1g above) that would have an impairment effect broadly equivalent to blood alcohol content (BAC) of 80mg / 100ml.
 4. To establish whether in some specific circumstances different concentrations of these drugs (broadly equivalent to a blood alcohol content (BAC) of 50mg/100ml and 20 mg/100ml may be deemed necessary for road safety
 5. To consider in cases where such concentrations can be identified, for an average member of the adult population the degree of variability across the population, including for habitual users of these substances;
 6. To establish the likelihood of whether these concentrations would be exceeded through prescribed or otherwise legally obtained drugs (as distinct from illicit drugs). See extract from North review below;
 7. To consider the evidence relating to poly-substance use, such as the interactions between the drugs listed and alcohol in order to determine the effects of such interactions and the prevalence of impairment (risk in relation to road safety) due to such causes; and
- To report on all of the above to the Secretary of State.

in the blood above the level specified for that drug (and other consequential amendments) May 2012.

Extract from North Review:

Medical defence for offence of driving above the statutory prescribed drug limit:

“Some drugs which may be proscribed for driving might also be used legitimately, in accordance with medical advice (for example morphine may be prescribed for chronic pain or diazepam (a benzodiazepine) may be prescribed for anxiety). Indeed, the Review recognises that in some circumstances it may be more dangerous for a person to drive having not taken their medically prescribed drug than driving without having taken it. Drugs have different effects on different people and levels at which they are prescribed are likely to reflect this. It would clearly be wrong to put in jeopardy of prosecution those who are properly and safely taking medically prescribed drugs and driving in accordance with medical advice, for whom, despite the presence of a proscribed drug, there is no evidence of any driving impairment”.

The existing offence of driving while unfit through drink or drugs (in section 4 of the Road Traffic Act 1988) is considered to be of limited use, with a disproportionately small number of proceedings brought under it and a large proportion of those proceedings withdrawn or dismissed. In order to secure a conviction for driving while unfit through drugs it needs to be proven that:

- The suspect was driving, attempting to drive or in charge of a vehicle;
- He or she was impaired so as to be unfit to drive; and
- The impairment was caused by the drugs.

The Panel held 8 meetings between April and November 2012 and at its first meeting in April 2012 agreed Terms of Reference in line with the draft terms provided by the Department for Transport (Box 1). The Panel’s remit was to make recommendations with regard to which Controlled Drugs (included in the Misuse of Drugs Act 1971) should be specified in the subsequent regulations and to advise what an appropriate limit for each of those drugs might be. The Panel brought together a wide range of expertise including pharmacokinetics, pharmacology and psychopharmacology, forensic toxicology, misuse of drugs, clinical practice, mental health, addiction science and transport safety.

Panel Members:

- Dr Kim Wolff, King's College London - **CHAIR**
- Dr Roger Brimblecombe, Member of Advisory Council on Misuse of Drugs (ACMD)
- Dr J. Colin Forfar, Commission for Human Medicines
- Professor Robert Forrest, Sheffield University
- Hon. Professor Eilish Gilvarry, University of Newcastle
- Professor Atholl Johnston, Queen Mary, University of London
- Dr Judith Morgan, Driver and Vehicle Licensing Agency (DVLA)
- Professor David Osselton, Bournemouth University
- Dr Lily Read, Northamptonshire Healthcare NHS Foundation Trust
- Professor David Taylor, King's College London and South London and Maudsley NHS Foundation Trust

Panel Observer

- Dr Mark Prunty, Senior Medical Officer with responsibility for Alcohol and Drugs at the Department of Health

Parallel drug driving related work

The Panel was kept informed of, but was not involved in, a number of related strands of work. This includes the work on the primary legislation, i.e. the drug driving provisions in the Crime and Courts Bill which were led by officials in the Home Office and the Department for Transport. Policy officials from the Department for Transport carried out the secretariat function for the Panel and provided policy steers and updates on the legislative process. There was also a separate policy group led by the Department for Transport which has been concerned with the issues around the implementation of the legislation and wider drug-driving policy. It included representatives from the following departments and organisations: the Home Office, the Department of Health, the Ministry of Justice and the Medicines and Healthcare Products Regulatory Authority (MHRA). The policy group met regularly and took note of the Panel's progress and discussed related drug-driving policy issues.

The Panel was also kept aware of on-going work concerning the devices to be used in police stations to carry out preliminary drug tests for suspected drug drivers. The 'Type-approval' testing of such preliminary drug testing devices is the responsibility of the Home Office Centre for Applied Science and Technology (CAST). Similarly, procedures relating to police enforcement of the new legislation will be handled by the Association of Chief Police Officers (ACPO) and the Home Office, as well as the Association of Chief Police Officers for Scotland (ACPOS) and the Ministry of Justice, Scotland. The Panel

considered the issues related to screening devices and wider police enforcement only to the extent that they were directly relevant to the Panel's developing recommendations. A scientist from CAST and an advisor with a background in roads policing provided advice to the Panel on these issues.

1. INTRODUCTION

The main challenge in establishing recommendations for driving under the influence of psychoactive drugs is the need to provide an easily-understood and justifiable scientific rationale for particular drugs being covered by the offence of drug-driving, whilst recognising that the evidence base is dynamic and will develop as our knowledge and understanding increases. The Panel aimed to establish whether there was sufficient evidence in the scientific literature to be able to determine a relationship between the use of psychoactive drugs and an effect on driving performance in average members of the general public.

The terms of reference and the draft legislation defined the Panel's role to consider Controlled Drugs (i.e. drug subject to the provisions of the Misuse of Drugs Act 1971 (the 1971 Act) (Box 1.). The Panel has considered any psychoactive drug classified as a Controlled Drug under the 1971 Act and scheduled in any one of the 5 schedules to the Misuse of Drugs Regulations 2001 (as amended) (the 2001 Regulations) including controlled drugs that have no recognised medicinal purpose (i.e. those placed in Schedule 1 of the 2001 Regulations). However, the focus on 'psychoactive' drugs means the Panel has excluded the drugs in Schedule 4 Part 2 (anabolic steroids) from consideration.

Schedule 1 drugs are not usually prescribed (e.g. Lysergic Acid Diethylamide (LSD) and tetrahydrocannabinol (THC), the main active component of cannabis) unless for research or clinical trials under Home Office licence. Schedules 2, 3, 4 and 5 of the 1971 Act include medicines with a formal UK Product Licence (e.g. morphine, codeine-containing products) which may be prescribed or sold in a pharmacy (Box 1.1). For such medicines, the Panel considered those where there is evidence of road safety risk related to their use. No Controlled Drugs or medicines containing Controlled Drugs are available over-the-counter outside registered pharmacies, so medicines available for general sales are outside the Panel's remit.

The Panel has considered Controlled Drugs which are primarily used illicitly or in the context of misuse and also drugs that are primarily prescribed for the treatment of medical conditions and where a therapeutic benefit is expected. For both groups the Panel has looked at the road safety risk associated with their use while driving. The

Panel recognises that therapeutic drugs are also misused and that a clear distinction cannot always be made between the two groups.

Box 1.1: Categories of drugs the Panel has considered

Controlled Drugs - This is a legal definition and refers to those drugs that are controlled under the 1971 Act. This regulates the import, export, possession, supply, and other aspects of activities relating to those drugs specified in the 1971 Act. The **Advisory Council on the Misuse of Drugs (ACMD)** was established under the 1971 Act and its role includes advising ministers on substances "*which appear to them likely to be misused and of which the misuse is having or appears to them capable of having effects sufficient to constitute a social problem*" and on measures which ought to be taken, for example to restrict the availability of such drugs or supervise the arrangements for their supply.

Psychoactive drugs - This is the medical term for all those drugs which have an effect on the brain and central nervous system and alter behaviour or cognition. This group includes freely available drugs (alcohol and tobacco) as well as illicit drugs (e.g. cannabis) and medicinal drugs (e.g. benzodiazepines).

Prescription only medicines - This refers to those substances which, by virtue of an entry in the Prescription Only Medicines (Human Use) Order 1997, as amended, may be sold or supplied to the public only on a practitioner's prescription. The vast majority of controlled drugs are prescription only medicines (with the exception of those in Schedule 1 and, for the most part, 5 of the 2001 Regulations, the latter covering preparations containing small quantities of controlled drugs available as Pharmacy medicines)

Over-the-Counter (OTC) medicines - This term refers to medicines that can be sold by a pharmacist but do not require a prescription by a medical practitioner. For the purposes of the Panel's work, this group of drugs is relevant as there are some medicines in this group which can contain small quantities of controlled medicines.

Illegal drugs - This term refers to the circumstances under which a drug is possessed, so any controlled drug can be an illegal drug, including medicines such as benzodiazepines, if they have not been acquired via a valid prescription.

Nevertheless, the Panel's consideration of drugs used primarily for medical purposes has taken account of the particular circumstances of drivers using such medication. The Panel was keen not to create any obstacles for those on prescribed medication to continue using their medication as instructed and carry on with their normal activities, so long as this does not create a significant road safety risk for the patients themselves and other road users. Due consideration was given to the "medical defence" in the new drug driving clause, which is designed to protect patients who take their medication in accordance with the directions from their doctor or pharmacist, and the instructions accompanying the medication (to the extent that these are consistent with the directions given).

The following defence is included in the draft legislation and is designed to safeguard those who take medication which may contain a Controlled Drug which is specified for the purposes of the new offence but who take it in line with the directions given to them by their doctor or pharmacist or contained in the Patient Information Leaflet (PIL):

"It is a defence for a person ("D") charged with an offence under this section to show that:

-(a) the specified controlled drug had been prescribed or supplied to D for medical or dental purposes,

-(b) took the drug in accordance with any directions given by the person by whom the drug was prescribed or supplied, and with any accompanying instructions (so far as consistent with any such directions) given by the manufacturer or distributor of the drug, and

-(c) D's possession of the drug immediately before taking it was not unlawful under section 5(1) of the Misuse of Drugs Act 1971 (restriction of possession of controlled drugs) because of an exemption in regulations made under section 7 of that Act (authorisation of activities otherwise unlawful under foregoing provisions).

(4) The defence in subsection (3) is not available if D's actions were—

(a) contrary to any advice, given by the person by whom the drug was prescribed or supplied, about the amount of time that should elapse between taking the drug and driving a motor vehicle, or

(b) contrary to any accompanying instructions about that matter (so far as consistent with any such advice) given by the manufacturer or distributor of the drug.

(5) If evidence is adduced that is sufficient to raise an issue with respect to the defence in subsection (3), the court must assume that the defence is satisfied unless the prosecution proves beyond reasonable doubt that it is not.”

The new offence does not change the existing legal position whereby those who legitimately take their medication may be guilty of a road traffic offence (under Section 4 of the Road Traffic Act 1988) if they are impaired or ‘unfit’ to drive due to the effects of that drug.

Drug possession laws

It is also important to clarify that the Panel has been solely concerned with the relationship between drug use while driving and this should not be confused with or taken as an extension to existing legislation about possession or supply of drugs or the Government’s wider drugs strategy. Drug driving legislation is contained in the Road Traffic Act 1988 and has a separate policy aim from wider drug related legislation – namely it aims to improve road safety. The Government’s drugs strategy aims to reduce illicit and other harmful drug use and to increase the numbers recovering from their dependence. In particular, the strategy wants to offer support for people to choose recovery as a way out of drug and/or alcohol dependence.⁴ The new drug driving offence does not change this principle that the 1971 Act offence relates to unlawful possession, not use of a controlled drug. It creates an offence only for those who drive, attempt to drive or are in charge of a motor vehicle with a specified drug above a specified limit in the body.

Panel Approach

Setting a concentration or “limit” for a psychoactive drug, for the new drug driving offence, means that if a driver exceeds this threshold the driver can be prosecuted without the requirement to prove that he or she was impaired and that this impairment

⁴ HM Government, Drug Strategy 'Reducing demand, restricting supply, building recovery: supporting people to live a drug-free life' on 8 December 2010

was caused by the drug in his body. The implications of setting such a limit in law are therefore far-reaching, and the Panel members accept that their task in advising Government on such limits is crucial. Before recommending drug thresholds the Panel have therefore properly considered both the empirical (epidemiological) and experimental evidence, in relation to blood drug concentrations and driving behaviour, whilst being mindful of stakeholders, practical and ethical considerations.

Simulated driving experiments

Negative effects on the ability to drive have been shown to occur at the same concentrations of drugs in the body as effects begin to occur in laboratory simulator tests, however, specific measures of psychomotor performance cannot fully replicate the real driving behaviour of an individual under the influence of psychoactive drugs. This has been shown to be the case particularly for cannabis where driving scenarios have generally focussed on experienced cannabis users consuming the drug in controlled (laboratory) surroundings and undertaking tasks: there is high internal validity but little relation to the complex nature of driving in commonplace traffic settings (Ashbridge et al, 2012).

Although driving simulator tests offer a safe alternative to on-road driving assessments the prediction of actual driving performance is flawed because of the artificial quality of the driver-vehicle environment. There is wide variability in the nature of the driving scenes and the perceptual feedback generated by the vehicle. In addition subjects performing simulated driving tests may not consider the safety factor as much as those who undergo real driving tests, such that driver errors in simulated tests may exaggerate the actual risk of driving errors in real-life driving (Dassanayake et al, 2011). For this reason, the Panel has chosen to concentrate on the evidence of driving behaviour in 'real-life' situations.

Characterisation of safe driving

Legislation is in place in Great Britain for driving whilst impaired under Section 4 of the Road Traffic Act 1988 (Driving, or being in charge, when under influence of drink or drugs), which sets out that:

(1) A person who, when driving or attempting to drive a mechanically propelled vehicle on a road or other public place, is unfit to drive through drink or drugs is guilty of an offence.

Therefore the Panel has not sought to define and measure or proportion a concentration of a drug in a person's body to a certain degree of impairment. There are two main reasons for this decision. Firstly, there is no universal agreement on how to objectively measure impairment for psychoactive drugs and driving. Secondly, the Panel considered that defining impairment for several different classes of drugs would prove too complicated and not sufficiently robust to inform drug-driving legislation, if such a task could be completed at all. Psychoactive drugs impair individuals in different ways, for instance stimulants by increasing alertness and confidence, depressants by decreasing responsiveness, and hallucinogens affect a person's perceptions, sensations and self-awareness. The North Report set out the diverse effects of drugs in terms of their effects on the skills required for safe driving and emphasised the fact that drugs such as stimulants which may have some performance enhancing effects, for example by improving reaction times, often also have adverse effects such as reducing critical judgement, increasing impulsiveness or increasing error rates.

2. METHODOLOGY

There are many potential sources of information that could be drawn upon to determine the feasibility of establishing and making recommendations for thresholds (cut-off concentrations) in relation to driving under the influence of controlled drugs. The Panel considered both epidemiological and experimental data in its quest to assess the relationship between the use of a psychoactive drug and the potential to affect the ability to drive safely.

Estimating Traffic Risk

The Panel have aimed to use an objective measure of the effect of a drug on road safety and has been concerned with the estimation of risk of a driver's involvement in road traffic accidents whilst under the influence of psychoactive substances. In order that the recommendations would be relevant to drivers in general, the Panel concluded that findings should be based on scientific risk analysis and in particular, research that showed that the use of a psychoactive substance by a driver had a negative effect on road safety, for example, by increasing the relative risk or likelihood of an accident (Box 2.1). If, in addition the increased risk was correlated with a concentration of a drug in the body then this would be used to help establish thresholds.

The Panel considered both the relative risk (RR) and the odds ratio (ORs) of traffic accident involvement as the estimator of risk. In drug-driving research these statistical concepts both involve comparison of two groups of drivers (e.g. drug driver versus non-drug driver) and give an indication of the likelihood of a road traffic accident happening to the one group compared to the other. The OR is the ratio between the odds of having the event (e.g. being seriously injured) among those positive for a given drug and the odds of having the event among those tested negative for that substance.

Note was taken of the control for confounding factors such as age, gender, distance travelled, drug use history, use of alcohol, health status and other mental health disorders. The Panel considered the difference between two levels of road accident risk (being a fatality or being seriously injured in an RTA). The European study DRUID (Driving under the Influence of Drugs, Alcohol and Medicines) has classified ORs as "low risk" (OR <2.0), "medium risk" (OR >2.0 – 10.0) and "high risk" (OR >10.0) and

these classifications have been adopted for the purposes of the Panel's work. The Panel has generally looked at ORs above 2, although ORs that are less than 2 but greater than 1, where there is a narrow confidence interval that does not include 1, can also indicate that risk is significantly elevated.

Box 2.1: Definition of an Odds Ratio (DRUID D2.3.5; Davies et al, 1998)

The odds ratio (OR) and the relative risk (RR) of an event are two distinct statistical concepts.

Relative Risk: The risk (or probability) of an event happening is calculated by dividing the number of those who experience the event by the total number of people at risk of experiencing that event. The relative risk is the ratio between the risk of having the event in one group e.g. drug-drivers, and the risk of having the event in a comparison group, e.g. non-drug drivers.

Odds ratio: The odds ratio of an event can be calculated by dividing the number of those who experience the event by the number of those who did not experience the event. The odds ratio is the ratio between the odds of experiencing the event in one group, and the odds of experiencing the event in a comparison group.

In drug-driving research these statistical concepts both involve comparison of two groups of drivers (e.g. drug driver versus non-drug driver) and give an indication of the likelihood of a road traffic accident (RTA) occurring for the one group compared to the other. Where the initial risk of the event (such as an RTA) is low, then the odds ratio approximates well to the relative risk of the event (for further discussion of relative risks and odd ratios, see DRUID deliverable D2.3.5 and Davies et al, 1998).

Confidence Intervals (CI) are used to indicate the reliability of an estimate, such as an odds ratio estimate. A confidence interval calculated for an OR shows the range within which the true value of that OR is likely to lie. It is conventional to create confidence intervals at the 95% level, i.e. predicting the lower and upper values (indicated in brackets) within which it can be 95% certain that the true OR lies. A narrow CI indicates greater reliability of the estimate. (For further discussion of confidence intervals, see Davies & Crombie 2009)

The Panel was also aware of the statistical, toxicological and analytical limitations that needed to be taken into account when interpreting risk estimations from an epidemiological study. For example, the time between accident and sample collection and sample collection and laboratory analysis, in addition to the fact that epidemiological research does not always focus on causality, but rather on the associative connection between exposure to the substance and involvement in an accident.

Where epidemiological studies involved research populations that had too few positive samples to conduct an effective risk analysis, the Panel considered in addition experimental research data and blood-drug-concentrations from anonymised drug driving cases. These data were available from the former Forensic Science Service (FSS), which was the Government Agency carrying out the laboratory analysis of drink and drug drive blood samples on behalf of the Home Office. Some data were available for the period from 2004 and also from 2009 to 2012 from the FSS. Furthermore, the Home Office Centre for Applied Science and Technology (CAST) contributed data gathered from a forensic service provider which detailed the results of the laboratory analysis of blood samples in suspected drug drive cases predominantly from England and Wales between January 2008 and October 2012. Both data sets provided some data for the concentrations of those drugs for which evidential tests were carried out in suspected drug drivers.

Epidemiological Evidence

Epidemiological studies were considered in order to establish the prevalence of controlled drug use within the general population and in drivers in particular. This has included studies from Europe and further afield, where evidence specific to Britain was scarce or where international evidence was considered to be applicable. In particular, consideration was given to the traffic accident risk (i.e. risk of a serious or fatal road traffic accident) at different concentrations of single drugs in the body (De Gier et al, 2000; Netherlands Advisory Committee, 2010). Where possible, the Panel considered evidence from prevalence studies of accidents in drug-free and drug-exposed populations and attention was given to ensure that the drug concentrations were measured in the same body fluids (Barbone et al 1998; Mura et al 2003; Elvik 2012).

Although epidemiological studies are observational and do not establish a 'cause and effect' - detection of a drug in an accident-involved driver does not necessarily mean that the drug was the cause of the accident (Longo 2000) - this type of study does provide important data on drug prevalence. Accident responsibility studies enhance these findings and help establish if the drug in question is more prevalent in drivers responsible for accidents than in those who are not responsible for accidents.

Experimental studies: Meta-analysis

The Panel made use of meta-analyses that have been published in the scientific literature. Meta-analysis is a statistical technique in which the results of a number of experimental studies similar in a number of characteristics are accurately combined. The general aim of a meta-analysis is to estimate more powerfully the true effect size as opposed to a less precise effect size derived in a single study under a given single set of assumptions and conditions. Studies of interest were those that calculated the risk estimate (as an odds ratio or 'OR') of being seriously or fatally injured in a road traffic accident (RTA) whilst testing positive for psychoactive drugs. Where possible studies were considered which compared the risk associated with driving with different drugs in the body to the standard risk level for driving with blood alcohol concentrations between 20 mg and 80 mg alcohol per 100 ml of blood. The evidence considered by the Panel in this evaluation has included:

- Meta-analysis of studies that estimated the effects of psychoactive drugs on driving performance and accident risk (Ashbridge et al, 2012; Berghaus et al, 2010; Rapoport et al, 2009; Elvik, 2012)
- Meta-analysis of studies concerning the effects of psychoactive medicinal drugs (analgesics, hypnotics and antipsychotics included in the Misuse of Drugs Act 1971) on safe driving and accident risk (Elvik, 2012)
- Meta-analysis of the effects of psychoactive medicinal opioids (morphine, methadone and buprenorphine) on driving performance (e.g. Dassanayake et al, 2012)

Where meta-analyses were not available other scientific studies were considered including:

- Estimation of risk of traffic accident (fatal or serious injury) involvement for patients using psychoactive medicines (e.g. Barbone et al, 1998, Engeland et al, 2007, Meuleners et al, 2011)
- Estimation of the risk of responsibility for road traffic accidents for drivers testing positive for psychoactive substances (e.g. Gedegbeku et al, 2011; Jones et al, 2004; Longo et al, 2001)
- Studies of the effects and influence of stimulant drugs, their interaction with sleep deprivation and with alcohol on driving performance and accident risk. (e.g. Bosker et al, 2012; Hjalmdahl et al, 2012)

Reference values

Experimental studies considered by the Panel have included investigations that measure drug concentrations in biological fluids collected under different circumstances. For instance, reference ranges have been published following pharmacokinetic studies in healthy volunteers for different psychoactive substances. Effective blood drug concentrations are also available for many psychoactive medicines and are set by The International Association of Forensic Toxicologists (TIAFT) in particular, as well as by other bodies. In the case of psychoactive medicines, this means therapeutic concentrations, whilst in the case of illicit substances effective concentrations means those concentrations where most individuals (not drug dependent) would be expected to experience psychoactive effects.

The Panel has also discussed the literature and legislation with regards to drug driving in other countries especially in Europe. It has been particularly interested in the work of expert groups in the Netherlands and Norway which have advised their respective Governments about possible legal limits within similar parameters to those of this Panel.⁵The Norwegian law, which was introduced in 2012, sets specific limits for 20 drugs including both illegal drugs and those medicinal drugs which are defined as having

⁵ Netherlands Advisory Committee, Recommendation with respect to limits for drugs in the context of the proposed amendment to the Road Traffic Act 1994 (March 2010); telephone conferences with members of the Netherlands advisory committee, Prof Dr J de Gier and Prof Dr Alain Verstraete on 21 August 2012; Norwegian Institute of Public Health Specialist Advisory Group, The establishment of set legal limits on the effect of substances other than alcohol, December 2010

abuse potential. The legal limits in Norway are based on scientific assessments of the effects seen after consumption of drugs by non-dependent individuals and do not take into account the development of tolerance or interpersonal variations in effect. The Norwegian Specialist Advisory Group (Mørland et al, 2010), in establishing limits based on the effects of substances other than alcohol for drug driving legislation reported on 'intoxicating doses' (which were defined as those which frequently caused effects on the central nervous system, including psychomotor skills) and the accompanying maximum drug concentration in blood (C_{max}). The Panel used this material for reference in their considerations.

The Panel have also considered the report by the Dutch Advisory Committee which produced recommendations for limits for specific drugs in the context of drug driving. While the limits had not yet been implemented in law in the Netherlands, the Panel considered the methodology used by the Dutch group in recommending limits. The Dutch group drew upon epidemiological data gathered by the Netherlands Forensic Institute, NFI (2010) which reported the expected concentrations in plasma (or serum) and blood for the most commonly used drugs likely to cause a hazard when driving after taking an effective dose, and the median in blood for individuals suspected of breaching article 8 of the Netherlands Road Traffic Act 1994 (NFI 1999-2008). The Dutch approach was to set limits for a single drug and not to take into account drug-drug combinations or drug-alcohol combinations.

The Panel also referred to the findings of the EU DRUID Project that aimed to combat the problem of driving under the influence of psychoactive substances by providing a solid scientific base for European policy makers. The project, which involved 36 partners from 18 countries in Europe, consisted of different sub-projects (work packages). For instance, DRUID Work Package 2 aimed to assess the prevalence and risk of the use of illicit drugs, alcohol and psychoactive medicinal drugs by drivers in Europe. A total of 25 partners from 15 countries took part in various epidemiological studies, collecting data on the prevalence of alcohol and other psychoactive drugs in driving populations.

Although the UK did not participate in the DRUID project, the Panel have considered the findings and drawn on the data.⁶

Contextualisation for the British driving population

The Panel was also able to consider the results of the analysis of whole blood specimens submitted by police forces for laboratory analysis to the Forensic Science Service (FSS), in drug-driving cases in England and Wales.⁷ The data relate to cases where a medical practitioner or field impairment officer had considered the donor of the sample as unfit to drive as a consequence of suspected drug use. Consideration of the frequency with which a drug was encountered at different concentrations provided insights into actual drug driving behaviours among British drivers. In addition cumulative plots of the data assisted the Panel by indicating the frequency with which a measured concentration is encountered (Chatteron et al, 2007; Chatterton et al, 2008).

The Panel was also fortunate to have the support of the Centre for Applied Science and Technology (CAST), who also made available contextual data from sub-populations of the British driver population. The data, which is predominantly from cases in England and Wales, relate to cases of Road Traffic Accidents (RTA) or impairment witnessed by the police, followed by assessment by a forensic physician. A blood (or urine) sample could be taken if, in the opinion of the forensic physician, the driver had a condition which may be due to a drug. The data relate to cases between January 2008 and October 2012. The data included 3,616 blood samples which screened positive for one or more drugs by enzyme-linked immunosorbent assay (ELISA) and 2,995 blood samples analysed by gas chromatography – mass spectrometry (GC-MS) and which contained one or more drugs. The Panel was able to benefit from these prevalence data as well as drug-blood concentration data. The Panel noted that the time

⁶The reports and presentations related to the different work packages of the DRUID project can be found on the following website: www.druid-project.eu.

⁷The Forensic Science Service (FSS), which was closed operationally in March 2012, was a government-owned company which provided forensic science services to government agencies, including the analysis of evidential blood and urines samples in drug driving cases for police forces in England and Wales. The Panel had access to data sets from cases from 2004 onwards. The more recent data from 2009 to 2012 was provided by the Forensic Archive Ltd, the company which holds the FSS's data.

between any witnessed impairment and sample collection was unknown and likely to be variable, and due to polydrug use, many different compounds (including alcohol) may be found in one sample.

Drugs where road safety risk is apparent but data is limited

In some cases where low prevalence of epidemiological data did not allow the calculation of risk estimates as odds ratios for substances the results of scientific studies were taken into account: a process reported and used previously (Penning et al, 2010). For instance, common therapeutic levels were considered in comparison with blood drug concentration data from drug driving samples where concentrations of prescribed medicines were measured to establish whether thresholds could be set that differentiated between compliant and unimpaired patients and those driving while impaired by these medicines. In some cases research has correlated drivers apprehended for impaired driving with specific blood-drug concentrations, and where this information was available the Panel have drawn on it for its recommendations.

Pharmacokinetic and Pharmacodynamic considerations

Pharmacokinetics has been variously defined as the study of the relationship between administered doses of a drug and the observed blood (plasma or serum) or tissue concentrations (Box 2.2).

Box 2.2: Definitions of the terms Pharmacokinetics and Pharmacodynamics

Pharmacokinetics:

This is a branch of pharmacology that explores 'what the body does to a drug' and hence concerns itself with the quantification of drug absorption, distribution, metabolism and excretion (ADME). The bioavailability (F) of a drug indicates the percentage of the administered drug which arrives unchanged in the general circulation. The plasma elimination half-life of a drug ($t_{1/2}$) is the time necessary for the living body to reduce the plasma concentration by half, for example to decrease from a concentration of 100 µg/L to 50 µg/L.

Pharmacodynamics:

This is a branch of pharmacology that explores 'what a drug does to the body' and is concerned with the biochemical and physiological effects of drugs and the mechanism of action(s) on the body.

The Panel considered pharmacokinetic data to support the determination of thresholds. For defining the pharmacokinetic profile of licensed medication, standard prescribed therapeutic doses were used; for defining the profile of illicit substances, the usual pattern of consumption was considered. When the concentration of a drug in whole blood was compared with the therapeutic range in plasma or serum, a starting point for the Panel was the scientific papers reporting the maximal drug concentration (C_{max}) after a single therapeutic dose and the concentration at steady-state (C_{ss}) after long-term therapy.

To understand the impact of a drug on driver behaviour the Panel has also concerned itself, where necessary, with absorption, distribution, metabolism and excretion (ADME) of a drug as explained in Box 2.3, particularly the elimination half-life of the drug e.g. for cocaine. The manner in which a drug affects behaviour (Pharmacodynamics) was also taken into consideration. The Panel took note of the 'desired' therapeutic effect for medicines and the 'sought after' effects for illicit drugs and where reported, the impact on driving behaviour.

Box 2.3: An explanation of drug absorption, distribution, metabolism and excretion (ADME)**ADME (Absorption, Distribution, Metabolism and Excretion):**

Absorption: is described as the movement of a drug across cell membranes in order to get to the site of action (in the case of a drug the receptor site) via the circulatory system. This is an important consideration for drugs consumed by the oral route.

Distribution: is the dispersion of a drug throughout the fluids and tissues of the body or the reversible transfer of drug from one location to another within the body after the

drug enters the circulatory system. Some drugs (cannabis) are widely distributed in the body whilst others (heroin) are only present at the site of the receptors (the brain)

Metabolism: is the irreversible transformation of drugs into more water-soluble compounds (metabolites) to render the drug compatible for excretion, usually through specialised enzymatic systems in the liver that on the whole, diminishes their psychoactive effect.

Excretion: is defined as the loss of the drug from the body by elimination mainly by the kidneys (renal route) in urine or via the pulmonary route (for inhaled drugs only) as exhaled air or minor sites of drug excretion that release drugs into sweat, saliva, tears or breast milk

Medicines

Many drugs included in the Misuse of Drugs Act (1971), for instance benzodiazepines and opioids/opiates, are legitimately prescribed to a number of patient groups.

However, characterisation of these compounds for drug driving purposes is conceptually difficult because several different user groups, who use the medication in different circumstances, are involved, including:

- those who legitimately use licensed psychoactive medication
- those prescribed psychoactive medication for the treatment of drug/alcohol dependence
- those who are legitimately prescribed more than one psychoactive medication
- those for whom compliance is a problem (failure to adhere to prescribing advice)
- those who obtain prescribed psychoactive medication illicitly and use it alone or with other drugs for recreational purposes
- those who consume alcohol in combination with prescribed medication

In consideration of these different sub-populations, the Panel has established what provisions currently exists for drivers who fall into one of these groups and then reviewed how these drivers might be affected by the new drug driving offence depending on where thresholds for blood concentrations may be set. Discussion

regarding the existing provision considered whether they were sufficiently robust to deal with road safety risk or whether there was evidence that setting a legal threshold concentration for these drugs when driving would be beneficial from a road safety perspective. The Secretary of State for Transport acting through the medical advisers at the Drivers Medical Group, of the Driver and Vehicle Licensing Agency (DVLA), has the responsibility to ensure that all licence holders are fit to drive. The Panel has taken into consideration the legal basis of fitness to drive which is laid down in different pieces of legislation.⁸

Long term prescribing (chronic dosing)

The occurrence of sub-populations of drivers who are prescribed long-term opioids for pain control (e.g. codeine or dihydrocodeine) or for dependence (e.g. methadone and buprenorphine) has been recognised by the Panel and efforts made to look for clear scientific evidence of risk estimates for road traffic accidents and of the issue of tolerance to psychoactive medication when on long-term stable doses. The Panel noted that the DVLA allows those on supervised methadone or buprenorphine maintenance programmes to hold driving licences pending medical assessments. However, only a small proportion of the known number of patients prescribed these drugs in Britain are actually registered with the DVLA (approximately 3,000/200, 000). There is clearly an additional contextual caveat with regard to prescribed medicines which was considered by the Panel.

The Panel was concerned to establish whether the use of psychoactive medicines under medical supervision provides sufficient safeguards to ensure that the road safety risk for the users of such medicines is low and that where road safety risks are deemed to exist, potential road-safe alternative medications are considered to reduce that risk.

⁸Standards for fitness to drive are set out in the 2nd EC Directive on driving licences (91/439/EEC), which came into effect in the UK in January 1997, the Road Traffic Act 1988 and the Motor Vehicles (Driving Licences) Regulations 1999. The 2nd Driving Licence Directive was amended by Directive 2009/112/EC with effect from September 2009 and these amendments came into force on 15 September 2010.

Box 2.4: The Legal Basis for the Medical Standards of Fitness to hold a Driving Licence (DVLA)⁹

Section 92 of the Road Traffic Act 1988 (requirements as to physical fitness of drivers) refers to prescribed, relevant and prospective disabilities, which include drug misuse, as set out below:

A prescribed disability: is one that is a legal bar to the holding of the licence.

Certain statutory conditions, defined in regulation, may need to be met before a licence can be issued. An example of a prescribed disability is epilepsy or persistent alcohol or drug misuse.

A relevant disability: is any medical condition that is likely to render the person a source of danger while driving; an example is a visual field defect.

A prospective disability: is any medical condition which, because of its progressive or intermittent nature, may develop into a relevant disability in the course of time; an example is insulin-treated diabetes. A driver with a prospective disability may normally only hold a driving licence subject to medical review in one, two or three years.

However, there is also legislation in place with regard to individuals with medical conditions (Box 2.4). The Road Traffic Act 1988 places an obligation on the applicant for a driving licence to notify the DVLA if he / she is suffering from a medical condition which is currently or which may, in the future, affect the person's ability to drive safely at all times. When such a notification is received at the DVLA, consent is obtained from the applicant / driver in order that suitable medical enquiries can be undertaken: this often requires a questionnaire to be sent to the individual's doctor(s) for confirmation of the diagnosis and the impairment caused by the medical condition. Information will be obtained as to whether the prescribed medication causes any impairment which is likely to affect safe driving. All the cases are treated individually; with due regard being paid to the applicant's medical history and the particular circumstances which pertain with respect to the medication and any impairment which may exist.

⁹The Driver and Vehicle Licensing Agency is an executive agency of the Department for Transport. These standards are reviewed following updated advice from the Secretary of State's Honorary Medical Advisory Panels.

The Panel acknowledges that certain medical conditions e.g. epilepsy, diabetes or depression will require medication to treat or control the symptoms, and that driver safety might be impaired without such medication, i.e. if the driver's capacity to drive safely without medication is impaired by the symptoms of their medical condition. It is not envisaged that any recommendations to the Secretary for State would interfere with or alter the way in which drivers with medical conditions are treated at present.

The role of the Medical Branch at the DVLA is to assess the impact of medical conditions on driving. It is not their remit to deal with individual driving offences (such as the existing offence of driving while impaired through drugs) if there is no underlying medical disorder. The medical standards of fitness to drive are summarised in the publication, 'At a Glance Guide to the Current Medical Standards of Fitness to Drive'¹⁰. Information is given in the guide on the dangers of driving or attempting to drive whilst unfit due to medication. It is advised that doctors have a duty of care to advise their patients of the potential dangers of adverse effects from medication as well as interactions with other substances, especially alcohol.

In relation to road safety the Panel considered two scenarios of how the provisions in the draft new legislation might apply for patients who are licensed to drive, having reported their prescribed methadone use to the DVLA. For such a patient, provided the methadone had been taken as directed by the prescriber, the statutory defence would be available, should he/she be stopped by the police (for example in the context of involvement in a road traffic accident) and subsequently found to have a methadone concentration in blood above any limit set in law. However, if such a person were using additional methadone obtained illicitly to top up their prescription and they were found with a concentration above the limit set in law, s/he would not be able to rely on the medical defence and would be likely to be found guilty of the new offence. The same would apply if they consumed alcohol in combination with their prescribed methadone dose and proceeded to drive against the directions by the prescriber or instructions given by the manufacturer or supplier.

¹⁰www.dft.gov.uk/dvla/medical/atagance.aspx

The Panel supported the view of the British Medical Association (BMA) who in response to the Queen’s Speech of May 2012 (which introduced the Crime and Courts Bill) stated that:

“if the legislation is to include any prescribed and over-the-counter medications, it will need to be accompanied by clear information for prescribers, pharmacists and patients on which drugs are proscribed for driving. Furthermore, a programme to raise awareness among the general public will be essential”

Although not in its specific remit, the Panel agreed that it should make recommendations that clear information would need to be made available to all those involved in the provision of prescribed and over-the-counter medication including the manufacturer or supplier, healthcare providers, practitioners (doctors, nurses, pharmacists) and the patients themselves about which medicines are ‘a risk’ when driving so that everyone is properly informed and fully conversant with the potential risks associated with the use of these medicines and driving.

Drug manufacturers: categorisation of labelling on medicines and driving

The Panel was also mindful of the important roles of the Medicines and Healthcare products Regulatory agency (MHRA), executive agency of the Department of Health and its independent scientific advisory committee, the Commission for Human Medicines (CHM). The MHRA acts under the Medicines Act 1968 and European Union legislation to regulate safety, quality and efficacy of medicinal products. During 2012, the CHM advised the MHRA of its support for an approved legal framework to address the problem of driving whilst under the influence of drugs.

Box 2.5: Legal status of Medicines (MHRA)

The Medicines Act 1968 and Council Directive 2001/83/EC control the sale and supply of medicines. The legal status of medicinal products is part of the marketing authorisation (MA) and products may be available:

- on a prescription (referred to as Prescription Only Medicines (Pomes))

- in a pharmacy without prescription, under the supervision of a pharmacist (P). This includes preparations containing small amounts of e.g. codeine, morphine, where the individual dose and total package size are limited.
- on general sale (GSL) and can be sold over the counter in general retail outlets without the supervision of a pharmacist. These medicines may not contain any amount of Controlled Drugs.

Prescriptions can be issued by doctors, dentists, nurse independent prescribers, pharmacist independent prescribers and supplementary prescribers.

Mirroring the work of DRUID (research deliverable 2.3.1) the Panel considered the advice in the Summary of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for relevant medicines and the advice given to the Licensing Authority on all matters relating to medicines and driving. The Panel noted in particular the anxiety about 'P' licensed medicines (such as codeine) which can be obtained from a pharmacy without prescription and the potential for differences in the information or warnings given by the pharmacist and contained in the PIL (Box 2.5). It was agreed that the medical information provided that advises individuals about their medication would need to be evaluated to ensure that the risk when driving was clear.

International approaches to setting concentration thresholds for drug driving

Several approaches to setting a concentration threshold for a psychoactive drug in relation to road traffic legislation have been implemented across Europe. These have been described in detail in the DRUID report. For instance, some countries have instigated a programme of zero tolerance, which equates to a complete ban on the use of a specified drug whilst driving. The "actual" impairment approach has also proved popular and the United Kingdom, like other EU countries, has legislation to prosecute someone who is driving while unfit through drink or drugs (Section 4, Road Traffic Act 1988). A third approach is often referred to as the '*per se*' approach and is based on the detection of a drug in a driver above a defined cut-off concentration in blood. *Per se* thresholds are concerned with a specific concentration of a psychoactive substance in a biological matrix. There are several different options for a '*per se*' threshold.

- A threshold can be analytical and can refer to a laboratory's limit-of-detection (LOD), commonly employed in that laboratory. This is the lowest concentration of the drug that the analytical procedure can reliably differentiate from a concentration of zero and can be positively identified according to predetermined criteria and/or levels of statistical confidence.
- A threshold can be technical and can refer to the laboratory limit-of-quantification (LOQ). This is defined as the lowest measurable quantity of a drug that can be detected according to the technological limits of the equipment with an acceptable level of accuracy and precision and that guarantees a valid and reliable analytical determination of the drug of interest.
- A threshold can specifically relate to the effects of a drug and can be set to where an effect on driving ability has been shown to occur. A 'lower effect threshold' is set at the lowest concentration where an effect on driving has been observed. Detection of psychoactive substances in blood below this concentration does not imply recent drug use or being under the influence. A 'lower effect threshold' limit is usually equivalent to a blood alcohol concentration (BAC) of 20 mg of alcohol per 100 ml blood.
- A threshold can also relate to risk and refers to a drug concentration threshold set in whole blood indicating a certain accident risk associated with driving under the influence of a drug above that threshold. 'Risk thresholds' for instance, have been determined showing the same level of accident risk as a BAC of 50mg alcohol per 100 ml blood (DRUID, 2010).

The Panel agreed to recommend a '*per se*' approach with risk thresholds, based on the detection of a drug in a driver above a defined cut-off concentration (threshold) in blood that could be related to the risk of a road traffic accident. Even though 'risk thresholds' have been determined in the scientific literature it is noted that they remain approximations. For instance, having a drug concentration in blood under a set risk threshold does not automatically mean that the drug cannot be the explanation for the impaired driving behaviour. However, this caveat also exists for alcohol, where drivers will experience some differing degrees of impairment when their blood alcohol

concentration is lower than 80mg alcohol per 100 ml blood, which is the legal limit in the UK.

Groups and individuals who were consulted by the Panel or who provided their opinion

Various groups, organisations and individuals contributed to the work of the Panel and provided evidence or opinions. Panel members also conducted interviews via teleconference with experts or interested parties. The Panel also made use of published guidelines and papers already in the public domain concerned with drug-driving and of reports put to the Panel for consideration, or specifically produced following a request by the Panel. The following list details those organisations and individuals that the Panel made reference to or held conversations with:

- The International Council on Alcohol, Drugs and Traffic Safety (ICADTS)'s list of medicinal drugs with ratings in relation to driving which categorises drugs as either: Presumed to be safe or unlikely to produce an effect whilst driving (level 1); Likely to produce minor or moderate adverse effect whilst driving (level 2); Likely to produce severe effects or presumed to be potentially dangerous when driving (level 3).
- The DVLA's "At a Glance" Guide to the Current Medical Standards of Fitness to Drive. This publication is produced by the Medical Branch of the DVLA and summarises the national medical guidelines of fitness to drive. It is publically available on the DVLA website and the information in the booklet is intended to assist doctors in advising their patients whether or not they should inform the DVLA of their medical condition and what the outcome of medical enquiry is likely to be.
- Department of Health, Drug Misuse and Dependence - Guidelines on Clinical Management, London: The Stationary Office, HMSO 2007
- The Royal College of General Practitioners' curriculum statement (15.3) on 'Drug and Alcohol Problems' (2009). This confirmed the responsibility of the General Practitioner for providing general medical care to drug-using adults and the role of substitution treatment (such as methadone) as part of a combined approach to the treatment of those with problematic use (RCGP Curriculum 15.3 Drug & Alcohol

Problems Feb 2009). This role includes giving advice about the dangers of driving whilst prescribed substitution treatment particularly during dosage induction and dosage alteration.

- Clockwork Research Ltd produced short reports requested by the Panel.
- Napp Pharmaceutical Group and their PR Company provided written briefing and met with members of the Panel on 13 August.
- Prof Richard Langford, president of the British Pain Society and Dr Martin Johnson, Royal College of General Practitioners' Clinical Champion for Chronic Pain joined the meeting between Panel members and Napp via telephone conference Panel on 13 August.
- Teleconferences or meetings were also held with the following experts: Prof Dr Johan de Gier (University of Groningen) Prof Dr Alain Verstraete (University of Ghent), Emeritus Prof Malcolm Lader (King's College London), and Emeritus Prof Ian Hindmarch (University of Surrey).
- A member of the public who wrote to the Department for Transport asking his letter to be submitted to the Panel.
- Presentations with subsequent discussion were given by the Panel Chair to the Advisory Council on the Misuse of Drugs (ACMD) on 11 October, to the Parliamentary Advisory Council for Transport Safety (PACTS) on 16 October and to interested members of the House of Lords on 24 October.
- The Medicines and Healthcare products Regulatory Agency (MHRA) was kept informed of the Panel's work and meetings were held.

Summary of Procedure for determining drug thresholds for the Panel's Recommendations

1. Agree psychoactive drugs to be recommended for inclusion in the offence
 - a. Determination of prevalence of drugs in general and driving populations (Epidemiological studies)
2. Consider evidence available for determination of risk estimates
 - a. Characteristics of drivers who use psychoactive drugs (prevalence of use in roadside surveys and or seriously injured or killed drivers)

- b. Data and research on road traffic accident risk for drug drivers (case-control studies, experimental data that identifies blood concentration data)
 - c. Consideration of meta-analysis of road traffic accident risk for drug drivers
- 3. Consider evidence available for determination of thresholds.
 - a. Limits recommended for or used in other countries' drug driving legislation.
 - b. Pharmacokinetic and pharmacodynamics data of drugs
 - c. Reference values for drug concentrations in biological fluids observed in drug driving cases of drug driving
 - d. Normal therapeutic ranges for medicines, and average concentration-data for illicit drugs
- 4. Recommend possible drug thresholds limits
- 5. Consider all of the above evidence with respect to combination of drugs with alcohol and recommend threshold limits

3. INITIAL FINDINGS

EPIDEMIOLOGICAL OVERVIEW

This section summarises the main generic findings from the Panel's work, with the drug-specific findings set out in detail in subsequent chapters. A discussion of alcohol in the context of driving is included. This is because alcohol as a psychoactive drug with very well understood effects and with well-established legislative limits for the purpose of driving is an important reference point for developing recommendations for limits for other more complex psychoactive substances. The Panel have therefore particularly considered the road traffic accident risk information (ORs) for driving with different concentrations of blood alcohol.

Alcohol

Alcohol is a legal substance and there are few restrictions to its general and unlimited availability to adults in Europe. Epidemiological research demonstrates very clearly that it is the most commonly used psychoactive substance in Europe including the United Kingdom. This is also true of driver populations: a hospital study of seriously injured or killed drivers reported that alcohol ($>0.1\text{g/L}$ or 20 mg alcohol per 100 ml blood) was the most common toxicological observation (DRUID Deliverable 7.3.2, 2011). DRUID researchers report that in Europe amongst the drivers that tested positive, most had a high blood alcohol concentration (BAC): 90.5% of injured drivers and 87% of killed drivers had a BAC of $\geq 0.5\text{g/L}$: that is ≥ 50 mg alcohol per 100ml blood. The mean and median values for alcohol concentration in these drivers were 159 mg per 100 ml blood (mg/dL) and 160 mg/dL (injured) and 161 mg/dL and 167 mg/dL (killed), respectively. Alcohol was the only substance amongst those tested that appeared more often alone than in combinations (DRUID, Main Findings). It has also been observed in the UK, that drink-drivers continue to drive despite very high BACs. In 2010, 23% of car driver fatalities had a BAC level above the UK legal limit of 80mg alcohol per 100ml blood, and

6% had a BAC level of 200mg alcohol per 100ml or above (Reported Road Casualties Great Britain 2011 Annual Report: Drinking and Driving).¹¹

In the DRUID case-control study (D2.3.5) the risk of being seriously injured or killed was calculated against control data from the roadside survey (D2.2.3) and case data from the hospital study on killed drivers. The risk estimates (odds ratios) were adjusted for age and gender: the controls were weighted with traffic distribution in eight time periods over a week and estimated at different BAC for European drivers as shown in Table 3.1 below. A clear relationship is shown between increasing alcohol consumption and risk of a road traffic accident. Alcohol has been shown to affect driving performance unequivocally and highly increases accident risk.

Table 3.1: Overview of Odds Ratios (ORs) of getting seriously injured or killed based on alcohol concentration from aggregated data from DRUID studies.

BAC Seriously injured drivers	Adjusted Odds Ratios (95% CI)	BAC Fatally injured drivers	Adjusted Odds Ratios (95% CI)
0.1 ≤ BAC < 50 mg alcohol per 100 ml blood (0.5 g/L)	1.18 (0.81-1.73)	0.1 ≤ BAC < 0.5 g/L	8.01 (5.22-12.29)
0.5 ≤ BAC < 80 mg alcohol per 100 ml blood (0.8 g/L)	3.64 (2.31-5.72)	0.5 ≤ BAC < 0.8 g/L	45.93 (23.02-91.66)
0.8 ≤ BAC < 120 mg alcohol per 100 ml blood (1.2 g/L)	13.95 (8.15-21.88)	0.8 ≤ BAC < 1.2 g/L	35.69 (15.68-81.22)
BAC ≥ 120 mg alcohol per 100 ml blood (1.2 g/L)	62.79 (44.51-8.58)	BAC ≥ 1.2 g/L	500.04 (238.07-inf)

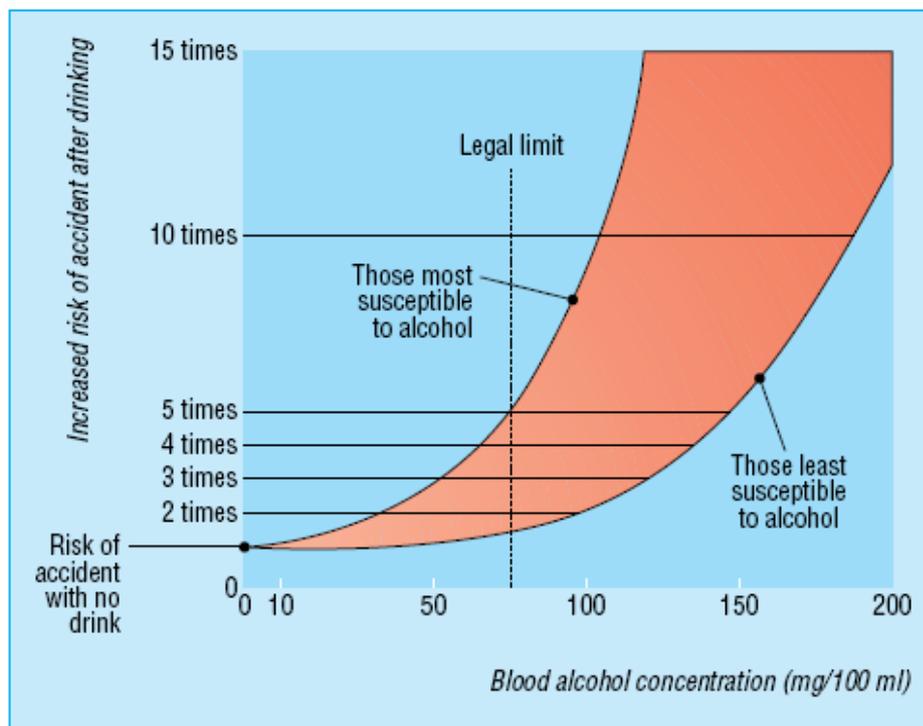
BAC = Blood alcohol concentration in g/L; CI = 95% confidence intervals

A reference curve (as shown in Figure 3.1) has been produced for alcohol that suggests that alcohol data delivered through different study methodologies - case control and responsibility studies, for instance - will lead to the same risk estimate and therefore alcohol may be used as a gold standard.

¹¹

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/9276/rrcgb2011-03.pdf

Figure 3.1: A reference curve to demonstrate the relationship between alcohol consumption and risk of a road traffic accident (Paton, 2005)



Effect of alcohol on behaviour

Alcohol affects driving behaviour by increasing reaction time and decreasing concentration, coordination and tracking. In addition, increasing alcohol consumption leads to risk-taking behaviour, since drivers overestimate their skills and underestimate the risk due to the effects of alcohol (Kelly et al, 2004). Different study designs have revealed different lower BAC concentrations for impaired behaviour. A recent epidemiological study on traffic accident risk indicated that the increased risk to the driver started at BAC below 50 mg alcohol per 100 ml blood (Blomberg et al, 2009). A meta-analysis revealed that in controlled experiments of real driving performance and complex divided attention tasks alcohol impairment occurred at BACs as low as 20 mg alcohol per 100 ml blood (Schnabel et al, 2010; Ogden & Meoskowitz, 2004).

Polydrug Use

The UK Focal Point on Drugs (United Kingdom Drug Situation, 2011) annual report to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) found that those

who consumed alcohol frequently had higher levels of recent drug use than those who consumed alcohol less frequently: drugs were used by 12.3% of adults who had drunk alcohol more than three times a week in the past month compared to 6.1% drug use by adults who drank alcohol less than once a week. In addition, those who visit nightclubs and pubs frequently are more likely to be recent drug users: drugs were used by 32.8% of those visiting a nightclub four or more times in the past month compared to 6.0% drug use by those who had not visited a nightclub in the last month. These findings have been mirrored elsewhere. Smith et al, (2010) explored patterns of polydrug use in Great Britain using data from the Psychiatric Morbidity Survey carried out in 2000: they found that hazardous alcohol use and tobacco use were strongly associated with illicit polydrug use.

The European DRUID Studies (deliverable 2.3.5) showed evidence of significantly increased risk, reported as odds ratio, for a driver being seriously injured or killed in an accident when testing positive for a combination of drugs and alcohol (Table 3.2). The odds ratio estimate for both events is in the region of OR: 20.0 (DRUID Deliverable 2.3.5).

Table 3.2: DRUID risk estimates for a driver being seriously injured or killed in an accident when testing positive for a combination of drugs or a combination of drugs and alcohol.

Populations compared	Odds ratio (OR) and 95% confidence interval (CI)	Reference
Multiple drug use compared with no drug use	OR: 6.05 (95% CI: 2.60-14)	Movig et al, 2004
Drugs + alcohol compared with no drugs	OR: 112 (95% CI: 14-893)	Movig et al, 2004

Oliver *et al.* (2006) analysed biological samples from drivers apprehended under suspicion of impaired driving. Drug combinations were often observed: 68% of methadone positive samples were also positive for heroin. Polydrug use was found in 56% of blood samples.

Illicit drugs

The DRUID deliverable 2.2.3 provides a good overview of prevalence and patterns of drug use in European drivers, though it noted some country-specific behaviours and patterns. For illicit drugs, cannabis (detected as tetrahydrocannabinol (THC), the main psychoactive ingredient) is the most frequently detected drug in European drivers, followed by cocaine. Cocaine, the second most frequently detected drug, was, on average, usually detected in combination with other substances. The most commonly used drugs in multi-drug combinations were cannabis (THC), cocaine and benzodiazepines. Amfetamines and illicit opiates were less frequently detected in European countries. Illicit drugs are, in general, mainly detected among young male drivers, during all times of the day but predominantly at weekends (DRUID deliverable 2.2.3).

In the last decade there has been huge growth in the use of 'designer drugs', a term coined to describe a synthetic version of a controlled stimulant-like amphetamine, produced with a slightly altered molecular structure to avoid being classified as a controlled drug (Merriam-Webster, 2008). The original contemporary designer drug groups were the: phenethylamines which includes ecstasy (3,4-methylenedioxymethylamphetamine, MDMA); the phencyclidines which includes ketamine and the third group, the piperazine-based drugs include for example, benzylpiperazine (BZP), which has been manufactured specifically for recreational use. Many 'designer drugs' have since been controlled under the Misuse of Drugs Act (1971) and some of these will be discussed with reference to driver safety in the drug-specific chapters.

Medicines

Among killed drivers in the DRUID studies the presence of benzodiazepines was the second most frequent toxicological finding after alcohol (DRUID, D2.2.5, 2010). In most European countries, benzodiazepines were the most common medicines detected in drivers but there was high national variability. Epidemiological Studies (Evik, 2012; Orriols et al, 2011; Gjerde et al, 2011; Gjerde & Verstraete, 2010; Vermeeren, 2004; Barbone et al, 1998) indicate a major increase in the consumption of antidepressants and drugs for addictive disorders in the general population in Europe within the last few

years. Medicinal drugs in Europe were mainly detected among older female drivers during daytime hours. (DRUID deliverable 2.2.3)

EPIDEMIOLOGICAL OVERVIEW: GREAT BRITAIN

Alcohol in the context of drug-driving

The Scottish Crime and Justice Survey (previously the Scottish Crime and Victimization Survey, SCVS) results for 2010-2011¹² show that 6.6% of adults aged 16 and over had used one or more illicit drug in the previous year. The majority (83.1%) of current users (i.e. those adults who had used at least one illicit drug in the last month) reported drinking alcohol at some point in their lives while taking the drug they had used most often in the last month.

The Panel considered the evidence of use of combinations of drugs and alcohol which showed that risk was increased, with the individual risk estimates associated with each of the substances being additive or even multiplied, when the substances were combined. The Panel have therefore agreed that it would be extremely important to take account of the use of alcohol in combination with other drugs. It was noted that the risk estimate as an OR for driving under the influence of psychoactive drugs and alcohol compared to no drugs at all was OR: 112 (95% CI: 14-893) and that drug-alcohol combinations among vehicle drivers increases the risk for a RTA accident requiring hospitalisation (Movig et al, 2004).

Evidence (DRUID Deliverable 7.3.2, 2011; Schnabel et al, 2010; Blomberg et al, 2009; Ogden & Meoskowitz, 2004) suggests that even a small amount of alcohol when combined with a drug leads to a significantly increased risk in drivers of a RTA, compared to drivers who do not use this combination of substances. It was agreed that **dual thresholds** would be recommended for those drugs where there was evidence of additional risk if they were consumed in combination with alcohol. A **specific lower limit would be recommended for that drug when it was detected in combination with alcohol**. The threshold recommended in whole blood for alcohol when detected in combination with one of the drugs in question is recommended to be 20 mg of alcohol per 100mL blood. The Panel recommends the setting of an alcohol concentration (when

¹²<http://www.scotland.gov.uk/Publications/2011/10/28142346/0>

in combination with a drug) below the current prescribed limit of 80 mg alcohol per 100 mL blood and which is closer to establishing mere 'presence' of alcohol. The Panel recognises that 20 mg is the blood alcohol limit already prescribed for aviation purposes (section 93(2) Railways and Transport Safety Act 2003) and believes that it is proportionate to risk recommending this limit for the purposes of dual alcohol and drug thresholds.

The Panel also agreed that it would recommend that when samples were analysed in the laboratory to confirm the presence of a drug from drug-driving suspects who had screened positive for several drugs that the laboratory procedure should be to look for all drugs of interest, to identify if any of the drugs was contained in concentrations above the specified limit, so that a conviction might be secured.

Illicit drug use

In order to capture data on adult drug use, national household surveys such as the Crime Survey for England and Wales (CSEW) and the Scottish Crime and Justice Survey (SCJS)¹³ were explored. The CSEW¹⁴, formerly known as the British Crime Survey (BCS), is a household survey of adults aged 16 and over, resident in England and Wales that consists of interviews with around 45,000 individuals. The survey contains a self-completion module that is restricted to those aged 16-59 years, and includes questions relating to alcohol and illegal drug use, drink driving and drug driving. Approximately half of the sample completes the self-completion module. Although these surveys may underestimate adult drug use due to their non-random non-response rates (Newcombe,

¹³<http://www.scotland.gov.uk/Publications/2011/10/28142346/0>

¹⁴ The Crime Survey for England and Wales (CSEW) is weighted to adjust for possible non-response bias and to ensure the sample reflects a profile of the general population. The CSEW has a fairly high response rate (76% in 2009/10 and 2010/11) and the user guide states the following regarding weighting:

"The weighting is designed to make adjustments for known differentials in response rates between different regions and different age by sex subgroups and also households with different age and sex composition. For example, a household containing a man aged 24 living alone may be less likely to respond to the survey than a household containing a man aged 24 living with a partner and a child. The procedure therefore gives different weights to different household types based on their age/sex composition in such a way that the weighted distribution of individuals in the responding households matches the known distribution in the population as a whole and also matches the known distribution of the regional population."

2007; Reuter & Stevens, 2007)¹⁵, they nevertheless give an indication of population levels of use.

The 2011/12 CSEW¹⁶ estimated that 8.9 per cent of adults aged 16 to 59 had used illicit drugs in the last year (almost three million people), and that 3.0 per cent had used a Class A drug in the last year (around a million people). Neither estimate was statistically significantly different from the 2010/11 survey. Since 1996, when BCS drug use estimates began, trends in levels of “last year” drug use among adults aged 16 to 59 show that: “Last year” use of any illicit drug has fallen from 11% (1996 BCS) to 8.9% in the 2011/12 survey, mainly due to decline in the use of cannabis. Class A drug use in the last year among adults aged 16 to 59 in the 2011/12 CSEW was 3.0% and has remained relatively constant overall. Within this category, there was an increase in last year use of cocaine powder between the 1996 and 2011/12 BCS (from 0.6% to 2.2%). Similarly, of the individual types of drug asked about in the survey, there has been an increase in last-year use of methadone (from 0.1% in 1996 to 0.2% in 2011/12).

As in previous years, among adults aged 16 to 59, cannabis was the most commonly used type of drug during the last year, (6.9% or around 2.3 million people), followed by cocaine powder (2.2%, 0.7 million people), and ‘ecstasy’ (3,4-methylenedioxymethamphetamine; MDMA; 1.4%, 0.5 million people). The 2011/12 CSEW shows that levels of ketamine use in the last year (0.6%) were around double those when questions on the use of this drug were first asked in the 2006/07 BCS (0.3%). New measures of drug use added to the CSEW for drugs recently classified under the Misuse of Drugs Act show that last year use of mephedrone among those aged 16 to 59 was 1.1% (mephedrone is the fourth most prevalent drug within this age group). For those aged 16 to 24, last year use of mephedrone (3.3%) was at the same level as

¹⁵ These surveys generally tend to miss those living in student halls, hostels and institutions; secondly, they exclude adults active in the night time economy who are more likely to be out when household surveys are conducted (Roe, 2005). It is reported that both of these groups have higher than average rates of drug use (Chivite-Matthews et al., 2005; Roe & Man, 2006); however, they are likely to contain a less than average share of drivers: the National Travel Survey data show that the groups aged 17-20 years and >70 years hold fewer driving licences than other age groups.

¹⁶ Drug Misuse Declared: Findings from the 2011/12 Crime Survey for England and Wales (2nd Edition)

<http://www.homeoffice.gov.uk/publications/science-research-statistics/research-statistics/crime-research/drugs-misuse-dec-1112/drugs-misuse-dec-1112-pdf>

ecstasy(3.3%); the third most used drug amongst young people. Many of the 'legal highs' (synthetic drugs with amphetamine-like effects) available today are too recent for anybody of evidence to have built up regarding possible deleterious effects on driving. However, the fact that their pharmacology is so similar to that of drugs for which we do have evidence makes it highly probable that they will pose similar risks. The Panel strongly recommends that monitoring of the use of such drugs, and older ones such as LSD-25, psilocybin and other tryptamine derivatives in driving populations is introduced and that in 3 years' time the drugs included in the new legislation and the proposed limits are reviewed.

Measures of illicit drug use by personal, household and area characteristics and lifestyle factors in the 2011/12 CSEW show that:

- Among adults aged 16 to 59, the level of any illicit drug use was highest among the 16 to 19 age group (19.6%)
- Class A drug use was highest among 20 to 24 year olds (7.2%) in comparison with other age groups.
- Single adults had higher levels of any illicit drug (17.4%) or Class A drug (6.0%) use in the last year in comparison with all other marital status groups.

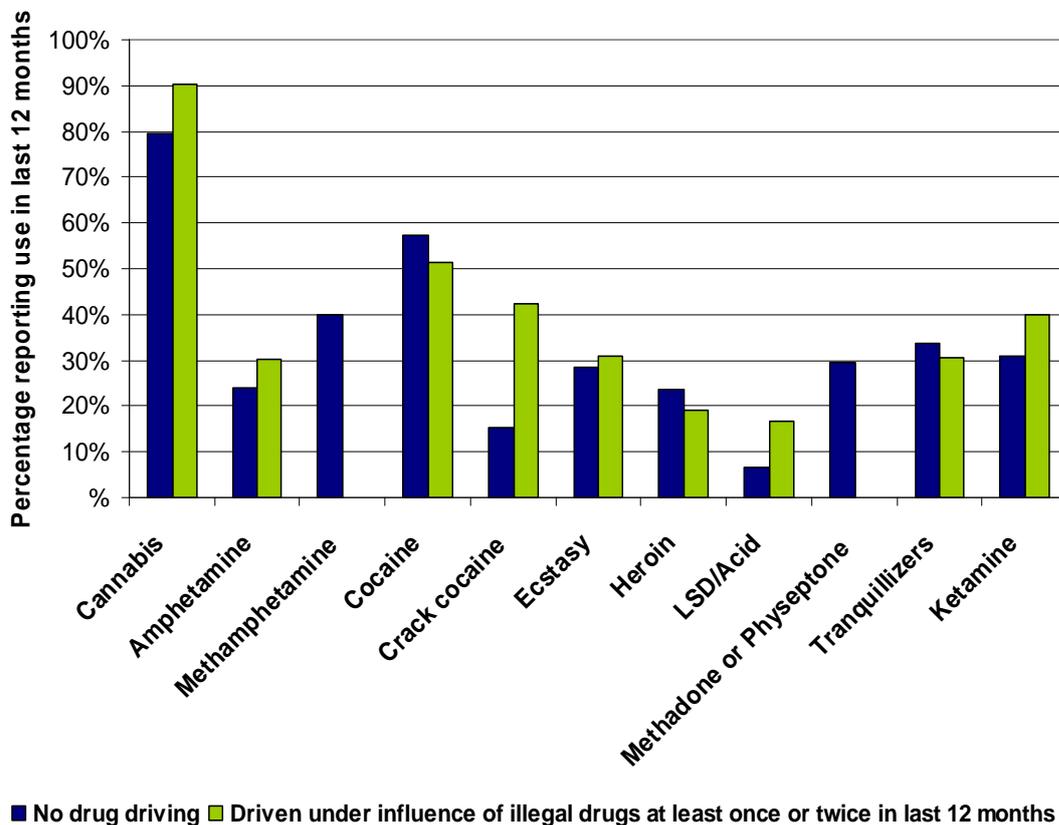
The SCJS results for 2010-2011 show that 6.6% of adults aged 16 and over had used one or more illicit drug in the previous year. The survey indicated that cannabis continues to be the most commonly used drug, followed by cocaine, for recent (in the previous year) and current use (in the previous month). However, for life time use, the prevalence rates for amfetamines and ecstasy were higher than for cocaine.

Prevalence of Drug Use in British Drivers

There were several sources of data from which the Panel gathered evidence in order to confirm the choice of substances for recommendation for inclusion in the new offence. For instance, approximately half of the total CSEW sample in 2010/11 (around 22,000 people in total) participated in a self-completion module (restricted to those aged 16-59 years) that included questions relating to drug use and drug driving (Figure 3.2).

There were 611 respondents in 2010/11 (unweighted base) who reported taking any drug in the last 12 months AND who reported driving in the last 12 months. In response to the question, “In the last 12 months how often, if at all, have you driven when you think you may have been affected by or under the influence of illegal drugs?”, 19% of these respondents reported having driven at least once or twice in the last 12 months when affected by or under the influence of illegal drugs, of which 3% reported having driven under the influence of illegal drugs a few times a week or every day/almost every day¹⁷.

Figure 3.2: Proportion reporting use of particular illegal drugs in the last year, by frequency of drug driving (2010/11)



¹⁷RRCGB: 2011 Annual Report. Self-reported drink and drug driving: Findings from the Crime Survey for England and Wales
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/9278/rrcgb2011-05.pdf

For those who reported driving under the influence of illegal drugs at least once or twice in the last 12 months, cannabis and cocaine were the most commonly used drugs during this time period (Figure 3.2). Ninety percent reported using cannabis, and 51% reported using cocaine, in the last 12 months. MDMA, ketamine and amphetamine use was also reported¹⁸. These findings help identify the drugs used by those individuals who admit to driving under the influence of drugs. Further evidence came from the Transport Research Laboratory (TRL) that collated data (Table 3.3) from fatalities in road accidents in 2010 (Smith and Martin, 2012).

Table 3.3: Summary of drug-driving toxicological data for fatal RTA

		Number	%
Driver fatalities aged 16 or over (Stats19)		1,037	-
Driver fatalities with drug data available (Stats19 matched with L407)		231	100%
Fatalities with the following drug group present	Any illicit drug of abuse:	46	20%
	Amphetamines, hallucinogenic amphetamines	3	1%
	Cannabinoids	26	11%
	Cocaine	10	4%
	Opiates, opioids, narcotic analgesics	15	6%
	New psychoactive substances	1	0%
	Methcathinone	1	0%
	Therapeutic drugs	72	31%
	Anti-depressants and mood stabilisers	20	9%
	Benzodiazepines, non-benzodiazepines	12	5%
	Other therapeutic drugs	60	26%

¹⁸Unweighted bases range from 22-576. For Methamphetamine, Crack cocaine, Heroin and Methadone/Physeptone, bases are all less than 95. Data should be interpreted with care as number of respondents is relatively low.

Smith and Martin (2012) considered blood and drug alcohol concentrations for road accident fatalities recorded by Coroners in England and Wales and by Procurators Fiscal in Scotland. The above table summarises the number of driver fatalities with drugs detected¹⁹. The percentages are based on the total number of fatalities that were tested for any drug. Cases were included in the analysis whatever the time elapsed between the collision, death and the sample, since different drugs are detectable for a different amount of time in the body and it would be difficult to identify an appropriate elapsed time for all drugs. It is clear that cannabis, cocaine, the opioids/opiates and the therapeutic drugs were an important characterisation of killed drivers.

Historical data derived from the Forensic Science Service (FSS) over a three year period (2004-2007) were also considered: they included samples submitted from drivers suspected to have been driving whilst impaired following drug use, data are shown in Table 3.4.²⁰

Table 3.4: Data from the analysis of whole blood specimens submitted to the FSS between 2004-2007.

Total No cases	Excess Alcohol	Amfet	BZ	THC	Coc	MDN	Opiates	2 or more drugs	Other Drugs	NDD
4,192	436	287	184	1,23	312	7.0	382	871	30	449
%	10.4	6.9	4.5	29.4	7.4	0.2	9.1	20.8	0.7	10.7

Key: BZ – benzodiazepines; coc – cocaine; MDN – methadone; NDD – no drugs detected

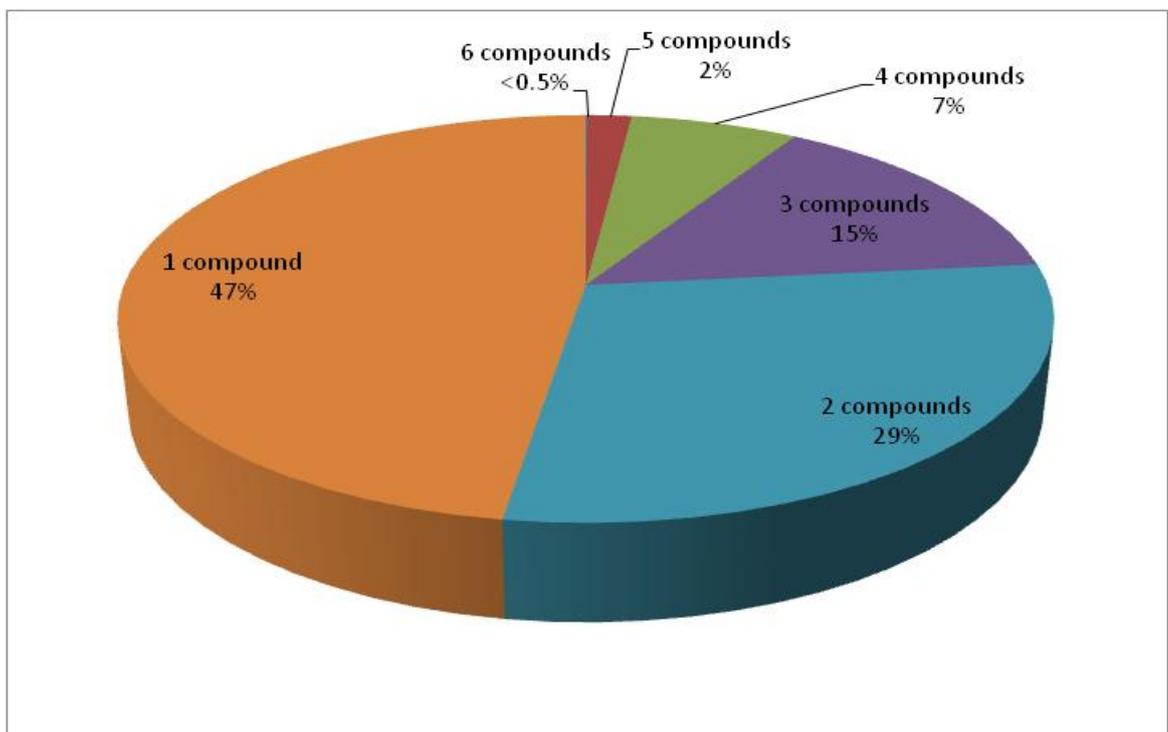
Prevalence data from a forensic service provider was presented to the Panel on 3616 blood samples (collected between January 2008 and October 2012) which had screened positive (by ELISA) for one or more drugs. The data, which is predominantly from cases

¹⁹Key: ‘Opiates, opioids, narcotic analgesics’ does not include morphine, codeine and ketamine; these are included in the ‘other therapeutic drugs’ group. Non-benzodiazepines include zolpidem, and its metabolite zopiclone. Toxicological analysis may have found multiple drugs or groups of drugs to be present in a fatality, and therefore the individual categories should not be summed

²⁰Excess alcohol would be those cases where a driver is suspected of driving under the influence of drugs but no breath test result available - procedure would test alcohol first and if blood alcohol of over 80 mg /100 mL blood is found, no drug analysis would follow.

in England and Wales, relates to cases of Road Traffic Accidents (RTA) or impairment witnessed by the police, followed by assessment by a forensic physician. A blood (or urine) sample could be taken if, in the opinion of the forensic physician, the driver had a condition which may be due to a drug. The data showed an approximate 50:50 split between single substance and polysubstance use. Figure 3.3 shows the percentage of drugs detected alone or in combination with other drugs. Cannabis (THC) and benzodiazepines were the most prevalent drug types, appearing in 58% and 41% of drug positive samples respectively. It was noted that benzodiazepines and/or cannabis were present in 81% of drug positive screening samples.

Figure 3.3: Percentage of drug positive samples containing single drugs and multiple drug combinations. Data from samples taken between January 2008 and October 2012 in cases of RTA or witnessed impairment



Finally, the DVLA receives approximately 6,000 notifications per year and estimates that about 6% of these concern drug use. Police forces make these notifications to the DVLA when there has been a RTA or incident where it is considered that a medical condition was instrumental in the incident. The number of notifications

received has gone down in recent years from 30,843 received in 2007 to 26,661 in 2011. In most cases, the licence holder is driving or has been in charge of a vehicle and evidence is found to support the use of drugs at the time or enquiries reveal that the driver is either a 'registered drug addict', is on a methadone programme or if it is believed that there is evidence of persistent drug misuse. The Panel felt that potentially useful information could be collected by the DVLA more systematically from police notifications and evaluated to better inform those concerned with road safety. In addition, the DVLA is also made aware of drug misuse in drivers as part of the High Risk Offender (HRO) scheme for drivers convicted of certain drink/driving offences: the DVLA is notified of such offences by the courts. When an application for licence re-instatement is made, an independent medical examination is conducted. The assessment process includes blood test and a driver-completed questionnaire which includes information on alcohol and drug use (prescribed, over-the-counter and illegal). Of the questionnaires returned in one randomly selected week in August 2012, the following numbers self-reported drug taking (Table 3.5).

Table 3.5: Drivers' self-reported drug use as part of the DVLA's HRO scheme

Drug Type	No drugs	Cannabis	Heroin	Cocaine	Others
Weekly total	299	91	15	17	9

The Panel also believe that the information collected from those on the HRO scheme could also be collected more systematically and analysed so as to better inform other bodies such as the Secretary of State for Transport's Honorary Medical Advisory Panel on Alcohol, Drugs and Substance Misuse and Driving.

Table 3.6 provides some specific information on the expected concentrations in plasma (or serum) and blood for the most commonly used substances likely to cause a hazard when driving after taking a quantity of a drug known to produce an effect that has been reported by the Netherlands Advisory Committee, 2010 (measured by the Netherlands Forensic Institute (NFI) 1999-2008), intending to provide a scientific foundation for setting possible limits for drugs.

Concentration data on blood concentrations of specific substances from samples taken from RTAs or witnessed impairment whilst driving including drivers suspected of

impairment, has also been considered by the Panel; these data are included and discussed at relevant points in the drug-specific sections of the report.

Table 3.6: Active concentrations (micrograms/L, µg/L) of the most common drugs found in plasma (or serum) and blood which are known to be a hazard when driving ²¹ (Netherlands Advisory Committee, 2010)

Substance	Expected concentration in plasma after taking an active dose ^a (µg/L)	Blood/serum ratio ^b	Estimated concentration in blood after taking an active dose ^c (µg/L)	Median in blood 1999-2008(µg/L) NFI
Amfetamine	50-150	0.6-1.0	50-150	230
MDMA	100-350	1.2	100-400	320
MDEA	approx. 200		100-400	50
MDA	approx. 400	1.2	100-400	30 ^f
THC	2-10	0.55	1-5 ^e	5.8
Cocaine	50-300	1.0	50-300	60
Morphine	10-120	1.0	10-120	40
Codeine	50-250	0.87	40-250	20
GHB	^d		> 20 mg/L	95 mg/L

²¹ Netherlands Advisory Committee report, 2010.

^aDerived from The International Association of Forensic Toxicologists (TIAFT) supplemented by data from other scientific sources where the TIAFT list was incomplete.

^b Blood/serum ratio: of the concentration in blood to the concentration in serum.

Concentrations in serum are generally the same as concentrations in plasma.

^c Concentrations in full blood calculated from concentrations in serum by multiplying by the blood/serum ratio.

^dThe literature refers to figures of 50-120 mg GHB per litre of serum during mechanical respiration.

^e Grotenhermen *et al.* (2007)¹⁸ put forward a limit for reduced ability to drive of 7 to 10 micrograms of THC per litre of serum (this is 3 to 5 micrograms of THC per litre of blood) which would be comparable with the limit of 0.5 grams of alcohol per litre of blood (0.5 per cent). This limit applies to occasional cannabis use and not where use is daily.

^f MDA is also formed in the body through the conversion of MDMA.

Biological fluid for determining thresholds for drug driving

The Panel was mindful of the need to recommend threshold limits that could be measured to evidential standard to inform a decision of whether or not an offence had been committed. The Panel explored the choice of specimen to use (blood, plasma, hair, urine, oral fluid or sweat) for determining appropriate thresholds. In practice, the presence of a drug in the body can be determined in any of these matrices. Although the standard procedure for large-scale laboratory based screening for illicit drug use typically involves the collection of urine samples, this can only provide retrospective information about past drug use rather than provide information about the 'here and now' - the current effect of the drug on the person. It is widely acknowledged that blood and, to a lesser degree, oral fluid are likely to give the most accurate measurement of drugs currently active in the body; urine provides a somewhat broader time frame (drug use over the last 2-3 days), but with less quantitative accuracy²², hair provides a substantially longer time frame (Wolff et al, 2006).

The analytical technology for urine drug screening is well-established and several studies have described how to interpret the drug findings (Vindenes, 2012). Although urine has the advantage of being fairly easy to collect in large volumes and is the biological fluid of choice for laboratory-based drug-testing programmes, the interpretation of urine tests is often complex with great variability with regard to the excretion of drugs from the body, some knowledge of the pharmacokinetics of the drug is usually necessary to interpret findings. There is a time-lag between the consumption of a drug and its appearance in urine which makes the relationship between urinary drug concentrations and driving behaviour difficult to describe, particularly as the time-lag may be affected by a myriad of factors such as gender, age, weight, disease state etc. Drug concentrations in urine are usually not relevant in terms of an impact on driving behaviour and it is generally accepted that urinary drug concentrations are not useful as an indicator of the effects of a drug on immediate driving safety.

²²Unless voidance of urine is observed the authenticity of the sample may be called into question since urine can easily be contaminated, with the probability of false negative results following adulteration of urine with chemicals or by dilution. Special facilities must be provided to be able to observe the sample collection to avoid adulteration, which may be time consuming. Artificial dilution can be a problem both before (by using diuretic agents widely available on the internet), or after voiding (by adding water) and has led many laboratories to establish criteria for "normally concentrated" or "dilute" urine specimens.

Over the last 10 years there has been growing interest in the use of oral fluid for drug testing as an alternative to urine (Drummer, 2006). The major advantage of oral fluid over urine is the easy, rapid and non-intrusive sampling procedure (Wolff 2006). Oral fluid has been shown to be a suitable matrix for community-based drug screening purposes and Toennes et al (2005) compared findings in oral fluid, serum and urine, and concluded that oral fluid was superior to urine in correlating with blood drug levels and driving behaviour. Attempts have been made to establish fixed ratios or conversion factors between the drug concentrations in blood and those in oral fluid for confirmation testing. However, there are large individual variations, which mean that ratios cannot be easily determined for most psychoactive drugs, although some correlation has been described (Wille et al, 2009; Walsh et al, 2004; Cone et al, 1988).

Currently, oral fluid tests cannot be used to give a precise prediction of the concentration of a drug in blood (or plasma or serum) for confirmation testing and therefore prediction of possible drug effects (Wille et al, 2009; Gjerde & Verstraete 2010). From the point of view of setting thresholds in a biological fluid, reference values (concentration/effect ratios) are more readily available for blood (plasma or serum), which remains the matrix of choice. For establishing thresholds in the context of drug-driving legislation, blood (or plasma or serum) is the preferred bodily fluid since it is generally well described in the scientific literature and best related to behavioural effects on driving. Blood is the 'gold standard' (Wille et al, 2009); it is well-known that drug concentrations in blood, plasma and serum cannot be used synonymously with each other since the concentration of a drug in plasma and serum may be higher than in whole blood. This will be discussed in more detail in the drug-specific chapters, where relevant.

Consideration of sampling time

There is often an unavoidable delay between the witnessed impairment or accident and the time of blood sampling such that concerns have been raised about the difficulty of relating blood concentration to driving under the influence of drugs. The Panel recommends that specimens should be obtained as soon as possible after the road traffic incident, given the relatively rapid decline of drugs such as THC, cocaine and heroin in blood. For alcohol, many countries employ back-calculation; for drugs, because

of variable pharmacokinetics, back-calculation is much more difficult and was considered to be impracticable by the Panel.

4. DRUG SPECIFIC FINDINGS: CANNABIS

Background

Cannabis (also known as marijuana) is the psychoactive product identified in the plant *Cannabis sativa L* and is comprised of at least 60 different cannabinoids. It is well known, however, that the main psychoactive constituent of cannabis is tetrahydrocannabinol (also known as delta-9-tetrahydro cannabinol or Δ^9 -tetrahydrocannabinol), commonly referred to as THC (Jager, 2012; Watchel et al, 2002). Different parts of the plant contain varying concentrations of THC and this is usually expressed as %THC per dry weight of material. Leaves contain <1% to 10% THC by weight and the herbal form (weed) consisting of dried mature flowering tops, contains approximately 15% THC. Hashish, the resinous sap of the cannabis plant can contain up to 20% THC. The form of marijuana known as *sinsemilla* (without seeds) is derived from the unpollinated female cannabis plant and has a high THC content of up to 17% (UNODC; National Highway Traffic Safety Administration, 2012).

Until the late 1990s, the cannabis market was dominated by resin smuggled into the UK: however, tighter border controls have led to increased farming indoors with intensive horticultural techniques to cultivate the drug in the UK. The hybrid called 'skunk' because of its distinctive, pungent smell was bred by crossing two varieties of cannabis. The more traditional 'non-skunk' strains of herbal cannabis are reported to contain only 3% to 4% THC - unchanged from a decade ago (EU Drug Agency, European Monitoring Centre for Drugs and Drug Addiction, 2010). Other strains are reported to have increased potency: Northern Lights has a THC content of 15-20% and Durban Poison is a South African strain reported to have THC concentrations of 8-15%²³.

In addition, several cannabinoids have been manufactured commercially for medical purposes. These include Marinol® (dronabinol, a pure form of THC), Sativex® (containing THC and cannabidiol (CBD), a natural component of *Cannabis sativa L*), Nabiximols (trade name Sativex®, a patented cannabinoid oromucosal mouth spray) and Cesamet® (nabilone, a synthetic form of THC) (Karschner, Eugene, Schwilke, 2009; 2011). These products are used, for example to treat and manage the side effects of

²³http://www.maryjanesgarden.com/northern_lights.php
<http://www.amsterdammarijuanaseedbank.com/seedshop/strains/durban-poison.html>

cancer treatment, central neuropathic pain and the treatment of loss of appetite in people with AIDS.

Most recently, synthetic cannabinoid receptor agonists have been detected in samples of smoking mixes such as 'spice' and are reported to have a pharmacology similar to that of cannabis. Synthetic cannabinoids are reportedly sprayed onto herbal tobacco products and marketed under a variety of names. For instance, a product called 'Annihilation' was found to contain synthetic cannabinoids in two seizures from Scotland (Strathclyde police, ACMD, 2012). Many of the mixtures available under different brand names contain the same compounds, one of which (AM2201) has been identified in products traded as 'Black Mamba', 'Annihilation', 'Tai High Hawaiian Haze' and 'Bombay Blue Extreme' (Talk to Frank, 2012)²⁴.

Epidemiological prevalence

Several surveys demonstrate that cannabis is the most widely used illegal drug in the UK. United Kingdom. For instance, the 2011/12 Crime Survey for England and Wales²⁵, reported that as in previous years, among adults aged 16 to 59, cannabis was the most commonly used drug in the last year (6.9% of respondents) which extrapolates to around 2.3 million people nationally. The survey reported that 0.1% 16 to 59 year olds used 'Spice' and other cannabinoids in the last year. For 2010/11, the figure was 0.2% (with 0.4% 16 to 24 year olds reporting last year use of synthetic cannabinoids) (Smith & Flatley, 2011). For Scotland in 2010/11, the SCJS reported that 5.6% of adults had used cannabis in the last year. Of those who reported any illicit drug use in the last year, 0.6% had used synthetic cannabinoids in the same time period²⁶. The Health and Social Care Information Centre, HSCIS (2011) has also reported that the number receiving help for primary cannabis use has increased by more than 4,000 in 2005/06 to 13,123 in 2009/10.

²⁴<http://www.talktofrank.com/drug/synthetic-cannabinoids>

²⁵ Drug Misuse Declared: Findings from the 2011/12 Crime Survey for England and Wales (2nd Edition)<http://www.homeoffice.gov.uk/publications/science-research-statistics/research-statistics/crime-research/drugs-misuse-dec-1112/drugs-misuse-dec-1112-pdf>

²⁶ 2010/11 Scottish crime and Justice survey: Drug Use
<http://www.scotland.gov.uk/publications/2011/10/28142346/0>

Cannabis and driving

The Panel considered prevalence data from laboratory analysis of 3616 blood samples taken in suspected cases of drug-driving which screened positive (by ELISA) for one or more drugs. The data, which is predominantly from England and Wales and was collected between January 2008 and October 2012, showed that cannabinoids were present in 58% of drug positive samples. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) found that between 0.3% and 7.4% of drivers tested positive for cannabis. In 2010/11, the CSEW carried a question relating to the prevalence of drug driving²⁷, and data shows that for those who reported driving under the influence of illegal drugs at least once or twice in the previous 12 months, cannabis was the most commonly used drug during this time period (with 90% reporting use in the previous 12 months). In addition, a survey of 537 drivers in Scotland reported that 15% of respondents aged 17-39 years admitted to driving a vehicle within 12 hours of consuming cannabis (Neale et al, 2000). Significant scientific evidence is also available with regard to the role of cannabis in road traffic accidents such that cannabis already features in road traffic legislation in many European countries, for instance as those shown in Table 4.1.

Table 4.1: International drug thresholds (set in or recommended for legislation): THC²⁸

Country	Approach to threshold	THC threshold in blood	Reference
Sweden	Zero tolerance	0.3 µg/L	Jones et al, 2008
Switzerland	Threshold for prosecution	1.5 µg/L	
Norway	Impairment limit	1.3 µg/L	Norwegian Institute for Public Health,

²⁷RRCGB: 2011 Annual Report. Self-reported drink and drug driving: Findings from the Crime Survey for England and Wales
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/9278/rrcgb2011-05.pdf

²⁸ It is important to note that the limits set in other countries need to be considered alongside their specific legal system and the specific drug driving legislation. Some countries have set very low limits, which are often referred to as a zero-tolerance approach, but they may use these limits in conjunction with an impairment-type drug driving offence, where the limits apply only if impaired driving is also recorded.

	Comparable to 0.5g/L BAC Comparable to 1.2g/L BAC	3.0 µg/L 9.0 µg/L	2012
Belgium	Analytical cut-off	1.0 µg/L	Nickel & de Gier, 2009
Portugal	Analytical cut-off	3.0 µg/L	

Patterns of use

Long term use of cannabis over many years is not unusual and regular use of cannabis over 19-20 years has been described. Daily use is also common in chronic users and is almost always associated with dependent use (Reilly, 1998). The amount of cannabis smoked or ingested at any one time varies and users often alter their own dose but it is suggested that approximately 200 mg cannabis is typically smoked in an average reefer (rolled cigarette). The quantities of THC in various preparations are given below:

- 5 mg to 30 mg active drug (THC) per reefer (Moffat et al, 2004)
- 10 mg to 20 mg THC intake of smoke from a pipe or joint (a hit).
- 35mg (25% extraction) THC edible cannabis (brownies)
- Approx. 64 mg of THC pumpkin cake
- 45 mg to 60mg of THC single chocolate bar²⁹
- 2.5 mg, twice daily is the initial starting dose of Marinol® (10 mg and 20 mg doses also available)
- 1 mg cesamet® capsule contains 1 mg of nabilone: usual dose 2-4mg/day, maximum 6 mg/day
- Sativex spray delivers a fixed dose of 2.7 mg THC and 2.5 mg CBD
- Synthetic cannabinoids - unknown.

It has been reported in a small number of controlled studies in the 1980s that THC can be detected in blood after passive exposure to cannabis smoke. However, modern analytical methods suggest that due to the rapid distribution of THC in the body, which also occurs after passive exposure to low doses, the THC concentration in serum after exposure would be less than 1 µg/L within an hour, whilst similar and very low serum concentrations of THC-carboxylic acid would also be observed (< 2 µg/L). Higher blood

²⁹ See for example: <http://www.bluelight.ru/vb/archive/index.php/t-549317.html>

concentrations were suggested as commensurate with the deliberate consumption of a psychoactive dose (Toennes, Röhrich & Wunder, 2010).

Pharmacokinetics (PK) and blood drug concentrations

THC, regardless of the strain or the preparation consumed, is a lipophilic compound and is widely distributed in the body. Recreational use of cannabis invariably involves smoking the drug, leading to the rapid passage of THC via inhalation into the blood stream. After inhalation absorption of THC is fast causing maximal blood concentrations within minutes. Following ingestion absorption of THC is slow and unpredictable, with maximal blood concentrations occurring 1–5 hours post dose (Ohlsson, Lindgren & Wahlen, 1980). Cannabis is a potent drug and produces significant effects despite only 6% THC reaching the blood stream (bioavailability) when orally administered, and up to 27% when inhaled (Ohlsson, Lindgren & Wahlen, 1982). THC is metabolised to the equipotent 11-hydroxy-THC (11-OH-THC) and 8 β -hydroxy- Δ^9 THC, which is also pharmacologically active. Inactive metabolites of cannabis (those which do not produce a pharmacological effect in the body) are also produced and include 8 α -hydroxy- Δ^9 THC, 8 α -dihydroxy- Δ^9 THC and 11-nor- Δ^9 THC-9-carboxylic acid (Δ^9 THC-11-oic acid (THCCOOH)).

The plasma elimination half-life (the time taken for the concentration of a drug in blood to reduce by half) is used to estimate how long a drug takes to leave the body, and is usually calculated as five times the half-life (Roland and Tozer, 2006). The half-life ($t_{1/2}$) of THC is marginally different for regular/frequent users and infrequent users of cannabis. For frequent users, $t_{1/2}$ is about 2 hours and in infrequent users about 1.5 hours respectively (Moffat et al, 2004): nabilone, synthetic THC ($t_{1/2}$) was also about 2 hours (Karschner, Eugene, Schwilke, 2011). Thus for the purposes of drug analysis the window of opportunity for the detection of THC after **a single dose** would be quite narrow and less than 9 to 12 hours.

As with alcohol and other drugs the influence of cannabis on drug driving behaviour depends on the dose taken and the length of time between dosing and driving taking place (Raemaekers et al, 2004). Unlike alcohol, however, regardless of the dose consumed and owing to its high lipid solubility and large volume of distribution, THC is stored in tissues and organs throughout the body. In regular/frequent users, this

results in the continual release of the THC into the blood stream, maintaining consistent concentrations in the general circulation.

In heavy long term users (daily or near daily use over a number of years) variable rates of release of THC from tissue stores during abstinence have been reported. A mean THC blood concentration after 24 hours abstinence was found to be 0.7 µg/L (SD 1.4 µg/L) and after 7 days abstinence 0.3 µg/L (SD 0.7 µg/L) (Karschner, Eugene & Schwilke, 2011), whereas in regular/frequent users blood concentrations of THC were detected between 1 µg/L and 6.4 µg/L. Smoking a single cannabis cigarette (infrequent user) leads to higher concentrations of THC in the body, ranging from 3 µg/L – 12 µg/L, and maximal THC blood concentrations after oral consumption were found to be in the range of 4.4 µg/L to 11.0 µg/L following a single 20 mg dose (Ohlsson, Lindgren & Wahlen, 1980; Karschner, Eugene & Schwilke, 2011): oral administration of a 2 mg dose of radio-labelled nabilone in comparison, achieved peak plasma concentrations of approximately 2 µg/L nabilone within 2.0 hours. However, it is known that plasma concentrations of THC are higher than those found in whole blood (see overleaf). A comprehensive review of the pharmacokinetics (PK) and pharmacodynamics of cannabis has been conducted by Grotenhermen, Leson & Berghaus (2007).

Collection of specimens for evidential analysis

The decision regarding the choice of biological fluid is important. It is commonly reported that cannabis can be detected for many days (up to 28 days) following urine drug screening (Wolff et al, 2006). This finding is related to the presence of the active metabolite 11-hydroxy- Δ^9 -THC, for which a half-life of 120 hours has been reported for frequent users (infrequent users 144 h) of the drug (Moffat et al, 2004). The THCCOOH metabolite is also detectable for a considerably long time: up to 3 days (range: 2-7 days) after a cannabis cigarette (Grotenhermen et al, 2003). The inactive metabolite (11-nor-9-carboxy- Δ^9 -tetrahydrocannabinol, or THC-COOH), which is detectable in urine for many days (Biecheler et al., 2011) is a less specific pharmacodynamic indicator of the impact of cannabis on driving performance. As the elimination half-life for THC metabolites is longer than the elimination half-life of THC itself urinalysis immunoassay drug screening tests that detect combinations of cannabis-like compounds may detect the presence of cannabis for several weeks (Grotenhermen, 2003). Although the

inactive metabolites of cannabis will contribute to a screening test, it is unlikely that a combination of metabolites alone would push the screening test above the screening threshold.

Oral fluid (of which, saliva is a key constituent) has gained increasing interest as a matrix for illicit drug testing, as it is easy to obtain. Many drugs detected in oral fluid have been shown to be highly correlated with plasma drug concentrations: hence, oral fluid testing is also indicative of recent consumption. Recent advances in technology have enabled the collection of very small amounts of oral fluid by commercial devices. However, contamination of the buccal cavity is an issue for the detection of cannabis use since the drug is often used by oral, intra-nasal or smoking routes of administration (insufflations). "Shallow depots" of cannabis may following recent use accumulate in the buccal cavity and produce elevated concentrations in oral fluid for several hours after ingestion. Unfortunately, the cannabinoids do not pass readily from blood into saliva and the detection of Δ^9 -tetrahydrocannabinol (THC) in oral fluid is largely reported to be due to contamination of the oral cavity following smoking.

Blood sampling is considered to be the most effective way to measure the concentration of THC in the body. However, if a blood sample is collected from a subject who has recently used cannabis and the sample is split into two portions, one being analysed as whole blood and the other centrifuged to prepare plasma analysis, then the concentration of THC, the main active component of cannabis will be about 2 times greater in the plasma sample than in the whole blood sample. For this reason whole blood was considered to be the most appropriate biological fluid for setting thresholds because it relates best to the scientific evidence in relation to driving. Therefore whole blood will be recommended as the biological sample of choice. In addition, THC has a rapid metabolism, and if the time between the stop or accident and the blood sampling is delayed, the blood concentration may have decreased markedly (based on a half-life for THC of 1.5 hours). For instance, 5 $\mu\text{g/L}$ of THC will be expected to decrease to 1.25 $\mu\text{g/L}$ after 3 hours. It is therefore recommended that blood sampling occur as quickly as possible after the road traffic incident for prosecution to occur.

Pharmacodynamics (PD)

Pharmacokinetic consideration of the blood-concentration-time profile of THC has been important in determining a significant dose effect for cannabis and driving performance. However, pharmacodynamics considerations are also important. Effects of cannabis include relaxation, giddiness and euphoria, introspective dreaminess, sleepiness and time distortion. The initial 'high' evolves into a sense of calmness and relaxed state. During this time, senses are heightened and smells and tastes are different from normal. In the USA synthetic cannabinoids are reported to have resulted in nationwide emergency department visits for severe agitation, sympathomimetic toxicity, and death (Rosenbaum et al, 2012). Texas Poison Centres recorded 464 cases of cannabinoid-related toxicity in 2010, the most common features being tachycardia, agitation, drowsiness, vomiting, hallucinations and nausea (Forrester *et al*, 2011).

The method of administration (smoking or eating) also plays a role in the length and intensity of the high. Physically, bloodshot eyes and a dry mouth are common symptoms, as well as a slight increase in heart rate and impaired short term memory. Following oral ingestion, psychotropic effects set in after a delay of 30-90 minutes, reach their maximum after 2-3 hours and last for about 4-12 hours, depending on the dose (Grotenhermen, 2003). In smokers, the maximal psychological effects of cannabis persist for 4-6 hours after use, despite very low blood concentrations (Kochanowski, 2005).

Cannabis and driving: the scientific evidence

The blood-concentration-time profile of THC shows a significant dose effect for cannabis and driving performance. It has been shown that a substantial dose-response effect can be observed in experimental and real-life situations (simulator, laboratory and forensic), in which raised concentrations of THC were associated with increased traffic crash risk. Meta-analysis of over 120 studies have found, in general, the higher the estimated concentration of THC in blood, the greater the driving impairment: more frequent users of marijuana show less impairment than infrequent users (unless used in conjunction with alcohol) at the same dose, either because of physiological tolerance or learned compensatory driving behaviour. In those given doses (often experimentally) to duplicate a **single** cannabis cigarette (18 mg THC or less), maximal psychotropic effect

was found 20-40 minutes after smoking, but effects had largely disappeared 2.5 hours later (Berghaus et al, 2002).

The acute use of cannabis and the risk of a motor collision have also been evaluated. A recent meta-analysis of 9 research studies summatively including 49,411 participants (Asbridge et al, 2005) that examined observational studies of the effects of acute cannabis use on the risk of traffic accidents showed that the pooled risk of a road traffic collision whilst driving under the influence of cannabis was significant and almost twice the risk compared to driving having not consumed this drug (odds ratio 1.92, CI 1.35 to 2.73; $P = 0.0003$). The summary estimate of risk for cannabis use was OR: 2.10 for fatal accidents and 1.74 for non-fatal accidents (Table 4.2). Cannabis use has an increased influence on the risk of motor vehicle collision for studies of fatally injured drivers, which might be explained by differences in THC concentrations in the blood (either heavier consumption of cannabis or owing to a shorter time between consumption and measurement) than those observed in studies of non-fatal injuries (Bramness et al, 2002; Jones et al, 2008; Mura et al, 2003)

There are good empirical data on THC blood concentrations in relation to driving performance. For instance, several studies, in different countries (Sweden $N = 1,276$; Norway, $N = 589$; Switzerland $N = 440$), have been conducted in apprehended drug drivers with THC as the only psychoactive compound in blood. Median concentrations of THC detected in blood in apprehended drug-drivers across 3 different countries were remarkably similar: $2.0 \mu\text{g/L}$ (range $0.3 \mu\text{g/L}$ to $67 \mu\text{g/L}$); $2.2 \mu\text{g/L}$ (range $0.3 \mu\text{g/L}$ to $45 \mu\text{g/L}$) and $3.0 \mu\text{g/L}$, respectively (Jones et al, 2008; Augsburger et al, 2005; Kronstrand & Jones, 2000). A further meta-analysis of 21 studies investigating cannabis ingestion and driving performance revealed that a blood concentration of $3.7 \mu\text{g/L}$ THC ($3.1 \mu\text{g/L}$ to $4.5 \mu\text{g/L}$) impairs drivers to a concentration equivalent to a BAC of $50\text{mg}/100 \text{ml}$ (Berghaus et al, 2010) and another meta-analysis of 78 studies investigating smoking cannabis revealed a blood concentration of $3.8 \mu\text{g/L}$ THC (range $3.3 \mu\text{g/L}$ to $4.5 \mu\text{g/L}$) impairing drivers to a concentration equivalent to BAC of $0.5\text{mg}/100 \text{ml}$ for smoked administration (DRUID D1.1.2b).

Furthermore, in a single-dose, double-blind, placebo-controlled study medicinal THC (10 mg and 20 mg Dronabinol) was administered to occasional and heavy cannabis users. A dose-dependent effect was observed on driving performance when under the

influence of THC regardless of the experience of the user (Bosker et al, 2012). Similarly, experimental studies found that Dronabinol (Marinol®, 10 mg to 20 mg) caused impairment in on-the-road driving tests in a dose dependent manner. These impairments were deemed bigger than the effects caused by a BAC of 50 mg alcohol per 100 ml blood, although effects were less pronounced after chronic dosing (DRUID Deliverable D1.2.2).

Table 4.2: Overview of the risks for involvement in, responsibility for or injury as the result of a traffic accident (as an odds ratio (OR)) for driving under the influence of cannabis or specific THC concentrations

Substances	Odds ratio (OR)	Reference
Cannabinoids	OR: 1.22 (95% CI: 0.55-2.73) OR: 2.79 (95% CI 1.23-6.33; P =0.01) Collision* OR : 2.10 (95% CI 2.10-3.36; P =0.002) Fatal collisions**	Movig et al 2004 Asbridge et al, 2005 Asbridge et al, 2005 Bernard et al, 2007 Laumon et al, 2005
-THC < 1 µg/L blood	OR: 1.29 (99% CI: 1.11-1.50)	Laumon et al, 2005
-THC 1-2 µg/L blood	OR:1.57 (95% CI: 0.84-2.95)	Laumon et al, 2005
-THC 3-4 µg/L blood	OR:1.54 (95% CI: 1.09-2.18)	Laumon et al, 2005
-THC ≥ 5 µg/L blood	OR: 2.13 (95% CI: 1.22-3.73) OR: 2.12 (95% CI: 1.32-3.38)	Mura et al, 2003
-THC < 1 µg/L blood	OR: 2.50 (95% CI:1.5-4.2) OR: 2.70 (95% CI:1.02-7.0)	Drummer et al, 2004 Drummer et al, 2004
-THC ≥ 5 µg/L blood	OR: 6.60 (95% CI:1.5-28) OR: 9.50, (95% CI: 2.8 – 32.3	Blows et al, 2004 DRUID (D2.3.5)*
Habitual cannabis use	OR: 1.38 (95% CI: 0.88 – 2.17)	DRUID (D2.3.5)**
THC or THCCOOH + THC	OR: 1.33 (95% CI: 0.48 – 3.67)	

***Seriously injured based on aggregated data, ** fatally injured based aggregated data**

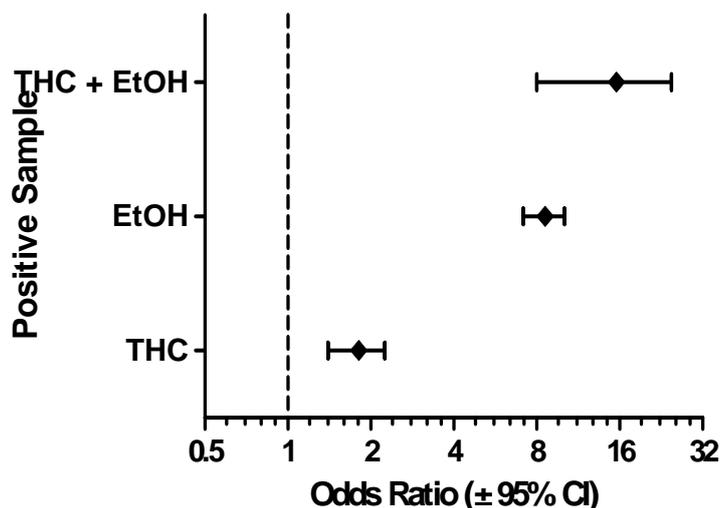
The increased risk of a road traffic collision whilst driving under the influence of cannabis ranges from OR: 1.22 to OR: 9.50 although it must be noted that studies used different criteria for calculating the risk estimate and in some cases lacked control of potentially confounding factors (Baldock, 2007). Consideration of the findings from

meta-analysis has helped to negate these methodological weaknesses. The DRUID report (2011), after taking age, and gender and confounding factors into account and controlling for traffic conditions, estimated that the use of cannabis increased the risk of serious or fatal injury in a motor vehicle accident by 1-3 times. It was noted that significant increased accident risk was apparent when the concentration of THC in the blood was $\geq 5 \mu\text{g/L}$, whether or not ingestion had occurred recently and regardless of the origin of the drug (medicinal or illicit). For this reason and based on the evidence (summarised above) available to the Panel, **the threshold recommended in whole blood for THC is $5 \mu\text{g/L}$** . At this concentration, the risks for involvement in, responsibility for, or injury as the result of a traffic accident when driving under the influence of cannabis are significant compared to a driver who has not consumed cannabis.

Cannabis and alcohol in relation to driving

The combined use of cannabis (as measured by THC) and alcohol produces severe impairment of cognitive, psychomotor, and actual driving performance in experimental studies and sharply increases the crash risk in epidemiological analyses (Ramaekers et al, 2004). The risk estimate as an odds ratio (OR) for involvement in, or injury as the result of a road traffic accident when driving under the influence of cannabis and alcohol are shown below (Figure 4.1, adapted from Laumon, Gadegbeku, Martin, 2005).

Figure 4.1: Relationship between the odds ratio (OR) for the risk of a traffic accident when cannabis and alcohol are detected alone and when alcohol and cannabis are detected concurrently (adapted from Laumon, Gadegbeku& Martin, 2005).



Laumon, Gadegbeku, Martin, (2005) investigated the relationship between combined use of cannabis and alcohol and driving performance interpreting risk estimates as odds ratio's (ORs). Adaptations of these results are shown in Figure 4.1, which demonstrates that the risk to a driver of a RTA was greatly increased (OR: 16.0). A similar OR was reported by DRUID in a responsibility study (D2.3.2): drivers involved in fatal accidents and detected positive for cannabis ($\geq 1 \mu\text{g/L}$), had a risk of about twice as high as that of drivers not positive for cannabis (OR: 1.89; CI 1.43-2.51), alcohol use also increases this risk (adjusted OR 8.39, CI 6.95-10.11), whereas combined use of alcohol and cannabis multiplies the risk of causing a fatal accident (OR: $8.39 \times 1.89 = \text{OR: } 15.86$) (Gadegbeku, Amoror & Laumon, 2011).

The DRUID³⁰ report found that in Europe, on average between 20% and 30% of cannabis use was in combination with other psychoactive substances and also noted that THC was most commonly detected when drugs were found in multi-drug combinations alongside cocaine, and (sometimes illicitly used) benzodiazepines. Data from the 2010/11 and 2011/12 CSEW shows that 7% of respondents who said they had used drugs in the last year used two or more drugs at the same time; the last time they took drugs.³¹ Cannabis was the most prevalent drug in cases of simultaneous polydrug use, being used in 73% of the most recent incidents. Where cannabis was used concurrently with other drugs, it was most often used with cocaine (42% of cases), followed by ecstasy (33%) or amfetamines (18%): the CSEW only asks about illicit drugs therefore benzodiazepines and alcohol were not included. The 2010/11 SCJS also found that 34% of adults who reported recent drug use i.e. within the last month, also reported polydrug use; 73% of those who had ever mixed the drug they used most often in the last month with any other drug, had mixed other drugs with cannabis³².

In all studies assessing cannabis use in conjunction with alcohol, the risk estimate as an odds ratio for cannabis and alcohol combined was higher than for cannabis use alone, suggesting the presence of a synergistic effect (Laumon, Gadegbeku, Martin,

³⁰DRUID 6th Framework Programme - D 7.3.2 Main DRUID results

³¹ Simultaneous polydrug and polysubstance use among adults aged 16 to 59
<http://www.homeoffice.gov.uk/publications/science-research-statistics/research-statistics/crime-research/drugs-misuse-dec-1112/polydrug>

³² 2010/11 Scottish Crime and Justice Survey: Drug use
<http://www.scotland.gov.uk/publications/2011/10/28142346/0>

2005; Mura, Kintz, Ludes, 2003; Longo et al, 2000; Drummer et al, 1995) or even multiplier effects on driver impairment (Chesher et al, 1986). Recently, DRUID has suggested that the effects of both drugs on driving performance are multiplied (DRUID, D2.3.2). For this reason and based on the evidence available to the Panel (summarised above), **a dual threshold is recommended** that takes account of the multiplicative effect of alcohol and cannabis use combined. The **threshold recommended in whole blood for THC when detected in combination with alcohol is 3 µg/L**. This concentration of THC alone doubles the risk as an odds ratio (OR) for involvement in, or injury as the result of a road traffic accident. The **threshold recommended in whole blood for alcohol when detected in combination with THC is 20 mg alcohol per 100 mL of blood**. This threshold for blood alcohol is already prescribed for aviation purposes (section 93(2) Railways and Transport Safety Act 2003).

Box 4.1: Basis for the recommendation of the THC threshold

Cannabis is the most widely used illegal drug in the United Kingdom: relating to its prevalence in drug driving, cannabis was the most commonly used illicit drug by drivers during 2011/12.

Significant scientific evidence is available with regard to the role of cannabis in Road Traffic Accidents (RTA) such that cannabis already features in road traffic legislation in many European countries.

Tetrahydrocannabinol (THC) the main active ingredient of cannabis is a potent, lipophilic, fast acting drug (half-life, 1.5 to 2 hours) that is widely distributed in the body. THC shows a significant dose effect for cannabis and driving performance, in which raised concentrations of THC were associated with increased road traffic crash risk. The risk (estimated as an odds ratio, OR) of serious or fatal injury from a RTA whilst driving under the influence of cannabis ranges from OR: 1.22 to 9.50.

Significant increased accident risk was apparent when the concentration of THC in the blood was ≥ 5 µg/L, whether or not ingestion had occurred recently.

The effects of drug-use setting (e.g. polydrug use, concomitant alcohol use and sleep deprivation) are intertwined and significantly contribute to unsafe driving

The risk to a driver of a RTA was significantly increased following combined use of alcohol (<80 mg/100ml blood) and cannabis ($\geq 1 \mu\text{g/L}$): the risk is multiplied (alcohol use alone OR: 8.39, cannabis use alone OR: 1.89 but combined use OR: 15.86).

Recommendations

- Based on the evidence available to the Panel (summarised above), it is recommended that a threshold in whole blood for THC is set at $5 \mu\text{g/L}$.
- In addition, a threshold is recommended for cannabis when detected in the presence of alcohol. It is recommended that the threshold in this circumstance be set for THC in whole blood at $3 \mu\text{g/L}$ and the alcohol level be set at 20 mg alcohol per 100mL blood.
- Blood sampling occurs as quickly as possible after the road traffic incident

5. DRUG SPECIFIC FINDINGS: COCAINE

Background

Cocaine is an alkaloid contained in the leaves of *Erythroxylon coca*, a small tree native to the mountainous region of Bolivia, Colombia, Ecuador, Peru and western Brazil. Leaves contain about 0.1 – 2.3% of cocaine (Daamen et al, 2012; Karch, 2012); content varies with age, the youngest leaves having the greater alkaloid content. Alkaloid cocaine is combined with acidic compounds to form various salts (the powder form). The hydrochloride (HCl) salt of cocaine is by far the most commonly encountered, although the sulfate (-SO₄) and the nitrite (-NO₃) are occasionally seen. Different salts dissolve to a greater or lesser extent in various solvents – the hydrochloride salt is quite soluble in water and easily injected intravenously or absorbed through mucous membranes (Warner 1993). A study by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) in 2007 showed that the purity levels for street-purchased cocaine powder were often less than 5% and on average about 50% pure; cocaine hydrochloride is used in concentrations of 1 to 25% for local anaesthesia (Moffat et al, 2011). It is known that cocaine is often adulterated ('cut') with inert bulking agents such as lactose or glucose which reduces the potency of a given weight of cocaine. However, there has, in recent years, been an increase in the use of active pharmaceutical ingredients (APIs) as adulterants. These include local anaesthetics, especially benzocaine or lidocaine but also phenacetin, caffeine and levamisole. There is some evidence that these can exacerbate some of the acute or chronic toxic effects of cocaine but there seems to be no specific evidence in respect of effects on driving performance.

Crack cocaine is a lower-purity form of alkaloid cocaine prepared by heating a mixture of cocaine hydrochloride and baking soda to form crystals that make a cracking sound when heated. The resultant product is a colourless, odourless, crystalline substance that is insoluble in water, but soluble in alcohol, acetone or ether. Crack cocaine is relatively heat stable and is usually smoked with a glass or regular pipe, or by mixing with tobacco or cannabis in cigarettes. Cocaine powder does not vaporize unless it is heated to a very high temperature but this often destroys the drug and yields a sharp, acrid, and foul-tasting smoke.

Epidemiological prevalence

Although cocaine is produced in South America, its use has been significantly distributed around the world. The EMCDDA data relating to drug use behaviour shows that cocaine is the second most frequently used illicit drug in Europe (Ravera and de Gier, 2007). Only a decade ago, cocaine use was very much more common in London than the UK more generally with 11% of the 16-29yr olds in the London sample reporting cocaine use in the previous year compared to a UK average of 5%. However, these geographical differences have equalised over time and the Focal Point³³ report produced in 2011 suggests very little regional variation in drug use more generally and cocaine specifically (Smith et al, 2011). The CSEW (2011/12) mirrors findings in the EU, reporting that cocaine is the second most widely used illegal drug with last year use estimated at 4.2 % of adults aged 16 to 59 years. Similarly, the SCJS 2010/11 found that cocaine was the second most commonly used drug, with 1.9% of adults reporting cocaine use within the last year.

Cocaine and driving

The Panel considered prevalence data from laboratory analysis of 3616 blood samples taken in suspected cases of drug-driving which screened positive (by ELISA) for one or more drugs. The data, which is predominantly from England and Wales and was collected between January 2008 and October 2012, showed that cocaine was present in 29% of drug positive samples. The EMCDDA report that between 0.1% and 3.0% of drivers tested positive for cocaine in the European Union (DRUID 2011). The Crime Survey for England and Wales (CSEW) has a self-completion module restricted to those aged 16-59 years that includes questions relating to drug driving. In 2009/2010 for those who reported driving under the influence of illegal drugs at least once or twice in the previous 12 months, cocaine was the second most commonly used drug and was used by 59% of respondents, during this time period (falling to 51% in 2010/11). Significant scientific evidence is available with regard to the role of cocaine in road traffic accidents such that cocaine already features in road traffic legislation in European countries (Table 5.1).

³³UK Focal Point on Drugs and is based at the Department of Health. It is the National Partner of the EMCDDA

Further evidence of the presence of cocaine in drivers in the United Kingdom is found in data regarding accident fatalities collected from HM Coroners and Procurators Fiscal by the Transport Research Laboratory (TRL)/Clockwork Research for the Department for Transport. In 2010, 1320 of the 1795 fatal road traffic accidents (RTAs) recorded in Stats19³⁴ were matched to HM Coroner and Procurators Fiscal cases and of these, 372 cases had blood drug and alcohol concentrations recorded: 5% of samples were found to be positive for cocaine.

Table 5.1: International drug thresholds (set in or recommended for legislation): cocaine and BZE

Country	Approach to threshold	Cocaine	BZE*	Reference
Portugal	Zero tolerance	5 µg/L (B)	5 µg/L (B)	Belgian Official Gazette 15.09.2009 Ed. 2
Germany	Zero tolerance	10 µg/L (Se)	75 µg/L (Se)	Nickel & de Gier, 2009
Finland	Zero tolerance	15 µg/L (Se)	10 µg/L (Se)	Belgian Official Gazette 15.09.2009 Ed. 2
Norway	Impairment limit Comparable to 0.5g/L BAC Comparable to 1.2g/L BAC	24 µg/L (B) <i>legal limits for graded sanctions not defined</i>	<i>no limits</i>	Norwegian Institute for Public Health, 2012
Netherlands	Threshold	50 µg/L (B)		Netherlands Advisory Committee 2010

Key: Biological fluids: B – blood; Se – serum; OF – oral fluid; *BZE (benzoylecgonine) is the main metabolite of cocaine,

³⁴ STATS 19 data refers to personal injury road traffic accident data recorded by police which is used for the development of national road accident statistics.

Patterns of use

Cocaine is firmly established as a recreational drug, frequently encountered in the clubbing fraternity as part of the repertoire of the polysubstance user. However, regular use is also commonplace and this incurs the need for increasing dosage levels to obtain the same degree of euphoria. Unlike alcohol there is no physical tolerance because an associated physiological abstinence syndrome does not exist. However, there is a definite withdrawal period that occurs after the cessation of dosing persisting for at least 24 hours and is characterised by fatigue, anxiety and depression. Drivers testing positive for illicit drugs in the European DRUID study (2009 - 2011) were predominantly young and male and illicit drugs were detected during all times of the day but mainly at weekends. Almost all cocaine users were younger than 50 years: logistic regression revealing the highest prevalence of use was found in the 25 to 34 year olds (DRUID deliverable D2.2.3). In Spain, the effect of cocaine use on non-fatal traffic injuries was assessed in a nationwide sample of 17,484 car drivers or motorcycle riders during 2005. Logistic regression was used to adjust for distance driven and potential confounders and determined that cocaine use ≥ 1 day/week was associated with more traffic injuries (Stoduto et al, 2012).

The amount of cocaine snorted in a 'line' varies widely from person to person and occasion to occasion (the purity of the cocaine is also a factor), but one "line" is generally considered to be a single dose and is typically 35 mg (a 'bump') to 100 mg (a 'rail') (Talk to FRANK, 2012). Nasal insufflation (known colloquially as 'snorting' 'sniffing' or 'blowing') is the most common method of ingestion of recreational powdered cocaine in the Western world. In a study of cocaine users, the average time taken to reach peak subjective effects of cocaine powder was 14.6 minutes (Volkow et al, 2000). By contrast crack cocaine is smoked by placing a 'rock' of the drug at the end of the pipe; a flame held close to it produces vapour, which is then inhaled by the smoker. The effects, felt almost immediately after smoking, are very intense: based on self-reports a 'peak high' was observed at a mean of 1.4minutes +/- 0.5 minutes, but does not last long- usually 5 to 15 minutes (Volkow et al, 2000).

Pharmacokinetics (PK) and blood drug concentrations

Both ingestion and insufflation of cocaine result in approximately the same proportion of the drug being absorbed: about 30 to 60%, although the faster absorption of insufflated cocaine results in quicker attainment of maximum drug effects. The acute effects of cocaine are measurable 0.5 to 1 hour after use (Perez-Reyes, Di Giuseppe, Ondrusek, 1982; Cone 1995; Jenkins, Keenan, Henningfield, 2002) and are consistent with a blood concentration of cocaine greater than 50 µg/L (Cone, 1995; Chow, Ambre & Ruo, 1995). Uges, 2011 reported similar blood drug concentration data (50 µg/L to 300 µg/L) after 'an effective dose' of cocaine.

Cocaine is extensively metabolised by plasma cholinesterase to benzoylecgonine (BZE), the primary metabolite. BZE is specific only to cocaine and is therefore indicative of cocaine use. Indeed, the identification of BZE increases the level of certainty of the toxicological result. BZE appears in the general circulation 15-30 minutes after cocaine administration. Other significant metabolites include ecgonine methyl ester (EME) and ecgonine, which are pharmacologically inactive (Sharpe et al, 2001). A small amount of cocaine is metabolised by N-demethylation to norcocaine, which has significant pharmacological activity (Askin, Diehl-Jones, 2001). Further minor metabolites of cocaine include p-hydroxycocaine, m-hydroxycocaine, p-hydroxybenzoylecgonine (pOHBE), and m-hydroxy benzoylecgonine (Kolbrich, Barnes& Gorelick, 2006). In the presence of ethanol, cocaine is transesterified by a liver esterase to cocaethylene (ethylcocaine), which is also pharmacologically active; with a median half-life of 2.5 hours. The contribution of cocaethylene to the spectrum of pharmacological activity and toxicity of cocaine is still controversial with some of the effects being due, probably, to alcohol inhibiting the metabolism of cocaine thus increasing concentrations of free cocaine (Harris, Everhart& Mendelson, 2003).

The plasma elimination half-life ($t_{1/2}$) of cocaine is dose dependent and ranges from 0.7 hours to 1.5 hours (Laizure et al, 2003). Thus for the purposes of drug analysis the window of opportunity for the detection of cocaine after **a single dose** would be quite narrow and between 3.5 to 7.5 hours: only about 1% to 5% of cocaine is excreted unchanged into urine. The $t_{1/2}$ of BZE is longer than that of cocaine: following a dose of 100 mg cocaine (snorted) the half-life of BZE was reported to be 4-6 hours and the window of detection up to approximately 30 hours and for at least 5 days in chronic

users (Verstraete, 2004). It should be noted that an investigational preparation (Esterom) for topical application for clinical reasons contains BZE but is not currently available in the UK (McDonald et al, 2008)

Several studies have investigated the relationship between cocaine and BZE concentrations and interpretation of analytical results have suggested that a distinction may be made between recent use and use that occurred in the past. It should be noted that for cocaine the ratio of the concentration in blood to the concentration in serum is one. Table 5.2 shows the plasma concentration time data for cocaine following a single dose administered by different routes under laboratory conditions (Cone & Weddington 1998; Peretti et al, 1990).

Table 5.2: Plasma/serum concentration data after consumption of cocaine under different circumstances in human volunteers*

Route of administration	Cocaine plasma conc (µg/L)	Time (h) between dose administration and sampling	BZE plasma conc (µg/L)	Time (h) between dose administration and sampling
25 mg Intravenous dose	775	3.9	15,611	5.6
32 mg Intranasal dose	412	5.1	13,681	7.8
42 mg Smoked cocaine base	707	2.6	9,395	4.1

*As the concentration ratio for cocaine in blood:plasma/serum is one, these results can be compared to other findings in whole blood.

Researchers have observed that when both cocaine and BZE are detected together, the BZE concentration in blood was uniformly higher than the cocaine concentration (mean cocaine concentration 836 µg/L) with a typical BZE to cocaine ratio being 14.2:1, range 1:1 to 55:1 (Jones et al, 2008). It was also noted that when cocaine and BZE were

detected together the concentration of BZE was significantly higher (mean 669 µg/L) than cases when BZE was detected alone (mean 209 µg/L, p=0.001).

The detection of cocaine alone is unlikely and would suggest immediacy of use whereas the detection of both compounds together is commonplace and suggests use within the last 12 hours. Detection of BZE alone would indicate cocaine use in the past and may be indicative of a transition to the drug-induced exhaustion phase which is expected after the consumption of cocaine. BZE alone may be detectable when the effect on the driver is sedation in the 'come down' period in the hours after cocaine use (Jones et al, 2008).

Collection of specimens for evidential analysis

The choice of biological fluid for the detection of cocaine is important. It is well documented that because of its instability in vitro cocaine is infrequently detected in biological samples. To this end it is necessary to collect blood samples in tubes containing a fluoride preservative. In the absence of such a preservative there is a rapid conversion of cocaine to BZE in the sample after collection. However, the use of the preservative sodium fluoride is thought to be only partially successful in stabilizing the analyte in the blood between sampling and freezing before analysis in the laboratory (Musshoff & Madea, 2010).

Cocaine and its major metabolites may also be detected in urine (Preston et al, 2002) and oral fluid. Most commercial cocaine immunoassay screening tests (for urine and oral fluid) cross-react appreciably with the major cocaine metabolites, which reduces test specificity and prolongs the window of detection. However, chromatographic techniques can easily distinguish and separately measure each of these substances. BZE is routinely determined in clinical settings as a biomarker of cocaine use.

The use of oral fluid for the quantitative detection of cocaine is problematic because different collection techniques can have a considerable influence on the concentration of drugs found in oral fluid samples (Crouch, 2005). The ROSITA-2 project³⁵ found an enormous variation in the concentrations of cocaine and BZE in oral

³⁵<http://www.rosita.org/execsumm.htm>

fluid and whole blood: the mean ratio for cocaine averaged 22:1 (range of 4:1 to 119:1) and the mean for BZE was 1:1 (range of 0.2:1 to 11:1). The Panel noted that scientists have concluded that the wide range of the ratios does not allow reliable calculation of the blood concentrations from oral fluid concentrations (Wille, Raes & Lillsunde, 2009; Moolchan et al, 2000). Data from the 2007 National Roadside Survey confirmed these findings reporting the mean oral fluid: blood ratio to be 40:1 for cocaine and BZE concentrations (Lacey et al, 2009).

The Panel concluded that blood sampling was the most effective way to measure the concentration of cocaine and BZE in the body, providing suitable preservatives were used and the length of time between the roadside incident and sampling was kept to a minimum.

Pharmacodynamics (PD)

Cocaine is a powerful euphoriant and central nervous system stimulant. Regardless of the route of administration cocaine can increase alertness, feelings of well-being, energy and motor activity (Ghodse 2002). Cocaine can increase confidence. Smoking or vaporizing cocaine and inhaling it into the lungs produces an almost immediate "high" that can be very powerful, this heightened stimulation is known as a "rush". While the stimulating effects may last for hours, the euphoric sensation is very brief, prompting the user to smoke more immediately (World Health Organization, 2004; 2007). In Sweden, typical signs and symptoms observed by police officers in drivers testing positive for cocaine were bloodshot eyes, agitation, restlessness and incoherent speech (Jones et al, 2008). When cocaine and BZE were detected together in blood samples donated by impaired drivers, those detained were reported to appear excited and stimulated. When only BZE, was detected roughly equal numbers of detainees were excited rather than appearing sedated (Jones et al, 2008).

Cocaine hydrochloride can be inhaled or used intravenously; by the latter route, it has an onset of action within 2 minutes, a peak effect at 5–10 minutes and duration of effects of about 30 minutes (Brubacher, Hoffman, 1997). With intranasal inhalation, cocaine causes local vasoconstriction and therefore limits its own absorption through the nasal mucosal. Physiological and psychotropic effects from nasally insufflated cocaine are sustained for approximately 40–60 minutes after the peak effects are

attained (Barnett, Hawks & Resnick, 1981) and cocaine may persist in the plasma for up to 6 hours (Brubacher, Hoffman, 1997). The euphoric effect of crack cocaine lasts less than 20 minutes (Brubacher, Hoffman, 1997), whilst its physiological effects can last from 15–60 minutes, depending on the route of administration. Cocaethylene the metabolite produced when cocaine and alcohol are consumed concurrently may also have a physiological effect; some researchers have reported that the effect is greater than cocaine hydrochloride, particularly on the heart rate and blood pressure (Askin, Diehl-Jones, 2001; Giroud & Colassis, River, 1993), but this view is not universally held.

Cocaine and Driving: the scientific evidence

Epidemiological research clearly identifies that cocaine is prevalent in the driving population of the United Kingdom and in relation to risk estimate of cocaine on the ability to drive there are numerous studies that indicate an increased risk to the driver of a traffic accident. The Panel noted that the risk of having an RTA was estimated to increase when cocaine had been consumed (OR between 2 and 22), with the extent and significance of the increase in risk depending upon the population of driver investigated (Table 5.3).

Table 5.3: An overview of the risk estimates as an odds ratio (OR) for involvement in, responsibility for or injury as the result of a traffic accident when driving under the influence of cocaine (based on a report by Clockwork Research Ltd. to the Panel)

Substances	OR	CI ((95%)	Reference and basis for OR
Cocaine	2.96 (p<0.05)	1.18 - 7.38	Meta-analysis of 4 studies analysing presence of cocaine in drivers fatally injured in road crashes, Elvik 2012
Cocaine	1.66	0.91 - 3.02	Meta-analysis of 3 studies analysing presence of cocaine in injured drivers. Elvik 2012; Movig, 2004
Cocaine	3.30	1.40 - 7.79	Analysis of blood samples collected from individuals seriously injured in road accidents in 6 European countries between 2007-2009. Bernhoft, 2011
Cocaine	22.34	3.66 - 136.53	Analysis of blood samples collected from individuals killed in road accidents in 4 European countries between 2007-2009. Bernhoft, 2011

Cocaine	2.04	0.69 - 6.09	Case-control study conducted in The Netherlands from May 2000 to August 2001 comparing 110 drivers hospitalised after a road accident with 816 drivers randomly selected from moving traffic. Movig 2004
Cocaine use	2.11	1.06-4.18	Risk of self-reported collision involvement within the past 12 months (N=7284).Soduto et al 2012
Cocaine use alone	3.30*	1.40-7.79	DRUID, OR for getting seriously injured*
Benzoylcegonine	22.34**	3.66-136.53	OR for fatal accident**

***Seriously injured based on aggregated data, ** fatally injured based aggregated data**

Researchers have investigated the effects of cocaine use on driving and found that drivers often overestimate their driving skills. Common physical effects for cocaine in drivers were heightened nervousness and greater alertness. In combination with poor decision making, this increases risk taking during driving. Cocaine is thought to affect driving ability negatively, especially, when used in combination with alcohol or another drug (Penning, Veldstra & Daamen, 2010). In terms of driving behaviour, reckless or reduced driving ability was frequently reported following cocaine use (MacDonald, Mann & Chipman, 2008). However, the issues relating to the effect of cocaine on the ability to drive safely are complex and the period of exhaustion and fatigue that follows cocaine use can also be detrimental to safe driving. There is sufficient research described in the literature to support the fact that cocaine can have a negative impact on the ability to drive (Couper & Logan, 2004; National Highway Traffic Safety Administration, 2007 & 2012) and the risk estimates (as odds ratios, OR) for driving under the influence of cocaine are summarised in Table 5.3.

The Panel also considered concentrations of cocaine as measured in the blood of individuals suspected of or proven to have been driving under its influence. In drug-drivers, the mean concentration of cocaine was 95 µg/L with the highest concentration found being 500 µg/L (median, 70 µg/L) (Musshoff, Madea, 2010); for BZE, the mean concentration was 1010 µg/L, with the highest concentration being 3100 µg/L. In the United Kingdom, data derived from 'Driving Under the Influence of Drugs' (DUID) cases where whole blood specimens were submitted for analysis to the DUID laboratory of the Forensic Science Service (FSS) during 2004-2007, showed that cocaine was detected in

254 cases. The concentration of cocaine and BZE measured in the drug drivers can be seen in Table 5.4 below.

The Panel also noted data from 2,995 blood samples taken between January 2008 and October 2012 and analysed by GC-MS and which contained one or more drugs. The data, which is predominantly from cases in England and Wales, relates to cases of Road Traffic Accidents (RTA) or impairment witnessed by the police, followed by assessment by a forensic physician. The Panel noted that the time between any witnessed impairment and sample collection was unknown and likely to be variable. These data are shown italicised in Table 5.4.

Table 5.4: DUID sample analysis undertaken for the FSS during 2004-2007, and additional data on samples taken between January 2008 and October 2012 (bold, italicised)

Compound	Mean blood Concentration (µg/L)	Median blood concentration (µg/L)	Range (µg/L)	Number of samples analysed
Cocaine	104	59	8 – 930	254
<i>Cocaine</i>	23	10	10 – 60	4
<i>Cocaine (with cocaine metabolites)</i>	66	20	10 – 1800	289
Benzoyllecgonine	1970	1690	150 – 6900	251
<i>Benzoyllecgonine</i>	301	200	20 – 1800	451
<i>Benzoyllecgonine (with cocaine and other cocaine metabolites)</i>	760	560	20 – 4500	289

A Swiss study found BZE in 13% of blood samples donated by drivers suspected of driving whilst drug impaired and concentrations in blood ranged from 39 µg/L to 2,430 µg/L (Augsburger et al, 2005). In a Swedish Study, 26,567 blood samples were examined from drivers investigated on suspicion of impaired driving over a 5 year period and of these, 795 (3%) were positive for cocaine or BZE. In 574 of the cases, the concentration of cocaine in blood was below the laboratory limit of quantification, but BZE was detected. The National Forensic Institute (Netherlands) estimated that the median concentration of cocaine in blood was 60 µg/L when driving after taking an effective dose (measured by the NFI 1999-2008).¹¹ It was also noted that when cocaine and BZE were detected together (mean cocaine concentration 836 µg/L) the concentration of BZE was significantly higher (mean 669 µg/L) compared to cases with a single detection of BE (mean 209 µg/L, p=0.001). Based on the concentrations of cocaine as measured in the blood of individuals suspected of or proven to have been driving under its influence the **Panel recommends that a threshold concentration of cocaine in blood might be usefully set at 80 µg/L** reflecting a level associated with risk of a RTA or impaired driving in line with the evidence in the literature. Since cocaine is a very fast-acting drug, a threshold for cocaine alone might miss many cases of cocaine use where a driver was still under the influence of the drug. BZE is the usual objective biomarker for cocaine use and is detected routinely in clinical and forensic laboratories. The Panel concluded that a threshold should be set high for BZE so as to exclude cocaine consumption that occurred several days ago. **A threshold of BZE³⁶ in whole blood was therefore recommended at 500 µg/L because this concentration of BZE in blood was deemed to be indicative of continued cocaine effect.**

Cocaine and alcohol in relation to driving

Cocaine is frequently used with alcohol and a specific metabolite (cocaethylene) is produced which has pharmacological activity: ethanol is known to prolong the euphoria of cocaine. It has been estimated that between 60 and 90% of cocaine users concomitantly consume alcohol. Data from the 2010/2011 and 2011/12 CSEW estimate

³⁶BZE: As Schedule 2 to the Misuse of Drugs Act 1971 lists "Ecgonine, and any derivative of ecgonine which is convertible to ecgonine or to cocaine" as being a controlled drug, and expert/scientific advice has been provided that BZE is a single step conversion derivative of ecgonine.

that cocaine was used with alcohol on almost all of the occasions on which it was used (91%)³⁷.

It is well known that alcohol alone impairs driving performance and significantly increases accident risk. A risk estimates as an odds ratio (OR) for involvement in, responsibility for or injury as the result of a traffic accident when driving under the influence of cocaine and other drugs has been estimated: OR 38.9: 8.2-185.0 (p<0.001), demonstrating a significantly increased risk compared to drivers who have not driven under the influence of cocaine or other drugs. The OR for driving under the influence of psychoactive drugs and alcohol compared to no drugs at all was OR: 112 (95% CI: 14-893) (Movig, Mathijssen & Nagel, 2004) whereas the OR for driving under the influence of **any** psychoactive drug and alcohol was hugely significant at OR:231.9: 33.3-1615.4 (p <0.001) (DRUID main findings report, 2012; Netherlands Institute Forensic Science Report, 2010). The significant risk to driver safety when alcohol and a psychoactive drug such as cocaine were used concurrently has led the Panel to **recommend halving the cocaine threshold when detected in blood in the presence of alcohol to 40 µg/L cocaine** and setting a threshold for blood alcohol concentration at 20 mg/100 ml blood.

Box 5.1: Basis for the recommendation of the cocaine and BZE thresholds

Cocaine is the second most widely used illegal drug in 2011/12: for those who reported drug-driving at least once or twice in the previous 12 months, cocaine was the second most commonly used drug.

Cocaine features in road traffic legislation in many European countries.

Cocaine acts rapidly in the body (half-life 0.7 to 1.5 hours) and is extensively broken down to benzoylecgonine (BZE), the primary metabolite.

BZE is specific only to cocaine and is therefore indicative of cocaine use when cocaine is no longer detectable in the body and is routinely measured for this purpose.

³⁷ Simultaneous polydrug and polysubstance use among adults aged 16 to 59.
<http://www.homeoffice.gov.uk/publications/science-research-statistics/research-statistics/crime-research/drugs-misuse-dec-1112/polydrug>

The effects of cocaine are very intense and felt almost immediately: there is a definite 'come-down' period that occurs after the cessation of dosing, persisting for at least 24 hours that is characterised by exhaustion, tiredness, anxiety and depression.

Both acute intoxication from cocaine use and the impact of exhaustion and tiredness following use have a negative impact on driver safety.

The odds ratio (OR) of serious or fatal injury from a RTA whilst driving under the influence of cocaine ranges from OR: 2 to 22, with the extent and significance of the increase in risk depending upon the population of driver investigated.

A threshold was recommended in relation to the mean concentration of cocaine in blood (from different studies) found in individuals suspected of or proven to have been driving under its influence: range of means considered were from 74 µg/L cocaine to 104 µg/L cocaine.

To identify drivers in the 'come-down period' a threshold was recommended in blood in relation to the mean concentration of BZE (from different studies) found in individuals suspected of or proven to have been driving under its influence: range of means considered were from 547 µg/L BZE to 1970 µg/L BZE.

A risk estimate (OR) for involvement in, responsibility for, or injury as the result of a RTA when driving under the influence of cocaine and other drugs has been estimated to be OR 38.9 (CI 95% 8.2 to 185.0, (P <0.001)) which led to the recommendation of a threshold for cocaine when detected in the presence of alcohol (<80mg/100 blood).

Recommendations

Based on the evidence available to the Panel which has been summarised above it is recommended that:

- A threshold in whole blood for cocaine is set at 80 µg/L.
- A threshold in whole blood for benzoylecgonine is set at 500 µg/L.
- A threshold is suggested for cocaine when detected in the presence of alcohol. It is recommended that the threshold in this circumstance be set for cocaine in whole blood at 40 µg/L and the alcohol level be set at 20 mg alcohol per 100 mL blood.

- Blood sampling should occur as quickly as possible after the road traffic incident and in blood sampling tubes with an appropriate preservative

6. DRUG SPECIFIC FINDINGS: AMFETAMINE-TYPE DRUGS

Background

Amfetamine is an illicit substance, a long standing member of the drug scene, and is widely available in the UK (Gossop, 2003). Amfetamines can be obtained by diversion from legitimate medical sources but most is manufactured illegally. The manufacture of amfetamine is relatively easy and 'home'-based laboratories have been able to produce substantial quantities of the drug as a salt or the free-base (Sievwright & McMahon, 1996). In 2004, the United Nations Office on Drugs and Crime (UNODC) reported that the largest seizures of amfetamines occurred in the UK, although in recent years the prevalence of amfetamine in the UK has fallen. Metamfetamine is an analogue of amfetamine and is popular in Thailand and North America, but use has not become widespread in the UK. The rate of production of new amfetamine-type drugs ("legal highs") has recently increased and regulatory authorities are experiencing great difficulty in identifying and controlling these drugs.

Amfetamines are also used in the treatment of narcolepsy and Attention Deficit and Hyperactivity Disorder (ADHD). In the United Kingdom, dextroamfetamine is the only compound recommended for narcolepsy. The most common treatment for ADHD in the UK is methylphenidate (such as Ritalin), a substance chemically similar to amfetamine, but is less liable to misuse. Amfetamine may also be prescribed however, for those for whom methylphenidate is unsuitable (Royal College of Psychiatrist, 2004; ACMD, 2005).

Epidemiological prevalence

Recent research from Norway and further afield in Australia (Davey et al., 2009), has reported that the illicit use of metamfetamines (Chu et al., 2012; Gjerde et al., 2011) and amfetamines (Gjerde et al., 2011) were more common than cannabis (THC). The CSEW results for the 16-24 year old demographic group for the years 2008/9 to 2011/12 are given below (Table 6.1).

Table 6.1: Prevalence of amfetamine use in 16-24 year olds in England and Wales Year (2008 to 2012).

CSEW Year of survey	2008-9	2009-10	2010-11	2011-2012
No. participants (16-24 years)	5428	3402	3621	3496
Any amfetamine use *	2.7%	2.4%	2.6%	2.0%

*Includes both amfetamine and metamfetamine.

The CSEW has a self-completion module that includes questions relating to drug use and drug driving. In 2010/11, for those who reported driving under the influence of illegal drugs at least once or twice in the last 12 months, 30% reported using amfetamine during the same time period. In addition, the SCJS household survey conducted in Scotland in 2001 to estimate the prevalence of driving whilst under the influence of recreational drugs (N =1,008) 17-39 year old drivers). This survey reported that amfetamines had been used by 8% of respondents at some point in their lives.

European data: amfetamines and driving

All DRUID investigations show that the prevalence of illicit drugs in the driver population (estimated EU mean, 1.90%) is lower than the alcohol prevalence (estimated EU mean 3.48%). Nevertheless, the mean EU prevalence for amfetamine alone was 0.08% and on average, it was reported that 50% of amfetamine use was in combination with other psychoactive substances. Amfetamine use alone was found to be more common in Northern Europe in seriously-injured drivers. In killed drivers, amfetamine was the third most prevalent drug detected in European drug use surveys, although the majority of cases of detection of amfetamine were in combination with other psychoactive substances (mainly alcohol). The detection of alcohol and another drug concurrently were, in seriously injured and killed drivers, the second most represented group in the majority of EU countries. The use of amfetamines by European drivers was not uniform across different countries. Use

was most prevalent among young men (18-35 years) but gender differences and the time of use differed by country (DRUID, D2.2.5; Report of main findings).

The Panel considered prevalence data from laboratory analysis of 3616 blood samples taken in suspected cases of drug-driving which screened positive (by ELISA) for one or more drugs. The data, which is predominantly from England and Wales and was collected between January 2008 and October 2012, showed that amfetamines were present in 13% of drug positive samples, and metamfetamine in 2% of drug positive samples. This is similar to the prevalence for amfetamine and metamfetamine found in Swiss drivers (Augsberger et al, 2005). Scientific evidence with regard to the role of amfetamines in road traffic accidents has led some countries to include these stimulants in road traffic legislation (Table 6.2). Most countries have used low cut-off thresholds in their legislation. Amfetamine use is often associated with sleep deprivation, which causes driving impairment (as a consequence of sleep loss). This is the basis that has been used in the Dutch legislation and a common threshold is often set for all stimulant drugs based on the fact that they all act in the same way (Stough et al, 2012)

Table 6.2: International drug thresholds (set in or recommended for legislation): amphetamine and metamfetamine

Country	Approach to threshold	Amfetamine (in blood)	Metamfetamine (in blood)	Reference
Netherlands	Threshold	50 µg/L *	50 µg/L *	NAC, 2010
France	Threshold	50 µg/L *	50 µg/L *	Mura et al, 2003
Sweden	Zero-tolerance			Jones et al, 2006
Norway	Impairment limit Comparable to 50 mg/100 ml BAC Comparable to 120 mg/100 ml BAC	41 µg/L <i>legal limits for graded sanctions not defined</i>	45 µg/L <i>legal limits for graded sanctions not defined</i>	Norwegian Institute of Public Health, 2012

* The sum of the concentration of amfetamine, plus metamfetamine, plus MDMA, plus MDEA, plus MDA must not exceed 50 µg/L. Key: NAC Netherlands Advisory Committee

Patterns of use

The duration of action of amphetamine is about 6 hours and many users take this stimulant over 2 to 3 days, keeping awake during the nights and eating little (Seivewright, et al, 2007). Amphetamine as a powder can be swallowed, wrapped in a cigarette paper, dissolved and consumed as a drink, snorted or injected. Some amphetamine users take the drug in an 'instrumental' way using the extra wakefulness and confidence to party all night or drive long distances (Gossop, 2003; Drummond et al, 2004).

The crystalline form of metamphetamine (known as ice or crystal meth) may be heated and inhaled from a pipe similar to those used to smoke crack cocaine (Cho, 1990). Metamphetamine can also be smoked with tobacco in a cigarette and is sold in powder form by the gram.

Often, a defining feature of amphetamine (and other CNS stimulants) use is the high-dose cyclical pattern of consumption. Amphetamine use often occurs in binges during which time repeated dosing occurs at frequent intervals lasting a few hours to several days, often until exhaustion sets in or the drug runs out (Gossop, 2003). With heavy use, ingestion of up to 2000 mg per day has been reported (Jenkins, 2008).

Medicinally, amphetamine is prescribed in an entirely different manner. Low dose amphetamine (dextroamphetamine) was once the drug of choice in the treatment for ADHD in children (now superseded by methylphenidate) and amphetamine sulphate has been used in the past for the treatment of narcolepsy (daily dose 5 mg to 60 mg). Metamphetamine hydrochloride is also available as a conventional or prolonged-release tablet for the treatment of obesity (Jenkins, 2008). The usual doses of different amphetamines used for therapeutic purposes are given below:

- Amphetamine sulphate (5mg - 60 mg/day)
- Metamphetamine hydrochloride (2.5 mg – 20 mg/day; 10-15 mg IV/day)
- Adderall XR™ (Dextroamphetamine) 10 mg/day
- Dextroamphetamine Spanules® (10 mg/day)
- Methylphenidate 5-10 mg/day increasing to 60mg/day maximum

Pharmacokinetics (PK) and blood drug concentrations

Amphetamine taken orally is well-absorbed and has no major pharmacologically active metabolites. The half-life of amphetamine is about 12 hours and after large doses, amphetamine may be detected in urine for several days. After normal therapeutic dosing, the plasma concentration of amphetamine is usually less than 100 µg/L (Baylor & Crouch, 1993). However, ingestion of ten to fifty times the therapeutic amount is not unusual in addicts: in such cases, the plasma concentration may be as high as 3000 µg/L. For the purposes of drug analysis, the window of opportunity for the detection of amphetamine in blood after **a single dose** would be around 60 hours. Steady-state blood concentrations of between 2000 µg/L and 3000 µg/L were observed in a regular user (addict) who ingested about 1g per day (Wan et al, 1978).

Metamphetamine is usually self-administered by the smoked route: both the free-base form and the hydrochloride salt are volatile. The elimination half-life of metamphetamine has been reported to be 11.7 h (range 8 hours to 17 hours) by Cook (1990). Maximal blood concentrations of metamphetamine occurred at 2.7 and 2.5 hours after intranasal and smoked doses (Harris et al, 2003). The therapeutic range for metamphetamine in plasma is reportedly between 10 µg/L and 50 µg/L. Amphetamine is a major active metabolite of metamphetamine and concentrations of urinary metamphetamine ranging from 24,000 µg/L to 33,300 µg/L and amphetamine 1000 µg/L to 90,000 µg/L, respectively, were observed in users of the drug (Lebish et al, 1970). For the purposes of drug analysis, the window of opportunity for the detection of metamphetamine in blood after a single dose would be similar to amphetamine.

Collection of specimens for evidential analysis

First-generation amphetamine urine screening tests often cross-react with compounds found in cough medication such as ephedrine, phenylpropanolamine and appetite suppressants (phentermine and fenfluramine), to give false positive results. However, newer screening tests (such as the EMIT[®] d.a.u. monoclonal immunoassay) have fewer problems with cross-reactivity. In practice, amphetamine can be easily detected in oral fluid using on-site tests; however, cross-reactivity with

amphetamine-type substances is also an issue with oral fluid immunoassay tests. Evidence that dried-blood spot (DBS) tests have potential as a precise option for determination of amphetamine might be investigated further (DRUID, Summary of main DRUID results 2012). However, for the detection of amphetamine and metamphetamine for drug-driving offences, whole blood was the matrix of choice for drug-driving confirmation tests, for the reasons previously identified for other compounds.

Pharmacodynamics (PD)

The effects of amphetamine-type drugs have been well described and were characterised by Seivewright & McMahon (1996) into three distinct phases: the first, early phase is defined by the release and inhibition of the re-uptake of catecholamines, with a direct action upon dopamine. Stimulation of the 'reward pathway' as it is known, causes increased energy, elation and reduced appetite. Amphetamine produces both central nervous system and cardiovascular stimulation, significantly increasing heart rate and blood pressure: confidence runs high. The euphoric effects of metamphetamine are thought to be longer lasting than those of amphetamine and depending upon the dose, range from 7 – 24 hours (Perzez-Reyes, 1991). However, this may in part be due to the presence of amphetamine (the primary metabolite).

There is a distinct difference between the early 'desired' effects and the second, later phase that supervenes approximately 6 hours after dosing and which tends to be adverse in nature. This phase is categorised by over activity, insomnia and confusion and is followed by the third and final phase that users commonly describe as the 'crash' and which often presents as irritability, agitation, craving, sleep disturbance, hyperphagia and depression. Heavy stimulant use often produces mood disturbances, confusion and aggressive behaviour that can result as a direct effect of the drug.

Amphetamines and driving: the scientific evidence

Some experimental studies investigating the effect of stimulants (dextroamphetamine) on driving did not reveal impairing effects on driving performance. For instance, Ramaekers

reported that therapeutic doses of stimulant drugs produce neutral or even stimulating effects on a range of psychomotor functions and driving skills and concludes that effects on driving behaviour are generally mild and safe (Ramaekers, 2011). In driving simulator performance at low doses (0.42 mg/kg) of metamfetamine (dextro-, and D/L-), driving tests were not significantly affected (Silber et al, 2012a, 2012b). However, the administration of metamfetamine in controlled experiments does not reflect the usual patterns of misuse. Consideration of the risk-estimates for seriously or fatally injured drivers who had amfetamine detected whilst driving compared to driving controls indicates that these drugs are indeed a hazard when driving (Table 6.3).

Table 6.3: Overview of the relative risks as an odds ratio (OR) for involvement in, responsibility for, or injury as the result of a traffic accident when driving under the influence of amfetamine/metamfetamine

<i>OR</i>	<i>95% CIs</i>	<i>Basis of the OR</i>	<i>References</i>
6.19 4.46 (p<0.05)	3.46-11.06 2.21 - 9.00	Meta-analysis of 8 laboratory studies analysing presence of amfetamines in drivers killed/ injured in RTA	Elvik, R. (2012)
8.88 (p<0.001)	4.54 - 17.39	Case-control study (Thailand). 200 cases admitted to hospital after RTA with 849 controls: most were motorcycle riders.	Woratanarat,2009
8.35	3.91 - 17.83	Analysis of blood samples collected from individuals seriously injured in road accidents in 6 European countries between 2007-2009.	Bernhoft, I.M. (2011)
8.35 Injured 24.09 Killed	3.91-17.83 9.72 - 59.71	Analysis of blood samples collected from individuals injured/killed in road accidents in 4 European countries between 2007-2009.	Bernhoft, I.M. (2011)
2.10	0.66 - 6.73	Case-control study conducted in The Netherlands from May 2000 to August 2001 comparing 110 drivers hospitalised after a RTA with 816 drivers randomly selected from moving traffic.	Movig et al, 2004

12.8	3.0-54.0	Risk of RTA driving under influence amfetamines.	Dussault, 2002
2.27	0.9 - 5.6	Case-control study of 3398 fatally-injured drivers in Australia: the effect of alcohol and drug use on the likelihood of culpability.	Drummer, 2004

The risk of serious or fatal injury whilst driving under the influence of amfetamine/metamfetamine as an OR ranged from 2.10 to 24.09, suggesting a medium to high risk of a traffic accident according to the criteria established by DRUID researchers. In a responsibility study, when lorry drivers were considered as a discrete driver population, the OR increased from OR: 2.27 to 8.8 and was borderline statistically significant (95% CI, OR: 1.0 to 77.8) (Drummond, 2004).

While the DRUID on-road studies did not find an impairment effect at therapeutic doses of stimulants, the risk to drivers was found to increase if the drugs were taken in conjunction with sleep loss or alcohol. The DRUID researchers concluded that **negative driving performance may only be detected at high doses and also after acute intoxication** which is frequently characterized by sleepiness and exhaustion. Some studies have shown that most RTAs occur when the effects of amfetamine-type drugs wear off and fatigue sets in. For instance, an analysis of amfetamine-positive cases found no relationship between symptoms described on police observation reports and medical examinations, but that impaired driving was likely due to sleep deprivation caused by 'bingeing' on amfetamines, and the 'come-down' effects of the drug (Musshoff & Madea, 2012).

The risk of a road traffic collision whilst driving under the influence of amfetamine/metamfetamine ranges from about OR: 2.10 to OR: 8.35 (injured or hospitalized drivers) to OR: 4.25 to OR: 24.09 (seriously or fatally injured). Although studies used different criteria for calculating the risk estimate and in some cases lacked control of potentially confounding factors (Baldock, 2007) the overall direction of the evidence was of increased risk.

With regard to metamfetamine, a double-blind, counter-balanced and placebo-controlled study of 61 young adults found that overall driving behaviour (inappropriate braking, signalling errors, not keeping a safe distance between cars) was most affected

at 3h post-dose (metamfetamine 0.42 mg/kg): there were significantly more signalling errors compared to placebo and the results approached significance ($p < 0.055$). Average blood-drug concentrations of metamfetamine at 3 hours post dose was 91.7 µg/L and 22.4 µg/L at 24 hours post-dose. It was concluded that metamfetamine significantly impairs driving ability and therefore poses a risk to road safety (Stough, 2012). Logan (1996) concluded 15 years earlier that metamfetamine at any concentration was likely to produce behaviour inconsistent with safe driving. In metamfetamine-related traffic fatalities (N= 17), the blood concentration was reported to range between 50 µg/L to 2,600 µg/L, with most deaths occurring at concentrations greater than 500 µg/L (Logan et al, 1998).

The Panel also noted data from 2995 blood samples taken between January 2008 and October 2012 and analysed by GC-MS and which contained one or more drugs. The data, which is predominantly from cases in England and Wales, relates to cases of Road Traffic Accidents (RTA) or impairment witnessed by the police, followed by assessment by a forensic physician. The data showed that the mean blood drug concentration of amfetamine (when not found in the presence of other amfetamines) was 456 µg/L (N= 193, range 20 – 6,800 µg/L, median 270 µg/L). For metamfetamine, the figure was 142 µg/L (range 60 – 230 µg/L, median 160 µg/L) although the sample size was very small (N= 5). The Panel noted that the time between any witnessed impairment and sample collection was unknown and likely to be variable.

Historical data derived from cases where whole blood specimens were submitted for analysis to the laboratory of the Forensic Science Service (FSS) over a three year period (2004 to 2007) was also considered by the Panel. The samples submitted from drivers suspected to have been driving whilst under the influence of drugs (N= 235 cases). For amfetamine (when not found in the presence of other amfetamines) the mean blood drug concentration was 651 µg/L (median, 498 µg/L, range 38 µg/L to 3,140 µg/L). Consideration of the findings from the DRUID case control studies, the relative risk of serious injury or fatality for amfetamines was about 5 to 30 times as high as that of drivers below the DRUID cut-off for any substance (DRUID deliverable D1.1.2). For this reason and based on the evidence available to the Panel (summarised above) **the recommended threshold in whole blood for amfetamine was 600 µg/L**. The decision to set this threshold high was based on the blood concentrations

observed for amphetamine in apprehended drivers taking into consideration the variable time period between the traffic incident and blood sampling. Metamphetamine is a more potent drug and concentrations in the blood are usually lower than for amphetamine. For this reason **the recommended threshold for metamphetamine was set at 200 µg/L.**

Amphetamine and alcohol in relation to driving

The stimulant effects of amphetamine and metamphetamine (increased alertness, concentration and wakefulness) are not sufficient to compensate for poor driving behaviour produced by concomitant alcohol use (Simons et al, 2012) or sleep deprivation (Hjalmdahl et al, 2012). Sleep deprivation is considered to be equivalent to the same degree of impairing effect as 50 mg alcohol per 100ml blood and is a serious concern following amphetamine or metamphetamine use. The pharmacological effects of stimulants and the effects of drug-use setting (e.g. polydrug use, concomitant alcohol use and sleep deprivation) are intertwined and significantly contribute to unsafe driving (Ramaekers, 2011).

The Panel was mindful that DRUID researchers in the context of a pan-European initiative to combat driving under the influence of drugs reported that any threshold in blood should distinguish between potential medicinal use of amphetamines (therapeutic doses) and the abuse of stimulants (polypharmacy, sleep loss). Stimulants are generally safe for driving when taken alone, in low doses as prescribed, in a therapeutic regimen, but are a significant risk to driver safety when used in a binge pattern of consumption and in combination with sleep loss as is often the case in drug abusers. Stimulant drugs have been shown to have the strongest measured association of culpability and descriptive studies have shown a high rate of aberrant driving among amphetamine misusers in the acute intoxication and the rebound fatigue phase (Logan, 2002).

For this reason and based on the evidence available to the Panel (summarised above) a dual threshold is recommended that takes account of the additive effect of alcohol and amphetamine use combined. **The threshold recommended in whole blood for amphetamine when detected in combination with alcohol is 300 µg/L and the threshold recommended in whole blood for metamphetamine when detected in combination with alcohol is 200 µg/L.** And the threshold recommended in whole blood

for alcohol when detected in combination with amphetamine is 20 mg alcohol per 100 mL blood.

Box 6.1: Basis for the recommendations of the amphetamine and metamphetamine thresholds

Amphetamine as an illicit drug is widely available in the UK: in cases of drivers suspected of drug-driving, amphetamine was present in 13% and metamphetamine in 2% of drug positive blood samples.

Significant scientific evidence is available with regard to the role of amphetamine and metamphetamine in RTAs such that amphetamine and metamphetamine already feature in road traffic legislation in many European countries.

Amphetamine and metamphetamine produce stimulatory effects, significantly increasing alertness and confidence. The half-life of both amphetamine and metamphetamine is about 12 hours.

About 6 hours after dosing adverse effects develop characterised by over activity, insomnia and confusion. The 'come-down' or "crash" that follows is defined by irritability, agitation, craving and sleep disturbance.

The risk of having a RTA (serious or fatal injury) when driving under the influence of amphetamine/ metamphetamine was estimated to range from OR: 2.1 to 24.1

A threshold was recommended in relation to the mean blood concentrations of amphetamine (when not detected in the presence of other amphetamines), found in individuals suspected of or proven to have been driving under its influence: the range of means (from different studies) varied from 456µg/L to 651µg/L.

After normal therapeutic dosing, the plasma concentration of amphetamine is usually < 100 µg/L.

A threshold was recommended in relation to the mean blood concentrations of metamphetamine (from different studies) found in individuals suspected of or proven to have been driving under its influence: the range of means varied from 142 µg/L to 300 µg/L metamphetamine.

The therapeutic range for metamphetamine in plasma is reportedly between 10 µg/L and 50 µg/L.

A further threshold was recommended when amphetamine or metamphetamine are detected concurrently with alcohol (<80 mg/100 ml blood) on the basis that the effects of drug-use setting (e.g. concomitant alcohol use and sleep deprivation) are intertwined and significantly contribute to unsafe driving.

Recommendations

- Based on the evidence available to the Panel which has been summarised above, it is recommended that a threshold in whole blood for amphetamine be set at 600 µg/L.
- Based on the evidence available to the Panel which has been summarised above, it is recommended that a threshold in whole blood for metamphetamine be set at 200 µg/L.
- In addition, a threshold is suggested for amphetamine when detected in the presence of alcohol: It is recommended that the threshold in this circumstance be set for amphetamine in whole blood at 300 µg/L and the alcohol level be set at 20 mg alcohol per 100 mL blood.
- In addition, a threshold is suggested for metamphetamine when detected in the presence of alcohol: it is recommended that the threshold in this circumstance be set for metamphetamine in whole blood at 100 µg/L and the alcohol level be set at 20 mg alcohol per 100 mL blood.
- Particular attention should be paid to driver safety initiatives in long-distance drivers who may not be aware of the deleterious effects of amphetamine-type drugs.

7. Drug-Specific Findings: MDMA ('Ecstasy')

Background

'Ecstasy' is the common name for 3, 4-methylenedioxymethamphetamine (MDMA); it is an illegal drug that is usually consumed as a tablet, capsule or powder by clubbers. There is no common name or colour for the illicitly-manufactured tablets being sold as ecstasy: although there is little guarantee of the content, the majority of tablets sold as ecstasy contains moderate doses (54 - 78 mg) of MDMA. Europe remains the centre for ecstasy production and trafficking, and the peak use of MDMA in European clubs, raves and other such venues (Schifano et al, 2006) was thought partly related to an apparently falling cost as well as a decrease in the concentration of MDMA present in the tablets. However, recent reports have seen the use of MDMA plateau (EMCDDA, 2011) but it remains one of the most popular clubbing drugs in the EU and beyond.

Epidemiological prevalence

Drug prevalence estimates suggest that about 11 million Europeans have tried ecstasy, and about 2.5 million used the drug during 2009. Use of MDMA tends to be concentrated among young adults, with males reporting levels of use much higher than females in all countries except Greece, Romania, Finland and Sweden. Data on the prevalence of ecstasy use in nightlife settings were only available for four EU countries (Belgium, Czech Republic, Netherlands, United Kingdom) and in 2009 showed considerable variation: levels of recent (last year) use ranged from 10 % to 75 % of clubbing populations. Ecstasy use, however, was more common than amphetamine use in the settings sampled (Focal point report, 2011). Lifetime prevalence of ecstasy use among the 15-34 age group ranges from under 0.6 % to 12.7 %, with most countries reporting estimates between 2.1-5.8 % (EMCDDA, 2006). Among 15- to 16-year-old school students in Italy, Slovakia, Sweden and the United Kingdom, lifetime prevalence of ecstasy use ranged from 1 % to 5 % in 2007 (EMCDDA 2007). It has been estimated by the Association of Chief Police Officers (ACPO) that between 2.5 and 5 million MDMA tablets are taken every month in the UK demonstrating the widespread use of the drug.

The latest data from the Scottish Crime and Justice Survey (SCJS) 2009/1030 show that amongst adults aged 16 to 64 years old in Scotland, cannabis continues to be

the most commonly-used drug across all recall periods (used ever, used in previous year). The next most common drugs reported to be used ever were amfetamines and ecstasy, whereas for previous year use the next most common drugs were cocaine and ecstasy.

The UK has a well-established clubbing population and the 2011/12 Crime Survey for England and Wales (CSEW) estimated that around one in five young people (19.3%, an estimated 1.3 million young people) aged 16 to 24 had used one or more illicit drug in the previous year, with previous year usage of ecstasy estimated at 3.3%. The prevalence of ecstasy (MDMA) previous year use was third behind cannabis (15.7%) and cocaine (4.2%) for previous year use: Last year of use of ecstasy was lower in 2011 than levels reported in 2008/9 (4.4%).

European data: MDMA and driving

There is good evidence that amfetamine-type drugs such as MDMA are present in the driving population of Europe, including the UK. In the DRUID roadside survey (Deliverable 2.2.3, 2011), the prevalence of amfetamines (which included amfetamine, metamfetamine, MDMA, methylenedioxyamfetamine (MDA) and 3, 4-Methylenedioxy-N-ethylamfetamine (MDEA)) in the driver population was estimated (EU mean) to be 0.08% and highest in the Czech Republic (0.38%). The prevalence of illicit drug use among all killed drivers shows that the amfetamine group (in parentheses above) was the third most prevalent illicit substance detected behind alcohol and benzodiazepines. In terms of the characteristics of drivers testing positive for illicit drugs (DRUID 3.2.2), amfetamines were mainly used by drivers younger than 35 years, although older drivers were observed in the Netherlands.

Table 7.1: Suggested prohibition limits by Norwegian Academic Advisory Group (2010)

SUBSTANCES	Intoxicating dose / dose causing impairment	Concentration /dose causing impairment µg/L (Cmax)	intoxicating causing µg/L (blood)	Impairment limit
MDMA ¹⁾	100 mg	251	48	

¹⁾The concentration is calculated after intravenous use

The CSEW has a self-completion module restricted to those aged 16-59 years, includes questions relating to drug use and drug driving. For those who reported driving under the influence of an illegal drug in 2010/11, 31% reported using ecstasy within the same time period. The Norwegian Academic Advisory Group (2010), in preparing advice for drug-driving legislation, reported on the following levels with regard to MDMA (Table 7.1).

Patterns of use

Various studies have concluded that the clubbing population has significantly more experience with drugs than the general population (Griffiths et al, 2008). Many studies have attempted to discover more about the pattern of MDMA use, as well as the characteristics of MDMA users (Cole et al, 2005; Wolff et al, 2006; 2012): a common feature is the high level of poly-drug use. Overall, these studies show that users tend to be young males, although females report higher rates of acute negative effects: individuals commonly consume about 1.9 mg/kg orally (Forsling et al, 2001).

Ecstasy is commonly sold on the street as tablets, although increasingly MDMA is sold as a powder and called by its chemical name, MDMA, or 'crystal': it has a relatively quick onset of action from about 20-60 minutes. MDMA powder can be 'dabbed' onto the gums or snorted. Ecstasy tablets are usually swallowed – although some people do crush them up and smoke or snort them (Talk to FRANK, 2012). Users generally consume 1-2 tablets, although other patterns of use have been described including 'double dosing', which means taking another tablet when the expected effect has not occurred; 'stacking' has been described where three or more ecstasy tablets are taken at one time and, the term 'piggy-backing' describes where multiple tablets are taken over a short period of time.

The Erowid website³⁸ provides recommended dosing levels for users (Table 7.2) which gives an approximation of quantities used. The likely quantity of tablets has been estimated according to the known published concentration of the drug present in tablet forms.

³⁸<http://www.drugs-forum.com/forum/showwiki.php?title=MDMA>

Table 7.2: Estimated quantity of MDMA required to achieve the desired effect and number of tablets required (adapted from Erowid)

MDMA Dosage	Amount of drug (mg)	Tablet required
Threshold	30 mg	half a tablet
Light use	40 – 75 mg	1 tablet
Common (small or sensitive people) dose	60– 90 mg	1 – 1.5 tablets
Common (most people) dose	75–125 mg	1 – 2 tablets
Common (large or less sensitive people) dose	110–150 mg	2 – 2.5 tablets
Strong use	150–200 mg	2 – 3 tablets
Heavy use	200mg and above	3 or more tablets

Pharmacokinetics (PK) and blood drug concentrations

MDMA and its main active *N*-demethylated metabolite, 3,4-methylenedioxyamfetamine (MDA) are both demethylated by enzymes in the liver (CYP2D6) to 3,4-dihydroxymetamfetamine (HHMA), and 3,4-dihydroxyamfetamine (HHA), respectively. HHMA and HHA are both then *O*-methylated by the catechol-*O*-methyl transferase (COMT) enzyme to 4-hydroxy-3-methoxymetamfetamine (HMMA) and 4-hydroxy-3-methoxyamfetamine (HMA) respectively (de la Torre et al, 2004).

MDMA displays non-linear (non-proportional dose-dependent) kinetics in the dosage range usually taken by recreational users and zero order kinetics at higher doses. This means that as the MDMA dose is increased, the rise in MDMA concentration does not follow the same proportionality (de la Torre 2004). It is thought likely that this can lead to sustained and higher plasma concentrations of the drug, especially if a clubber consumes more than one dose consecutively. Farre et al, 2004, detected higher plasma concentrations of the drug 24 hours after a second dose.

MDMA reaches peak plasma concentrations between 1.5 and 3 hours after ingestion (De La Torre et al, 2000) and may be slowly metabolised (De La Torre, 2000b); this variability is likely to be genetically influenced (Aitcheson et al, 2012). The contribution of the pharmacologically-active metabolites of MDMA (3, 4-methylenedioxyamfetamine, MDA, 3, 4-dihydroxymetamfetamine, HHMA and 3, 4-dihydroxyamfetamine, HHA) to the overall drug effects remain unclear, with some (such as MDA) likely prolonging effects. The plasma elimination half-life of MDMA has been reported to be about 7.6 hours (Moffat et al, 2004) and clearance from the body of a typical MDMA dose (50 mg) moderately slow. For the purposes of drug analysis, the window of opportunity for the detection of MDMA after a **single dose** would be up to 38 hours, longer for multiple dosing. Plasma concentration data after a single oral dose of MDMA have been reported in the scientific literature as follows (Table 7.3).

Table 7.3: Mean plasma concentration of MDMA after a standard experimental dose

MDMA Dose	Mean plasma concentration of MDMA	Reference
1.5mg/kg	300 µg/L	Helmlin et al (1996)
75mg oral dose	180 µg/L (MDA peak of 78 µg/L 5 h after administration)	La Torre et al (2000)

Collection of specimens for evidential analysis

Some immunoassay tests for amfetamines possess considerable cross-reactivity with MDMA and MDA. Some ELISA assays have kits specifically designed for the analysis of either D-metamfetamine (or MDMA). The heavy use of MDMA tablets may lengthen detection time by immunoassay because of the presence of metabolites. In the epidemiological studies of the DRUID project toxicological analysis of blood and oral fluid samples were undertaken to try and find a universal conversion factor between whole blood and oral fluid concentrations. The concentration of MDMA in oral fluid varies according to the dose and the time of drug intake in relation to the time of sampling. The mean oral fluid: blood ratio for MDMA was 13.6 (3.6-26.8). The laboratory cut-offs for MDMA, MDEA and MDA in whole blood compared to oral fluid are shown in Table 7.4.

Table 7.4: DRUID recommended laboratory cut-offs for whole blood and oral fluid

Substance	Whole blood (µg/L)	Oral Fluid (µg/L)
MDMA/MDEA/MDA	20	270

Blood sampling is considered to be the most effective way to measure the very recent use of MDMA in the body. However, the blood/serum ratio for MDMA is 1.2 – 1.3 (Baselt, 2008) and this suggests that blood and serum drug concentrations cannot be assumed to be equal. Whole blood was considered to be the most appropriate biological fluid for setting thresholds because most of the scientific evidence in relation to drug-driving has been carried out in whole blood and was therefore recommended as the biological sample of choice.

Pharmacodynamics (PD)

MDMA is a powerful CNS stimulant and acute use acts to boost the mood state, bringing about elation and euphoria. MDMA is known to impair hypothalamic thermoregulation and increase body temperature as well as alter homeostatic water balance (Wolff et al, 2012). The most sought-after effects are euphoria, empathy and increased sensory awareness.

Behavioural effects begin quickly, within 5-20 minutes, and may plateau for 2-3 hours, lasting approximately 4-6 hours. Negative effects tend to become more prominent at higher doses and include excessive stimulation, muscle tension (especially in the jaw), nystagmus and anxiety. The stimulatory properties of MDMA are more pronounced at high doses (increased blood pressure, heart rate and, body temperature) and has been known to lead to hyperpyrexia in some. The days after MDMA are typified by low mood, lethargy, tiredness and depression and in some cases, physical exhaustion. Stimulant use such as MDMA consumption is often associated with sleep deprivation which itself is known to generate the same degree of impairment as a blood alcohol level of 50 mg alcohol per 100 ml blood (0.5g/L). It was noted that the stimulatory effects of MDMA are not sufficient to overcome or compensate for deficiencies in driving performance produced by concomitant alcohol use or by sleep deprivation (DRUID, 2011 D3.2.4).

MDMA and Driving: the scientific evidence

In the DRUID hospital studies (seriously injured and killed drivers), case control studies calculated the relative risk of RTAs for amphetamine-type drugs including MDMA³⁹, to be about 5-30 times as high as the risk for drivers below the DRUID cut-off for any substance, although there was much variability among single countries. As part of the EU project IMMORTAL, oral fluid samples were collected from 1,312 drivers at the road side in Glasgow (Assum et al., 2005). The most common drugs detected were ecstasy (estimated prevalence 4.6% of drug used in isolation or combination) and cannabis that was estimated at 3.3% prevalence (Assum et al., 2005).

Experimental studies on stimulants (DRUID Deliverable D1.2.1) showed that MDMA (25 mg, 50mg and 100mg doses) did not reveal impairing effects or increased risk caused by the consumption of MDMA itself. It could be argued that some of the doses used were low compared with usual dosing habits of clubbers (see Table 7.2), but higher doses could not be tested due to ethical constraints. Table 7.5 documents the concentration in blood of MDMA known to be a hazard when driving according to research compiled by the Netherlands Forensic Institute (NFI, 2010).

Table 7.5: Active concentrations of the most common drugs found in plasma (or serum) and blood) which are known to be a hazard when driving (NFI, 2010)⁴⁰

Substance	Expected concentration in plasma after taking an active dose (µg/L)	Blood/serum ratio ²	Estimated concentration in blood after taking an active dose ³ (µg/L)	Median in blood NFI 1999-2008 (µg/L)
MDMA	100-350	1.26	100-400	320
MDEA	approx. 200		100-400	50
MDA	up to approx. 400	1.2	100-400	30 ⁴¹

³⁹ The definition of different illicit drugs within the DRUID roadside survey (D2.2.3) for amphetamine-type drugs included amphetamine, metamphetamine, MDMA, MDA and MDEA.

⁴⁰ Derived from The International Association of Forensic Toxicologists (TIAFT; Baselt, 2008; Uges et al, 2008; Moffat et al, 2004). ² Blood/serum ratio: of the concentration in blood to the concentration in serum. Concentrations in serum are generally the same as concentrations in plasma (Moffat et al, 2004). ³ Concentrations in full blood calculated from concentrations in serum by multiplying by the blood/serum ratio. ⁴ MDA is also formed in the body through the conversion of MDMA. In most cases, MDA is probably measured as a metabolite of MDMA which may explain the relatively low median.

Some of the effects of amfetamines on driving-related skills have been explored. Stough et al, (2012) studied drivers apprehended under suspicion of impaired driving: 75% of analysed biological samples (N=283) tested positive for illicit drugs. More recent studies from Norway (Gjerde et al., 2011) and further afield in Victoria (Chu et al., 2012) and Queensland (Davey et al., 2009), Australia, have found that among drug positive drivers, MDMA (Queensland 52%), metamfetamines (Norway 40%; Victoria 77%), and amfetamines (Norway 50%) were more common than cannabis (Norway 30%; Victoria 42%; Queensland 46%).

The Panel looked at the concentrations of the drug measured in the blood of individuals suspected of or proven to have been driving under the influence. It was noted the greatest risk of a RTA was when the median concentration of MDMA in the blood was 320 µg/L, which was approximately equivalent to an intoxicating dose 1.5mg/kg. Of the 1100 samples received by the Forensic Science Service submitted from drivers suspected to have been driving whilst under the influence of drugs MDMA was quantified in eight blood samples and the mean and median concentrations of MDMA in whole blood were 256 µg/L and 230 µg/L, respectively (Burch et al, 2012). This is within the range reported by the Netherlands Forensic Institute (Table 7.5 above). The Panel also considered UK drug concentration data confirmed by laboratory analysis (Gas chromatography-mass spectrometry, GC-MS) of 2995 blood samples collected in cases suspected of drug-driving which when analysed, detected one or more drug. The data, which was collected between January 2008 and October 2012, showed that the mean blood drug concentration found in drivers for MDMA was 452 µg/L (range 20 µg/L – 2,540 µg/L, median 305 µg/L) from 76 cases. Based on the evidence available to the Panel (summarised above), **the threshold recommended in whole blood for MDMA is 300 µg/L** because at this concentration the drug is not compatible with the skills required for driving.

MDMA and alcohol in relation to driving

The combined use of MDMA with alcohol has been reported in European studies. In nine European countries, general population surveys show that frequent or heavy alcohol users report levels of prevalence of amfetamines or ecstasy use that are much higher than the population average (EMCDDA, 2009). Similarly, the European School

Survey Project on Alcohol and Other Drugs(ESPAD)data (from 22 EU countries) show that 86% of the 15- to 16-year-old students who reported using ecstasy during the previous month also reported drinking five or more alcoholic drinks on one occasion (EMCDDA, 2009).

A relationship between MDMA and alcohol use has been reported: plasma concentrations of MDMA increased by 13% when alcohol was co-administered with MDMA compared to concentrations observed when MDMA was taken alone (Hernandez-lopés, 2002). The UK drug concentration data confirmed by laboratory analysis (GC-MS) of 2995 blood samples collected in cases suspected of drug-driving also identified 16 cases where alcohol and MDMA were consumed concurrently and the mean blood drug concentration found in drivers for MDMA was 464 µg/L (range 50 µg/L – 1,800 µg/L , median 255 µg/L).

Based on the evidence available to the Panel and the frequency with which the two drugs are used together, a dual threshold is recommended that takes account of the effects of alcohol and MDMA use combined. **The threshold recommended in whole blood for MDMA when detected in combination with alcohol is 150 µg/L.** The threshold recommended in whole blood for alcohol when detected in combination with MDMA is 20 mg alcohol per 100 mL blood. The measurement of alcohol at this threshold already exists in legislation concerning aviation in this country.

Box 7.1: Basis for the recommendation of the MDMA ('ecstasy') threshold

'Ecstasy' (3, 4-methylenedioxymethamphetamine, MDMA); it is an illegal drug that is usually consumed as a tablet, capsule or powder mainly by young people.

The prevalence of MDMA previous year use in the UK was third behind cannabis (15.7%) and cocaine (4.2%): Users generally consume 1-2 tablets, although other patterns of use have been described.

For those who reported driving under the influence of an illegal drug in the UK in 2010/11, 31% reported using ecstasy within the same time period.

The half-life of MDMA has been reported to be about 7.6 hours and clearance from the body of a typical MDMA dose (50 mg) is moderately slow.

MDMA consumption produces increased energy, alertness and feelings of empathy: the 'come-down' period is often associated with sleep deprivation which itself is known to generate the same degree of impairment as a blood alcohol concentration of 50mg/100mL.

The risk of a RTA for amphetamine-type drugs including MDMA is estimated to range from OR: 5 to 30 when compared to drivers who were not tested positive for amphetamine-type substances.

A threshold is recommended in relation to the mean blood concentrations of MDMA (from different studies), found in individuals suspected of or proven to have been driving under its influence: the range of means varied from 256µg/L MDMA to 452µg/L.

A further threshold is recommended when MDMA is detected concurrently with alcohol (<80 mg/100 ml blood) on the basis that the effects of drug-use setting (e.g. concomitant alcohol use and sleep deprivation) are intertwined and significantly contribute to unsafe driving.

Recommendations

- It is recommended that a threshold in whole blood for MDMA be set at 300 µg/L.
- In addition, a threshold is suggested for when MDMA is detected in the presence of alcohol. It is recommended that the threshold in this circumstance be set for MDMA in whole blood at 150 µg/L and the alcohol level be set at 20 mg alcohol per 100 mL blood
- Blood sampling occur as soon as possible after the road traffic incidence
- It is recommended that harm-reduction initiatives are organised to ensure that those attending clubbing/dance/rave/festival events recognise that MDMA is not safe to consume if intending to drive and that combining the drug with alcohol is contraindicated for safe driving.

8. DRUG SPECIFIC FINDINGS: KETAMINE

Background

Ketamine (2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone) was developed by Parke Davis laboratories in 1962 and is an anaesthetic derivative of phencyclidine (PCP). Manufactured as a hydrochloride, ketamine has been utilized effectively in several areas of medicine including paediatrics, anaesthesia (pre-operative, emergency and high altitude), dentistry, obstetrics as well as battle-zones (White et al, 1982). Ketamine is also widely used in veterinary practice, and has been used to sedate large uncooperative animals at a distance, for example in the case of free-ranging giraffes and gorillas (Bush et al, 2001).

The recreational use of ketamine was first reported in 1971 in North America (Petersen & Stillman, 1978) and linked by some to returning Vietnam veterans who may have been exposed to the drug on the battlefield (Dotson et al, 1995). Law enforcement seizures in the USA of ketamine intended for non-medical use have increased by over 5 times in the last decade (Drug Enforcement Administration 2001), whilst in Hong Kong, ketamine has replaced ecstasy as the primary drug of misuse: of all reported drug users under the age of 21 in 2002, 59% were using ketamine (Tori, 1996). In the UK, a substantial quantity of ketamine for non-medical use is brought or smuggled into the country from regions where it is legally manufactured (Tori, 1996). Ketamine may also be purchased entirely from legitimate medical suppliers (Gough, 2003) or diverted directly from hospitals and veterinary clinics. The illicit manufacture of ketamine is almost unknown because it is very difficult to synthesize, although those selling the drug for non-medical use reportedly add various adulterants to make the drug go further.

Epidemiological prevalence

Sporadic reports of misuse in the 1970s and 1980s have developed into growing numbers of recreational users of the drug during the 1990s, especially among dance and rave scene attendees in the United Kingdom (Release, 1997) and elsewhere including Sweden (Stovmand et al, 1996) and Australia (White, 1996). In a survey of club drug users in 1997, 32% of clubbers reported having used ketamine (Release, 1997). The

appearance of ketamine in the dance scene has taken two forms. It appeared in its own right under various pseudonyms for instance 'Vitamin K', 'Green', 'Mean Green', 'Jet', 'K' or 'Special K' as tablets or capsules specifically sold with ketamine as its marketable content. Ketamine has also appeared as a constituent of tablets purporting to be ecstasy, often in combination with drugs such as ephedrine (Wolff & Winstock, 2006). A survey in 1999 of over 1100 UK clubbers reported a lifetime prevalence of use of 25% (half of these in combination with ecstasy), which had increased to 43% in 2004 (Mixmag, 2004). Similar surveys in Australia report an increase in 'ever use' of ketamine from 6-15% between 1997 and 2001 (Topp, 1998; 2001) and surveys of year-on-year trends have reported similar findings (McCambridge et al., 2007). Knowledge of the drug has also grown: 31% of young people surveyed aged 11–14 and 50% of 15 year olds reported knowing what ketamine was (Drugscope, 2007). The 2011/12 Crime Survey for England and Wales (CSEW) reported that 1.8% of 16-24 year olds had used the drug in the previous 12 months compared to 0.8% in the 2006/7 survey (Murphy and Roe, 2007).

In Europe, estimates of the prevalence of ketamine use in the adult and school populations are much lower than those for the use of cocaine and ecstasy. However, use of ketamine can be higher in specific groups, settings and geographical areas. Targeted surveys that report prevalence estimates for the use of these substances have recently been conducted in Belgium, the Czech Republic, the Netherlands and the United Kingdom (EMCDDA, 2009). These studies report prevalence estimates of ketamine between 2.9% to 62% for lifetime use and 0.3% to 28% for previous month use. There are marked differences between surveys and countries.

The high prevalence of ketamine use is uniquely reported in a 2010 UK music magazine survey (Winstock, 2011). Such high ketamine prevalence may be due to the self-selection of respondents to the survey and their particular drug-use profiles and attitudes (EMCDDA, 2010). However, collaborative evidence for the high levels of use of ketamine is available. The Druglink Street Drug Trends 2011 survey, carried out among frontline drug services, police forces, drug action teams and user groups in 20 towns and cities across the UK, report that the use of ketamine has increased in 15 of the 20 areas

since 2010⁴¹. The most recent CSEW (2011/12) estimates that 0.6% of adults aged 16-59 had used ketamine within the last year. The survey first measured ketamine use in 2006/7, where levels of previous year use were estimated at 0.3%.

European data: ketamine and driving

The CSEW has a self-completion module restricted to those aged 16-59 years that includes questions relating to drug use and drug driving. In 2010/11 for those who reported driving under the influence of illegal drugs within the last 12 months, 40% reported using ketamine within this same time period. The Norwegian Academic Advisory Group (2010), in preparing for drug driving legislation, reported on the following information with regard to ketamine (Table 8.1). The prohibition limit in blood was suggested to be 48 µg/L.

Table 8.1: Drug Thresholds in Norwegian legislation: Ketamine

SUBSTANCE	Impairment limit (µg/L)	Limit for graded sanctions (µg/L)	Limit for graded sanctions (µg/L)
	Comparable to 120 mg alcohol/100 ml blood (1.2g/L) BAC	Comparable to 50 mg alcohol/100 ml blood (0.5g/L) BAC	Comparable to 120 mg alcohol/100 ml blood (1.2g/L) BAC
Ketamine	55	137	329

Patterns of use

Medicinally, ketamine may be effectively administered by a number of routes (oral, intranasal, intravenous, intramuscular, intrathecal, intra-articular) (Huang et al, 2000); transdermal (Azevedo et al, 2000); rectal (Marhofer et al, 2001) and subcutaneously. Ketamine can be purchased for recreational use in a number of forms but is available mainly powdered or in liquid form, or as a crystalline powder for intranasal use. The government-sponsored drug information web site, 'Talk to Frank' (FRANK, 2010) states that ketamine usually comes as a grainy white powder. In powdered form, ketamine's appearance is similar to that of cocaine and the drug can be insufflated (inhaled), injected, or placed in beverages. The nasal route of administration of ketamine tends to

⁴¹www.drugscope.org.uk

be favoured with users, snorting or inhaling lines of powdered ketamine, although ketamine has also been reported available as an intranasal spray. There are some reports of 'freebasing' ketamine, produced by the removal of various salts to achieve fewer unwanted side-effects. It is also possible to smoke the drug in a joint or pipe, usually mixed with marijuana and tobacco (Muetzelfeldt et al. 2008). The smoke has a distinctive, bitter taste but the effects of the high occur much faster than when insufflated, ingested or injected intramuscularly. Oral use usually requires more of the drug, but results in prolonged effects due to metabolism via the liver to nor-ketamine (the psychoactive metabolite).

Recreationally, ketamine has been reported to have the advantage of being easy to administer: the clear dose-response effect and relatively short half-life make the effects simpler to control than LSD (Dillon, 2003). The spectrum of effects has been reported to be reflected in the different groups of individuals who choose to use ketamine. For instance, communal events where individual or small groups of users participate in sequential dosing over the evening are preferred by some and may well evoke different effects to the over-stimulation of a dance club venue (Dillon, 2003). There is wide variation in consumption patterns among users with tolerant and experienced consumers reporting use of 1g or more of ketamine over the course of an evening/weekend (Wolff & Winstock, 2006). A standard street-dose of ketamine in a Scottish study was found to be much lower, typically around 125 mg ($\frac{1}{8}$ g) (Dalgarno & Shewan, 1996). The following give some indication of the different doses of the drug used in different settings, both clinical and illicit:

- Anaesthesia is achieved at oral doses of 5-10mg/kg (300-800 mg)
- Doses for intravenous analgesia are <1mg/kg (<80 mg)
- A small line (for snorting) 30-50 mg
- A standard street-dose of ketamine is typically around 125 mg ($\frac{1}{8}$ g)
- Paper wraps of street ketamine powder have been found to contain 80 mg –290 mg of ketamine.

Pharmacokinetics (PK) and blood drug concentrations

Ketamine is well absorbed and has excellent bioavailability. The Intranasal route favoured by recreational users is associated with a rapid onset of action and an estimated duration of action of 2-3 hours (Siegal, 1978). Elimination is variable, depending upon the route of administration. When ketamine is ingested orally, less than 20% of the parent drug reaches the blood and has a plasma elimination half-life of around 2.5 hours (Domino, 1984). Effects may be prolonged due to the presence of the active metabolite, nor-ketamine, with anaesthetic potency approaching one-third, that of the parent compound. When taken intranasally, it takes 2-3 hours before the nor-ketamine concentrations in blood equal those of the parent compound, ketamine (Malinovsky et al., 1996). Ketamine is mainly eliminated by hydroxylation as conjugated metabolites, with < 4% appearing in urine as the parent compound or as nor-ketamine and also 5-hydroxynorketamine.

The US National Highway Traffic Safety Administration (NHTSA) fact sheet on ketamine suggests that blood-ketamine concentrations are found in the range 2,000 µg/L to 3,000 µg/L “during anaesthesia” and that people begin to wake up when plasma concentrations fall to between 500 µg/L and 1,000 µg/L (Bree et al, 1967). There is no direct correlation between ketamine blood concentrations and behaviour; although drowsiness, perceptual distortions and intoxication may be dose related in a concentration range of 50 µg/L ketamine to 200 µg/L ketamine (Bowdle et al, 1982).

Collection of specimens for evidential analysis

Testing for the presence of ketamine in an intoxicated individual is difficult because of the short-acting properties of the drug. Nevertheless, ketamine can be detected in blood, plasma, urine (Bolze et al, 1998) and oral fluid. Point-of-care devices for immunochemical tests are available for ketamine (OratectXP Oral Fluid Drug Screen Device) and have been proposed for testing drivers under the influence of drugs, with a confirmation cut-off concentration for oral fluid ketamine suggested to be 25 µg/L ketamine (Tsui et al, 2012).

However, in order to assess drug concentrations at the time of a road traffic incident blood sampling is most effective: whole blood was considered to be the most appropriate biological fluid for setting thresholds because it relates best to scientific

evidence in relation to driving. Therefore, whole blood is recommended as the biological sample of choice.

Pharmacodynamics (PD)

Recreationally, ketamine is most frequently taken for its psychedelic properties, sometimes as a dance drug and sometimes to 'explore the mind' (Weiner et al, 2000). The effects of ketamine used for recreational purposes have been reported to be a collection of 'paradoxes' and many of the effects are associated with other substances: 'cannabis-like imagery', 'alcohol-like intoxication', cocaine-like stimulation and opiate-like calming (Jansen, 2000). Users experience hallucinations lasting about 60 minutes when ketamine is insufflated or injected, and up to 2 hours when ingested (Oye, 1991).

If smoked the onset of effects is immediate; if snorted effects begin 1-5 minutes after dosing and; if ingested 15-20 minutes after consumption. The effects of ketamine are very short-lived. Ketamine is often re-administered due to its short duration of action (Dotson et al, 1995). In healthy male volunteers given a standard 2.2mg/kg bolus dose of the drug intravenously, the duration of action for anaesthesia was less than 20 minutes (Domino et al, 1984). When used as a recreational drug, the symptoms of ketamine intoxication also appear to diminish reasonably quickly, with 18 of the 20 patients discharged from the emergency department within 5 hours of presentation (Weiner et al, 2000).

Dissociation occurs at doses as low as 50mg-100mg typically, eyes remain open with a disconnected stare (Siegel 1978; Ahmed & Petchkovsky, 1980; White et al, 1982). The recreational drug-user may appear to be awake but is dissociated from the environment, immobile and unresponsive to pain. At large doses (>150 mg), ketamine induces a dissociative state commonly referred to as the 'K hole' – a sense of detachment from one's physical body and a tendency toward a sense of disconnection from one's immediate surroundings. It is the parent compound that is responsible for the majority of both the anaesthetic effects as well as the undesirable post-anaesthetic sequelae (Leung and Baillie, 1986). A further study examined the effects of ketamine at plasma concentrations up to 200 µg/L and found concentration-dose effects. At a plasma concentration of 200 µg/L euphoria, time disturbance, drowsiness and feelings

of unreality were prominent. At the highest plasma concentration, self-rating of drowsiness averaged a score of 62.6mm on a 133mm scale (0 = not at all; 133 = extremely) (Bowdle et al, 1998). A summary of information about the plasma concentration-pharmacodynamic effects can be found in Table 8.2.

Table 8.2: Summary of the ketamine plasma concentration – effect relationships:

Effect	Plasma Concentration
Unconsciousness/anaesthesia	Up to 3,000 µg/L
Waking from ketamine anaesthesia	500-1,000 µg/L
“Moderate” drowsiness	200 µg/L
“Moderate” to “extreme” disturbance of perceptions	200 µg/L

Ketamine and Driving: the scientific evidence

In a study to assess driving under the influence of ketamine, (the most popular abused drug in Hong Kong), 62 volunteers exiting from a dance-event were recruited: 39 had ketamine detected in oral fluid. Of these, 21 (54%) had only used ketamine while the others had other drugs (i.e. metamfetamine, MDMA, benzodiazepines and/or THC) detected in addition to ketamine. It was found that when oral fluid ketamine concentrations were >300 µg/L, signs of impairment were clearly evident(Cheng et al, 2007).The Norwegian Academic Advisory Group (2010), in preparing for drug driving legislation, reported that a ketamine blood concentration causing impairment was 238 µg/L (Vindenes et al, 2011).

Historical data derived from cases where whole blood specimens were submitted for analysis to the laboratory of the Forensic Science Service (FSS) over a three year period (2004 to 2007) was also considered by the Panel. The samples submitted from drivers suspected to have been driving whilst under the influence of drugs detected the presence of ketamine and nor-ketamine concentrations in 14 cases. The mean and median blood concentrations of ketamine were 421 µg/L and 385 µg/L, respectively (range 170-850 µg/L) and those of nor-ketamine were 605 µg/L and 410 µg/L (range 190-1,400 µg/L), respectively (Burch et al (2012). The Panel also considered UK drug concentration data confirmed by laboratory analysis (GC-MS) of 2995 blood

samples collected in cases suspected of drug-driving which when analysed detected one or more drug. The data, which was collected between January 2008 and October 2012, showed that the mean blood drug concentration of ketamine was 345 µg/L (range 20 µg/L – 1,300 µg/L, median, 300 µg/L) from 207 cases.

Based on the evidence available to the Panel (summarised above) **the threshold recommended in whole blood for ketamine is 200 µg/L** because at this concentration the drug is not conceivably compatible with the skills required for driving. A concentration of 200 µg/L ketamine would capture 70% of those drivers tested positive for ketamine in the UK data presented above.

Ketamine and alcohol in relation to driving

There is little documented evidence regarding the use of alcohol and ketamine, although ketamine is thought to increase the effects of other sedatives and thus the combination of ketamine and alcohol may not be considered safe for driving. Since ketamine use alone is not compatible with driving at concentrations at or above 200 µg/L a dual threshold is recommended that takes account of the likely additive effect of alcohol and ketamine use combined. The **threshold recommended in whole blood for ketamine when detected in combination with alcohol is 100 µg/L** and the threshold recommended in whole blood for alcohol when detected in combination with ketamine is 20 mg alcohol per 100 mL blood. The Panel noted that the Norwegian Academic Advisory Group (2010) when proposing thresholds for the new Norwegian legal limits recommended a concentration of 137 µg/L ketamine in whole blood as comparable to 50mg alcohol per 100 ml blood (Vindenes et al, 2011).

Box 8: Basis for the recommendation of the ketamine threshold

Ketamine (2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone) is an anaesthetic derivative of phencyclidine (PCP).

In 2011/12 1.8% of 16-24 year olds surveyed had used ketamine in the previous 12 months in the UK: in those attending large parties, prevalence estimates of ketamine use ranged between 0.3 % and 28 % for previous month use.

Relating to the prevalence in drug driving in 2010/11, for those who reported driving under the influence of illegal drugs within the last 12 months, 40% reported using ketamine within this same time period.

Ketamine has a half-life of about 2.5 hours and an active metabolite nor-ketamine with anaesthetic potency approaching one-third, that of the parent compound.

The Norwegian Academic Advisory Group (2010), in preparing for drug driving legislation, reported that a ketamine blood concentration causing impairment was 238 µg/L

Drowsiness, perceptual distortions, time disturbance, drowsiness and feelings of unreality were prominent in the blood concentration range of 50µg/L to 200 µg/L ketamine.

A threshold is recommended in relation to the mean blood concentration of ketamine (from different studies) found in individuals suspected of or proven to have been driving under its influence: the range of means for ketamine was 345 µg/L to 421 µg/L.

The threshold was recommended to be lower than blood concentrations detected in some drug-drivers because the adverse effects experienced at lower concentrations in blood were deemed unsafe for driving.

Recommendations

- Based on the evidence available to the Panel which has been summarised above, it is recommended that a threshold in whole blood for ketamine be set at 200 µg/L.
- In addition, a threshold is suggested for ketamine when detected in the presence of alcohol. It is recommended that the threshold in this circumstance be set for ketamine in whole blood at 100 µg/L and the alcohol level be set at 20 mg alcohol per 100 mL blood.
- Blood sampling should take place as soon after the road traffic incident as possible
- It is recommended that harm-reduction initiatives are organised to ensure that those attending clubbing/dance/rave/festival events recognise that ketamine is not safe to consume if intending to drive and that combining the drug with alcohol is contraindicated for safe driving.

9. DRUG SPECIFIC FINDINGS: OPIOIDS

Background

Opioid drugs can be broadly classified as natural opiates (morphine and codeine), semi-synthetic opioids (heroin and oxycodone) or purely synthetic opioids (methadone, buprenorphine, and fentanyl). Opioid drugs whether natural or synthetic exert their actions by binding to different receptors. The opioid drugs encompass a large drug class that ranges from over-the-counter medication to illicitly procured drugs. Although opioid drugs are used globally for analgesia and pain relief many have great potential for misuse, notably heroin. To this end, the medical use of strong opioids such as diacetylmorphine, morphine, and fentanyl etc.) are controlled by the Misuse of Drugs Act, 1971, as class A drugs subjected to guidelines surrounding their storage, administration and destruction. The British National Formulary (BNF, 2012) currently lists 17 opioid drugs including, codeine phosphate, diamorphine hydrochloride, dihydrocodeine tartrate, hydromorphone hydrochloride, morphine salts, oxycodone hydrochloride, pavaereturum, methadone, buprenorphine and fentanyl.

Natural opiates: Opium is one of the oldest medications known to man and it is derived from the poppy plant, *Papaver Somniferum*. The main active ingredient of opium is morphine which is widely used as an effective analgesic for the relief of severe and chronic pain. Morphine acts on the central nervous system (CNS) and produces respiratory depressant effects, somnolence and mood changes. Hundreds of derivatives of morphine have been synthesized in the search to find an equipotent analgesic but with less respiratory depressant effects. The search has not been successful and morphine is still widely prescribed as a first choice medicine for pain relief and palliative care (Jones, 2010). Chronic intake of morphine may lead to physical and psychological dependence. Codeine is a less potent opiate but also causes sedation, drowsiness and depresses breathing. Codeine is frequently used in combination with acetaminophen (Solpaedeine, Paracodol) or aspirin for more effective pain relief.

Semi-synthetic opioids: Heroin is a trade name for diacetylmorphine and is a close structural analogue of morphine. As an illicit substance heroin is usually produced as the freebase form of the drug whereas the pharmaceutical grade product (diamorphine) is more often the hydrochloride salt, diacetylmorphine hydrochloride. As with other

opioids the frequent and regular use of heroin brings about tolerance and dependence and is characterised by a physical withdrawal syndrome. The average purity of street heroin in the UK varies between 30% and 50% and heroin that has been seized at the border has purity levels between 40% and 60% (United Nations, 2012). Mexican illicit heroin, commonly called black tar, which results from a simplified, quicker synthesis procedure reportedly contains a high percentage of 6-monoacetylmorphine (6-MAM).⁴²

Oxycodone is synthesized from thebaine a derivative of opium. Oxycodone oral medications are generally prescribed for the relief of moderate to severe pain. Oxycontin® is the most commonly found modified release preparation of Oxycodone. Oxycodone is indicated for the management of moderate to severe pain. It is one of the most widely prescribed drugs in North America. Around the equivalent of half a billion (500 million) 80 milligram tablets a year were prescribed there in 2007 (Chu et al, 2012). The drug is far less commonly used in the UK; the Prescription Pricing Authority Data⁴³ for 2011 suggests that Oxycodone preparations account for slightly more than 17% of the prescriptions written for opiate drugs (United Nations, 2009). Some common examples of compounding are oxycodone with acetaminophen/paracetamol or non-steroidal anti-inflammatory drugs such as ibuprofen. The formulations are available as generics but are also made under various brand names.

Dihydrocodeine (DHC) is an analgesic developed as an antitussive (cough suppressant) to help reduce the airborne spread of diseases such as tuberculosis, pertussis and pneumonia. It is prescribed for pain, severe shortness of breath, or as an antitussive, either alone or in combination with aspirin or paracetamol. Dihydrocodeine may be used as an alternative to methadone in the treatment of opioid dependence, although the percentage of people treated by this method tends to be small (usually under 5%).

Synthetic opioids: Methadone is a synthetic opioid, used in the treatment of heroin dependence but also as an analgesic (pain killer) and antitussive. Methadone is largely used to prevent the emergence of withdrawal symptoms in individuals addicted to illicit opiates such as heroin. Adverse effects include sedation, cognitive impairment,

⁴²http://en.wikipedia.org/wiki/Black_tar_heroin, accessed December 2012

⁴³<http://www.ppa.nhs.uk/index.htm>

respiratory depression and constipation. Some tolerance to sedation and respiratory depression develops in chronic use. Buprenorphine, a partial opioid agonist, has become an increasingly popular choice in clinical practice in recent years in a number of developed countries, particularly in France, USA and Australia and the UK for the treatment of heroin dependence with lower overdose risk. Fentanyl is a powerful opioid estimated to be 80 times as potent as morphine as an analgesic. Fentanyl is used in medical settings as an anaesthetic agent or for postoperative pain but has also been abused under the pseudonym 'China White'. Tramadol is an opioid of moderate strength used both for chronic moderate to severe pain and in emergency situations such as accidents or acute organ injury.

Epidemiological prevalence

The difficulty with epidemiological data concerning the opioids is that these drugs are often presented as a drug class rather than as individual substances and the terminology used to classify substances are not always mutually exclusive. The following terms have been used recently illicit opiates, opioids, medicinal opiates and medicinal opioids in epidemiological studies (EMCDDA 2009; DRUID 2010). Nevertheless, surveys from the EMCDDA provide data in a European context and in 2011 reported that methadone; morphine and codeine were most common and cited emerging trends in the misuse of opioids such as fentanyl, oxycodone and hydrocodone (EMCDDA, 2011). The 2011/12 CSEW estimated that 0.3% of 16 to 59 year old respondents had used illicit opioids (heroin and methadone) in the previous year (a level that has generally remained stable for many years). Similarly, the 2010/11 SCJS estimated that 0.2% of adults had used heroin and methadone in the last year⁴⁴.

Opioids and driving

Medicinal opiates and opioids (that is morphine, codeine, methadone and tramadol) in the general EU driving population were mainly detected among drivers 35 years of age and older. The logistic regression analysis generally indicated that there was a higher prevalence among female drivers who drove during daytime hours (04:00 – 21:59h,

⁴⁴ Estimates of illicit opioid misuse are likely to be low from general household surveys.

DRUID roadside survey; 6th Framework programme – D 7.3.2). However, the profile was different in seriously injured or killed drivers. The DRUID hospital studies showed high national variability but medicinal opiates and opioids were generally used in combination with other psychoactive substances (D2.2.5) and by older age groups (>35 years). In North America the National Highway Traffic Safety Administration (NHTSA)⁴⁵ drug use prevalence study (2007), found that donated oral fluid samples in randomly selected volunteer drivers had day-time prevalence for oxycodone of 0.37% and night-time prevalence of 0.8% (National Roadside Survey, 2007). The prevalence of oxycodone in drivers in the UK is less well described.

The CSEW has a self-completion module restricted to those aged 16-59 years that includes a question relating to drug driving. In 2010/11, for those who reported driving under the influence of illegal drugs at least once or twice in the last 12 months, 19% had used heroin within the last year. This was similar to 2009/10, where 20% of those who had driven under the influence of illegal drugs at least once or twice in the last 12 months had also taken heroin within that time period.⁴⁶

The Panel considered prevalence data from laboratory analysis of 3,616 blood samples taken in suspected cases of drug-driving which screened positive (by ELISA) for one or more drugs. The data, which is predominantly from England and Wales and was collected between January 2008 and October 2012, showed that opiates were present in 33% of drug positive samples. The data also demonstrates that opiates are commonly found in combination with other psychoactive substances in drivers (Box 9.1). This level (33%) was higher than submissions to the FSS of blood samples for analysis following Field Impairment Test (FIT) tests at the roadside, a road traffic accident, or witnessed impairment whilst driving where the percentage frequency of opioid drugs was found to be 15% in a sample collected between 2007 and 2009 (Lamping, 2009).

The CAST data demonstrates that opioid drugs were commonly found in combination with other psychoactive substances in drivers (Box 9.1).

⁴⁵<http://www.nhtsa.gov/>

⁴⁶ The unweighted base numbers used to estimate heroin use by those admitting drug driving were low and data should be interpreted with some care.

Box 9.1: Prevalence of opiates in drug positive blood samples screened by ELISA⁴⁷

- Of 1721 samples analysed and found to contain 1 compound, opiate drugs were detected in 16% of cases
- Of 1052 samples analysed and found to contain 2 compounds, opiate drugs were detected with benzodiazepines in 13% of cases and THC in 11% of cases;
- Of 530 samples analysed and found to contain 3 compounds, opiate drugs were detected with benzodiazepines and cocaine in 18% cases; with benzodiazepines and cannabis in 15% of cases and with cannabis and cocaine in 10% of cases.

Further evidence of the presence of opioid drugs in drivers in the United Kingdom was confirmed by the Transport Research Laboratory (TRL) that analysed alcohol and drugs data in road traffic fatalities (Smith & Martin, 2012). Data was collected from HM Coroners and Procurators Fiscal and found that ‘opiates, opioids and narcotic analgesics’⁴⁸ were the second most frequently detected drug and were identified in 24 fatalities (6%) from 373 cases for which drug data was available. However, there was some overlap in the data in that the ‘opiate, opioid and narcotic analgesics’ category did not include morphine and codeine, which were included in the ‘other therapeutic drugs’ category, for which there were 96 cases (26%) of the original 373.

It was also noted that toxicological analysis may have detected multiple drugs or groups of drugs present in a fatality, so that individual categories could not be summed.

Although the dataset for drug driving fatalities was small findings showed similar trends to European epidemiological studies: the highest percentage of positive tests for any illicit drugs was the 20-24 years age group (22% male Vs 12% female), in contrast the highest prevalence for ‘other therapeutic drugs’ was in the >60 years age group (47% female Vs 28% males). It was also noted that ‘opiates, opioids and narcotic analgesics’ were commonly detected in combination with other drugs and were rarely detected

⁴⁷Data from samples taken between January 2008 and October 2012 in cases of RTA or witnessed impairment.

⁴⁸Opiates, opioids and narcotic analgesics included dihydrocodeine, EDDP primary metabolite of methadone, heroin (metabolite), methadone, 6-monoacetylmorphine, 0-desmethyltramadol, opiates and tramadol. ‘Other therapeutic drugs’ included morphine, codeine, benzodiazepines, anti-depressants and mood stabilisers, SSRIs and barbiturates, hypnotics and others

alone, whereas 'therapeutic drugs' were most commonly detected as single drugs, with a blood alcohol (BAC) level below the legal limit. In epidemiological studies examining populations involved in RTAs or apprehended for drug-driving methadone was the third most frequently detected drug and was the fifth most frequent in traffic accident cases (DRUID, Main Findings report, 2012). The Panel considered prevalence data from laboratory analysis of 3,616 blood samples taken in suspected cases of drug-driving which screened positive (by ELISA) for one or more drugs. The data, which is predominantly from England and Wales and was collected between January 2008 and October 2012, showed that methadone was present in 9% of drug positive samples.

Patterns of use

Heroin can be injected, smoked or snorted according to the consistency and purity of the drug and is the opioid drug most popular for recreational use largely because of the intense rush and acute euphoric state that users experience when heroin reaches the brain. Some believe that heroin produces more euphoria than other opioids following intravenous use; one possible explanation is the presence of 6-monoacetylmorphine, a metabolite unique to heroin - although a more likely explanation is the rapidity of onset.

Quantity of use of heroin varies widely from person to person although regular use requires increased dosing to achieve the same 'sought after' effect and doses in excess of 1g per day are not unusual in dependent addicts. Many natural and semi-synthetic opiates are misused. For instance, DHC is commonly used recreationally because of the relaxing and euphoric high when taken in higher than therapeutic doses. It is available as several salts, the most common being bitartrate, phosphate, hydrochloride, tartrate and hydroiodide and is usually consumed orally: recreational doses varying between 70 mg to 500 mg/day. Codeine is also popularly misused and addicts may use doses in excess of 10 times the normal therapeutic dose (Moffat et al, 2011).

In 2009, 306,150 individuals were recorded as opiate/crack cocaine users (47,173 aged 15 to 24; 117,920 aged 25 to 34 and 133, 424 aged 35 to 64 years,

respectively).⁴⁹ In the UK during the period from April 2011 to March 2012, 197,110 adults were in treatment contact with substance misuse services, with the majority using illicit opioids (81%). A third of these used opioids alone, with the remaining two thirds combining heroin with cocaine (National Drug Treatment Monitoring System (NDTMS) statistics, 2012). In England in 2004, 532,700 individual items of buprenorphine and 1,954,700 of methadone were prescribed for opioid dependence. There is no reliable data on the number of people on these drugs who drive. In the UK those on a methadone replacement therapy are required to notify the DVLA. There is considerable discrepancy between estimates of numbers of people on methadone programmes and the number of declarations to DVLA. Those who declare to the DVLA are subject to annual medical review in order to keep their driving licence entitlement. The usual doses of different opioids in various preparations are given below:

- Heroin: sold in wraps 1/16 of gram (62.5 mg)
- Diamorphine: 5mg – 10 mg intravenous dose (IV)
- Codeine: usual dose for pain relief 15 mg – 60 mg, up to a usual maximal dose of 240 mg/day (Moffat et al, 2011).
- Morphine: usual dose 5 mg – 20 mg morphine hydrochloride, sulphate or tartrate, by mouth or parenterally, every 4 hours
- Methadone: linctus or mixture 30 mg – 150mg daily for heroin dependence
- Buprenorphine: tablet-form (sublingual), patches and injectable solution (2 mg - 32 mg)
- Hydrocodone tartrate: 5 mg – 10 mg by mouth every 4-6hours
- Oxycodone, Oxynorm®: 10 mg – 40 mg by mouth or intravenously
- Fentanyl patches: one 25 µg (microgram) fentanyl patch is equivalent to about 60 mg – 90mg of oral morphine in 24 hours.
- Dihydrocodeine tartrate: 30 mg, and modified release 60 mg, 90 mg and 120 mg respectively.
- Tramadol: 25 mg for relief mild to moderate pain (maximal dose 300 mg/day) (Moffat et al, 2011)

⁴⁹National Treatment Agency for Substance Misuse facts and figures: Available from <http://www.nta.nhs.uk/facts.aspx> accessed on 23/12/2012

Pharmacokinetics (PK) and blood drug concentrations

Morphine: Morphine is well absorbed following subcutaneous, intravenous or intramuscular administration but is less well absorbed after ingestion where there is substantial 'first-pass' metabolism: bioavailability is low (20-30%). The major metabolites of morphine are morphine-3 and morphine-6 glucuronide: the latter thought to contribute to the pharmacological effect. Morphine, as well as being a prescription drug in its own right, is a primary metabolite of heroin and a minor metabolic product of codeine. Following morphine administration just over half of the dose will be eliminated as 3-glucuronide, whilst 10 per cent appears as 6-glucuronide. Less than 1% of morphine is methylated to codeine, whilst around 10% will appear in urine unchanged. The plasma elimination half-life of morphine is 2 to 3 hours and for the purposes of laboratory analysis the window of opportunity for the detection of morphine would be up to 10 to 15 hours after ingestion of **a single dose**. In cancer patients at steady-state receiving 209 mg morphine/day blood concentrations of morphine were found to average 66 µg/L (Vianio et al, 1995), whilst a single intramuscular dose 8.75mg/70 kg resulted in a peak 70 µg/L serum concentration 10 to 20 minutes after dosing (Berkowitz et al, 1975).

Codeine: Codeine is well absorbed after oral administration with peak plasma concentrations occurring after about 1 hour. Codeine is metabolised in the liver by the cytochrome P450 enzyme CYP2D6 to morphine, nor-codeine and various glucuronides: although about 5-10% Caucasian individuals are genetically predisposed and unable to convert codeine into morphine due to the absence of the P4502D6 enzyme. After an oral dose up to 70% of codeine is excreted unchanged in urine within 24 hours: 5%-15% as morphine and 10%-20% as nor-codeine (Moffat et al, 2011). The plasma elimination of codeine is reported to be between 2 to 4 hours and thus for the purposes of laboratory analysis the window of opportunity for the detection of codeine would be from 10 to about 20 hours after ingestion of **a single dose**. Maximal concentrations in serum have been reported for codeine, one hour after a single dose of 60 mg (111 µg/L to 126 µg/L) and 120 mg (256 µg/L), respectively (Walker & Zacny, 1998; Findley et al, 1978; Brunson & Nash, 1975).

Heroin: is a lipophilic drug, with a half-life of between 2 and 5 minutes so that following administration it reaches the CNS rapidly and penetrates the blood-brain barrier

efficiently to bring about the euphoric 'rush' sought after by users. Heroin a pro-drug shows little activity at receptor sites and is rapidly hydrolysed to 6-monoacetylmorphine (6-MAM) a potent metabolite (break down product): 6-MAM has a half-life of 6-25 minutes (Moffat et al, 2011)) and is often used as conclusive evidence of heroin consumption. The plasma elimination half-life ($t_{1/2}$) of heroin is too short for the purposes of drug detection and would only be detectable in blood for between 10 and 25 minutes after dosing. Similarly, the detection of 6-MAM would be best achieved between 30 minutes and two hours after **a single dose**. Morphine is a metabolic breakdown product of 6-MAM.

Dihydrocodeine: DHC is chemically similar to, and at least as potent as codeine. The pharmacologically active metabolites are nordihydrocodeine, dihydromorphine and dihydromorphine-6-glucuronide (Moffat et al, 2011). The plasma elimination half-life of DHC is about 4 hours and thus for the purposes of laboratory analysis the window of opportunity for the detection of DHC would be less than 20 hours after ingestion **of a single dose**.

Methadone: is well absorbed when given in liquid form, reaching peak plasma concentrations after about 4 hours (Wolff et al, 1997) and is metabolised in the main to EDDP (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine) a non active compound. In a study of five subjects given a single dose of methadone (15mg), plasma concentrations peaked at around 70 $\mu\text{g/L}$, falling to 30 $\mu\text{g/L}$ at 24 hours (Inturrisi & Verebely, 1972). In methadone maintenance clients prescribed a fixed daily dose, plasma concentrations have been shown to peak at around 850 $\mu\text{g/L}$ methadone, about 4 hours after a dose of 100 mg -120 mg methadone (Inturrisi & Verebely, 1972a). The plasma concentration had fallen to 500 $\mu\text{g/L}$ methadone after 24 hours. There is some variation in concentration although a linear relationship between concentration and dose has been reported for doses up to about 100 mg/day (Wolff et al, 1997). The elimination half-life is estimated to be in the range of 33-46 hours (Wolff et al, 1997) and therefore detection in blood should not be a problem in terms of drug-driving incidents. Upon cessation of dosing, although blood concentrations would fall methadone would remain in the body for between 7.5 and 9.6 days.

Oxycodone and hydrocodone: oxycodone has nearly double the pharmacological activity of morphine whereas hydrocodone is less potent than oxycodone and

structurally related to codeine. Both drugs are popular as analgesics and are mainly N-demethylated to nor-oxycodone and nor-hydrocodone, respectively. Oxycodone is also metabolised to oxymorphone which is pharmacologically active. The plasma elimination half-life of oxycodone is about 2 to 3 hours and the half-life ($t_{1/2}$) for hydrocodone, a metabolite of codeine, is about 4 hours. Both compounds thus have relatively short periods of detection for drug screening purposes after a single administration. Chronic dosing would maintain low therapeutic concentrations of the parent drug in the body, reported to range in serum between 20 µg/L and 50 µg/L. The blood to serum ratio of oxycodone is 1.48:1 (Jantos et al, 2011).

Tramadol: is 5 to 10 times less potent than morphine (Giusti et al, 1997). It is rapidly absorbed after oral or parenteral administration, reaching peak plasma concentrations after about 2 hours (Moffat et al, 2004) and is metabolised to *O*-monodesmethyltramadol, *N*, *O*-didesmethyltramadol and their conjugates: *O*-monodesmethyltramadol is an active metabolite and has greater pharmacological activity than tramadol. The therapeutic tramadol blood concentration is 100 µg/L to 800 µg/L. The plasma elimination half-life of tramadol is about 6 hours (7 hours with multiple dosing) and the half-life ($t_{1/2}$) for *O*-monodesmethyltramadol is about 9 hours.

Collection of specimens for evidential analysis

For opiate drugs, initial immunoassay tests for morphine cross-react with codeine, dihydrocodeine, pholcodeine, 6-monoacetylmorphine (6-MAM), morphine-3-glucuronide and morphine-6-glucuronide. Consequently, if more than one of these substances is present in a biological fluid the test result will relate to the concentration of the sum of all these drugs and their metabolites (Wolff, 2006). Immunoassay screening tests used for oral fluid or urine therefore serve only as a nonspecific guide, and results would need to be confirmed (Karch, 2002).

There is no 'Near-Patient-Testing-device' (NPT) that can detect all opioids and their metabolites in oral fluid: some opioids are challenging even for the fully equipped toxicology laboratory. For instance, whilst in some European countries 6-MAM and tramadol are the most commonly found opioids in oral fluid donated by impaired drivers; not all immunochemical screening can detect tramadol (Baselt, 2008). Usual

screening tests for opiates are also unlikely to show a positive result for oxycodone unless the concentration of the drug is very high (DRUID, Main results, 2012).

Recreational use of heroin is unlikely to be detected in biological samples because of its rapid onset of action and rapid metabolism to 6-MAM (Wolff et al, 1999). The presence of morphine in oral fluid or urine can be indicative of either medicinal (diamorphine or morphine) or illicit opioid (heroin) use, whereas the presence of codeine may indicate illicit drug use or legitimate consumption of antitussive or analgesic preparations. The laboratory limit of quantification (cut-off) is important with regard to the detection of a drug in a biological sample (positive test result). For total morphine, urine analysis detection would be possible for 24-36 hours, at a cut-off concentration of 300 µg/L morphine, but is reduced to less than 12 hours at a higher cut-off concentration of 2,000 µg/L morphine, used by specialist drug treatment settings to confirm heroin dependence (Cone et al, 1995).

During the ROSITA-2 project the relationship between oral fluid and blood concentrations of drugs of abuse in drivers suspected of driving under the influence of drugs was investigated (Wille et al, 2009). Blood and oral fluid samples were collected from drivers stopped during random controls by the police in Belgium, Germany, Finland, and Norway and the oral fluid to blood (OF:B) ratios were calculated for various drugs including the opioids. The ratios found in this study were comparable with those that were published previously, but the range was wider. It was concluded that the variability of the OF:B ratios does not allow reliable calculation of the blood concentrations from oral fluid concentrations in drivers thought to be under the influence of drugs. Therefore oral fluid testing is at present only suitable for screening purposes.

In order to determine individual drugs for confirmatory purposes whole blood was therefore considered to be the most appropriate choice for setting thresholds: blood concentrations provide an accurate picture of the amount of drug(s) present in the body at the time of sampling and provides the strongest scientific evidence in relation to driving. The time between the stop or traffic incident and blood sampling is important for short-acting drugs. If sampling is unduly delayed, decreased concentrations of drug will be detected. Based on a half-life of 2-3 hours, 100 µg/L of

morphine would be expected to have decreased to about 50 µg/L morphine 2-3 hours after administration.

The Panel noted the importance of blood sampling as soon after the road traffic incident as possible. Blood-drug concentrations for opioids (morphine and codeine) known to have an impairing effect on driving have been produced by the Netherlands Forensic Institute (NFI 1999-2008) and are shown in Table 9.1.

Table 9.1: Expected and estimated blood concentration data for morphine and codeine as compiled by the Netherlands Forensic Institute (NFI 1999-2008)

Substance	Expected concentration in plasma after taking an active dose ^a (µg/L)	Blood/serum ratio ^b	Estimated concentration in blood after taking an active dose(µg/L)	Median in blood (µg/L)
Morphine	10-120	1.0	10-120	40
Codeine	50-250	0.87	40-250	20

^aDerived from The International Association of Forensic Toxicologists (TIAFT), supplemented by data from other scientific sources where the TIAFT list was incomplete. The upper and lower limits for these substances are not absolute: they are 'soft' limits with transition from non-active to active and active to toxic.

^b Blood/serum ratio: the ratio of the concentration in blood to the concentration in serum. Concentrations in serum are generally the same as in plasma; therefore no differentiation is made between serum and plasma. Data is derived from scientific literature.

Pharmacodynamics (PD)

All medicinal and illicit opioids are central nervous system depressants and universally cause drowsiness, and lethargy. Heroin is a powerful euphoriant and regardless of the route of administration (intravenous or intranasal) decreases alertness, and motor activity (Ghodse 2002). Similarly, morphine (oral or intramuscular dosing) has been shown to be capable of causing sedation and significant psychomotor impairment for up to 4 hours after a single dose and 36 hours after repeated doses (Baselt 2001; Couper 2004). Methadone is also a potent opioid and causes significant nausea, sedative and respiratory depressant effects in naive users (Wolff, 2002). Itching and flushing are common side effects of natural opiates and some semi-synthetic opioids, due to

histamine release in response to the drug. Combining medicinal opioids with antihistamines (who have their own impact on performance related to safe driving) is common for this reason.

All medicinal and illicit opioids are characterised by the onset of tolerance with regular dosing and a well-defined withdrawal syndrome upon cessation of dosing. The degree of tolerance that an individual develops on regular use, the loss of tolerance that may occur after a period of abstinence and the intrinsic capacity of the individual to metabolise opioids together with the idiosyncrasies in the effects that the drug may have on the individual are thought to be important but, as with alcohol, not definitive in terms of driver safety. The degree of tolerance that an individual achieves following daily dosing with opioid/opiate drugs is quickly lost if dosing is interrupted. For instance, a methadone maintenance patient is required to undergo a medical re-assessment if the daily dose is interrupted for 3 days because of the loss of tolerance, before prescribing can recommence (National Clinical Guidelines, 2007). The impact of poor compliance with dosing on the development of tolerance to the different effects is unknown.

Opioids and driving: the scientific evidence

An extensive review of the effects of opioid drugs on human performance and behaviour has been carried out by Stout & Farrell (2003), which affirms that with opioids, indications for driver performance are mixed. With many opioids, pain control in individuals improves performance and this complicates the findings of studies measuring driving behaviour. For this reason the Panel has concentrated upon risk estimates for being seriously injured or killed in a RTA in different populations: those who drive under the influence of opioid drugs compared to those who do not.

In the DRUID case control studies (D2.3.5) odds ratios (OR) of a serious or fatal road traffic accident in drivers under the influence of medicinal opioids and illicit opiates were calculated by means of data from 6 EU countries (seriously injured drivers) and data from 4 EU countries (killed drivers) for all countries as a whole. The odds ratios were adjusted for confounding factors such as age, gender, and the controls were weighted with the traffic distribution, in eight different time periods. The 'illicit opiates' group was defined as drivers that were positive for heroin (as indicated by the presence of 6-monoacetylmorphine) or the combination of morphine and codeine where the

concentration of morphine was equal to or higher than codeine. If the concentration of codeine was higher than that of morphine, use was categorised as ‘medicinal opiates and opioids’. The risk of serious injury or death for those drivers who were tested positive for illicit opiates was between OR: 2 and 10, whereas the risk for those tested positive for medicinal opioids (including methadone) was between OR: 4.8 and 9.0 compared to drivers who did not have a positive opiates/opioids test result (Table 9.2).

Table 9.2: European overview of OR for getting seriously injured or killed based on aggregated data (DRUID, summary of main findings)

Substances	Odds ratio (OR)	CI (95%)	Reference and basis for ORs
Medicinal opioids	Seriously injured		
	Crude OR:7.99	5.73 – 11.15	DRUID (D2.3.5)
	Adjusted OR: 9.06	6.40 – 12.83	Greenland et al, 2000
	Killed		
Illicit opiates	Crude OR: 4.82	2.61 – 8.88	Countries providing data for Seriously injured OR: BE, DK, FL, IT, LT, NL
	Adjusted OR: 4.82	2.60 – 8.93	
	Seriously injured		
	Crude OR: 4.03	1.32 - 12.32	Countries providing data for Killed OR: FL, NO, PT, SE, NL
	Adjusted OR:2.47	0.50 – 12.10	
	Killed		
Crude OR: 10.04	2.04 – 49.32*	Bernhoft, 2011 DRUID Deliverable 2.4.1)	
Adjusted OR n/a			

*The variations in the risk estimate reflect sparse data in some countries.

Key: BE (Belgium), DK (Denmark), FL (Finland), IT (Italy), LT (Lichtenstein), NL (The Netherlands), NO (Norway), PT (Portugal), SE (Serbia).

A recent study conducted in Australia illustrates the growing epidemiological evidence linking the therapeutic use of opioids to an increased crash risk but there is

inconsistency in the literature (Leung, 2011). Studies to assess the involvement of drugs in drivers killed in traffic accidents have been conducted in Australia (Drummer et al, 2004) and the involvement of psychoactive substance use and the risk of RTA in the Netherlands (Movig et al, 2004) show an increased risk, although not statistically significant, for drivers using opioids (Drummer et al, 2004) and non-significant, weakly positive associations of opiates with culpability (Movig et al, 2004). The Panel noted that the risk of a RTA was increased when medicinal opioids and illicit opiates had been consumed, with the extent of the increased risk depending on the population of driver investigated. Although limitations in study methods have resulted in different findings results tend to point in the same direction of increased risk. The outcome of interest for the Panel in epidemiological studies was traffic accidents (in most instances injurious or fatal accidents), for which there was good evidence of the dangers of medicinal opioids and illicit opiates for safe driving (Table 9.2).

Research on the medicinal opioid methadone and driving has been unclear. Some studies show little or no effect for methadone (Chesher, 1995), others show increases in reaction time and decision time when prescribed the drug (Schindler et al, 2004). When plasma concentrations of the drug were between 90 µg/L and 132 µg/L methadone maintenance treatment (MMT) patients achieved scores necessary to pass a driving test (Rossler et al, 1993). A dose related slowing of reaction time has been reported and the rate of information processing was deemed problematic in MMT patients in many studies (Staak et al, 1993; Moskowitz & Sharma, 1979; Rothenberg et al, 1977), particularly distance perception (Kelley et al, 1972) and driving at higher speeds (Specka et al, 2000). In reviewing the effects of methadone on driving Staak et al, (1993) concluded that individuals were generally not fit to drive.

DRUID researchers⁵⁰ who investigated accident risk for driving with opioid medicines found that even at low doses methadone and buprenorphine caused impairment when given as **a single dose** to healthy subjects and reported that no clear evidence exists if patients under maintenance treatment are able to drive safely. DRUID researchers recommended that as maintenance patients often use other illicit substances in addition, screening for other substances be carried out if a maintenance

⁵⁰DRUID 6th Framework Programme - Deliverable 7.3.2 Main DRUID results to be communicated to different target groups

patient should be allowed to drive (Deliverable 1.1.2c). In Norway, methadone and buprenorphine are considered to impair driving and attract legal sanctions at a laboratory (LOQ) concentration of 25 µg/L and 0.9 µg/L in whole blood respectively.

Driving records for MMT patients in Great Britain were not sufficient to provide an accurate picture of the driver safety in this population. More systematic effort is needed to monitor driving behaviour of those prescribed methadone and buprenorphine and in those attending drug treatment settings in general. It is widely accepted that MMT patients in the UK regularly use drugs known to be of considerable risk for safe driving such as alcohol (Senbanjo et al, 2007), cannabis, cocaine (Haskew et al, 2008) and heroin (Senbanjo et al, 2009). The use of methadone obtained illicitly to supplement prescribing is also commonplace. For these reasons and in consideration of the epidemiological evidence, the Panel **recommended a threshold should be set at 500 µg/L methadone in whole blood**, indicative of high dose consumption: high doses having been shown to have greater risk of a RTA than low doses. The Panel also acknowledged the role of the medical branch of the DVLA in assessing patients prescribed methadone and wishing to drive (Box 2.4). There was insufficient evidence in the literature to set a threshold for buprenorphine and the Panel recommended efforts should be made to gather evidence about its use in driving populations.

The Panel noted that age was also an important consideration for medicinal opioids. A recent Australian population based study (Meuleners et al, 2011) investigated 616 individuals aged 60 and older hospitalized as the result of a RTA between 2002 and 2008. The evidence suggests that there is a greater risk of a RTA for drivers aged >65 years who are prescribed opioid drugs than the risk for those in the same age group not prescribed medicinal opioids (Leveille et al, 1994; Movig et al, 2004). Further research is needed to contextualise this situation for drivers in Great Britain. Meuleners et al, (2011) also highlighted that females prescribed opioid analgesics had a significantly greater crash risk (OR=1.8, 95% CI=1.1–3.0, P=0.03) than males under the same conditions. Therapeutic use of opioids (as a defining characteristic) has also been associated with a higher risk of traffic accidents in young drivers (Engeland et al, 2007; Gibson et al, 2009).

An overview of the risk estimates as an odds ratio (OR) for involvement in, responsibility for or injury as the result of a traffic accident when driving under the

influence of opioid drugs calculated by different researchers and the EU project DRUID are shown below (Table 9.3). Because of the lack of specific studies and the small numbers, many authors have reported studies that combine opioid medicines and hence make broad class claims instead. The DRUID researchers have used this approach and hence the odds ratios for medicinal opioids considered by the Panel fall into this category.⁵¹

Table 9.3: Overview of the risk estimates as an odds ratio (OR) for involvement in, responsibility for or injury as the result of a traffic accident when driving under the influence of opioid drugs (based on a report by Clockwork Research Ltd. to the Panel).

Substances	OR	CI (95%)	Reference and basis for OR
Opioids	Incident rate ratio		Gibson et al, 2009 (UK study)
Opioids (all) first 4 weeks	1.70	1.39 – 2.08	Individuals 17 – 74 yrs met with RTA whilst taking prescribed medication
Extended use	1.29	1.08 – 1.54	
Codeine first 4 weeks	1.61	1.11 – 2.32	
Codeine extended use	1.33	0.88 – 2.00	
Morphine first 4 weeks	1.16	0.39 – 3.45	
Morphine extended use	0.87	0.43 – 1.75	
DHC** first 4 weeks	1.60	1.14 – 2.25	
DHC extended use	1.05	0.78 – 1.42	
Tramadol first 4 weeks	1.46	1.02 – 2.11	
Tramadol extended use	1.34	1.02 – 1.76	
Opioids	2.35	0.87 – 6.32	Movig et al, 2004 Injured and non accident involved drivers, 110 car/van drivers hospitalised after RTA and control group of 816 drivers randomly selected for testing
Opiates: Injured	1.89	1.47 – 4.43	Elvik 2012 (Meta-analysis)
Killed	1.44	0.86 – 2.40	
Opioids*			Leveille et al, 1994, USA 234 drivers aged >65 yrs; Current exposure within 60 days *codeine most commonly detected
Current exposure	1.8	1.0– 3.4	
≥ 2 types drugs	2.0	1.0 – 4.0	
Past exposure	1.0	0.5 – 1.8	

⁵¹ Oipids

	SIR		Bachs et al, 2009 Norway
	1.9		18 to 69 yrs, first 7 days after dispensing; Traffic accident that resulted in personal injury
Codeine (all)	1.5	1.6 – 2.2	
Tramadol		0.9 – 2.3	
Opioids	1.41	0.7 – 2.9	Drummer et al, 2004 Fatal crashes analysed. Drivers culpable
Opioid analgesics	1.5	1.0 – 2.3 (p<.05)	Meuleners et al, 2011
Male	1.2	0.6 – 2.4 (p<.66)	
Female	1.8	1.1 – 3.0 (p<.03)	
Chronic condition	2.1	0.9 – 4.7 (p<.09)	

The evidence (Table 9.3) suggests that codeine (Bachs et al, 2009; Gibson et al, 2009), dihydrocodeine (Gibson et al, 2009); tramadol (Gibson et al, 2009; Bachs et al, 2009) and methadone-often found in the blood of those killed in traffic accidents (Drummer et al, 2003) may be associated with increased risk of traffic accidents at least in the first 4 weeks of treatment. Bachs et al (2009) evaluated the risk of RTA involving drivers with prescriptions for codeine and tramadol. Over 33 months 181 accidents that resulted in injury involving drivers with codeine exposure (defined as within 7 days after the date of dispensation) were evaluated; 20 accidents involved tramadol. The risk of being involved in an accident was significant for drivers using codeine (standardized incidence ratio (SIR) for both sexes and all age groups combined (SIR 1.9; CI: 1.6–2.2).

The Standardised Incident Ratio (SIR) for tramadol (1.5; CI: 0.9–2.3) was not significant but showed an upward trend. However, when data from those who had been exposed to other impairing drugs during the relevant time period were excluded from consideration, the SIR for RTA no longer showed any increase. Reaction times were significantly slower for the chronic pain patients prescribed codeine (mean daily dose 180 mg), in both rural and urban driving conditions, compared to the healthy controls. The chronic pain patients missed almost twice as many reactions to traffic signs, although there were no differences between the groups in steering precision (Halvard et al, 2011). However, for these drugs the risk for involvement in, responsibility for or injury as the result of a traffic accident is less than OR: 2.0 when considered individually.

The Panel has therefore decided not to set thresholds for codeine, dihydrocodeine and tramadol, but agreed that the advice given to patients prescribed these drugs should be strengthened, particularly around the reported increased risk of traffic accidents in the first 4 weeks of treatment.

Internationally, several countries have set thresholds in blood for morphine as the opioid drug most consistently found in driving populations (Table 9.4). It was noted that most European countries had set concentrations around the laboratory limit of detection $\leq 20 \mu\text{g/L}$.

Table 9.4: International drug thresholds (set in or recommended for legislation): morphine

Country	Approach to threshold	Morphine	Reference
France	Legal cut-off	20 $\mu\text{g/L}$	Vindenes et al, 2011
Norway	Impairment Limit Limit for graded sanctions equivalent to BAC 0.5 g/L Limit for graded sanctions equivalent to BAC 1.2 g/L	9 $\mu\text{g/L}$ 24 $\mu\text{g/L}$ 61 $\mu\text{g/L}$	Norwegian Institute for Public Health, 2012
Netherlands	Limit of quantification Threshold	20 $\mu\text{g/L}$	The Netherlands Forensic Institute 2010
Poland	Limit of quantification	20 $\mu\text{g/L}$	Vindenes et al, 2011

In Norway, in cases of suspected drug driving a blood sample is taken from the suspect shortly after the incident. Results of the blood test are sent to the Norwegian Institute of Public Health, Division of Forensic Toxicology and Drug Abuse in Oslo for further evaluation. The mean blood morphine concentration in the ‘not impaired’ group as determined by a single physician using a ‘clinical test for impairment’ was $34 \mu\text{g/L} \pm 19 \mu\text{g/L}$ (median $30 \mu\text{g/L}$ morphine). The mean blood morphine concentration in the ‘impaired’ group was $31 \mu\text{g/L} \pm 15 \mu\text{g/L}$ (median $27 \mu\text{g/L}$ morphine). The findings in Norway demonstrate the difficulty of using impairment as the basis for drug-driving thresholds. The Panel chose instead to use a ‘risk estimates’ approach and found that ORs in the scientific literature were greater for morphine alone compared to ‘opiate’ drugs as a broad drug class (Table 9.5).

Table 9.5: Overview of the risk estimates as an odds ratio (OR) for involvement in, responsibility for or injury as the result of a traffic accident when driving under the influence of morphine. (Based on Netherlands Advisory Committee 2010)

Substances	Odds Ratio (OR)	CI (95%)	Reference and basis for OR
Opiates	OR: 2.35 OR: 1.41	CI: 0.87-6.32 CI: 0.7-2.9	Movig et al, 2004 Drummer et al, 2004
Morphine	OR: 32.0	n/a	Assum et al, 2005
Morphine <20 µg/L	OR: 8.20	CI: 2.5-27.3	Mura et al, 2003

The risk estimate of serious injury or death for those drivers who tested positive for morphine was between OR: 8 and OR: 32, whereas the risk for those tested positive opiates was between OR: 1.4 and OR: 2.35 compared to those who did not have a positive test result (Table 9.5). To establish a threshold for morphine in blood historical data was considered from 'Driving Under the Influence of Drugs' (DUID) cases where whole blood specimens were submitted for analysis to the DUID laboratory of the Forensic Science Service (FSS) over a three year period (from 2004-2007). Data for free morphine was identified in 399 cases.

A summary of blood drug concentration data from cases submitted from drivers suspected to have been driving whilst impaired following drug use are shown in Table 9.6. The Panel also noted the data from 2,995 blood samples taken between January 2008 and October 2012 and analysed by GC-MS and which contained one or more drugs. The data, which is predominantly from cases in England and Wales, relates to cases of Road Traffic Accidents (RTA) or impairment witnessed by the police, followed by assessment by a forensic physician. The Panel noted that the time between any witnessed impairment and sample collection was unknown and likely to be variable. These data are shown in bold, italicised text in Table 9.6.

Table 9.6: Drug concentrations of morphine detected in blood samples collected from UK drivers (FSS), and additional data on samples taken between January 2008 and October 2012 (bold, italicised)

Compound	Mean blood Conc (µg/L)	Median blood conc (µg/L)	Range (µg/L)	Number samples analysed
Free morphine	81 43	61 20	15-711 10-1000	399 238
<i>Morphine</i>	36	10	10 – 950	82
<i>Free morphine + other opiate</i>	70 38	50 30	10 – 270 10-100	40 44
<i>Morphine + other opiate</i>	38	30	10 – 100	44

In recognition of the blood concentration values found in drivers and the epidemiological evidence discussed above the Panel **recommended a threshold of 80 µg/L morphine in whole blood.** The limit of 80 µg/L morphine was noted to be at the higher end of the therapeutic range for the drug, according to the data produced by the Netherlands Forensic Institute (2010) in Table 9.1 above. The Panel discussed the merits of both a higher and a lower morphine threshold in its recommendations to the Government, as both could be justified from a scientific basis. It was decided to recommend a higher limit in recognition of the greater risk associated with use of illicit opiates.

Opioids and alcohol in relation to driving

Meta-analysis of experimental studies show that there are many factors related to opioid/opiate use that influence driver safety such as the route of drug administration, dose, time of day, adherence to the dosing regimen, and disposition of the patients as

well as concomitant use of additional drugs. The onset of therapy is often described as a crucial phase in relation to driver safety. A significant confounder is poly substance use.

The risk estimate as an OR for driving under the influence of psychoactive drugs and alcohol compared to driving not influenced by drugs was found to be significant OR: 112 (95% CI: 14-893) (Movig et al, 2004) and the OR for driving under the influence of **any** psychoactive drug and alcohol was hugely significant was 231.9: 33.3-1615.4 (P<0.001) (Bogstrand et al, 2012; DRUID and Netherlands Institute Forensic Science 2010).

In light of these findings three new Norwegian limits have been published (Vindenes et al,2011), for morphine reducing limits in whole blood to the laboratory limit of detection (9 µg/L) or 'zero tolerance' as it is known and for impairment comparable to BAC, 50 mg alcohol per 100 ml blood (0.5g/L)a threshold in whole blood have been set at 24 µg/L and for impairment limits comparable to 120 mg alcohol per 100 ml blood (1.2g/L)was set at 61 µg/L in whole blood.

The Panel was in agreement that in the absence of specific evidence about the risk associated with the combination of morphine and alcohol this should be set at half the threshold for morphine on its own. The Panel **recommended that a threshold for morphine at 40 µg/L could be recommended where alcohol was detected in the body above 20 mg/100ml blood**, which is the lowest level of alcohol that is reported in the literature to have an effect on driving performance.

Box 9.1: Basis for the recommendation of the morphine threshold

The main active ingredient of opium derived from the poppy plant, *PapaverSomniferum* is morphine, which is widely used as an effective analgesic for the relief of severe and chronic pain.

In European surveys in 2011 methadone, morphine and codeine were the most prevalent medicinal drugs in drivers.

The prevalence of morphine in data (predominantly from England and Wales) collected from cases suspected of drug-driving (January 2008 and October 2012), showed that opiates were present in 33% of drug positive samples.

Morphine acts on the central nervous system (CNS) and adverse effects include respiratory depression, somnolence and mood changes. The half-life is approximately 2-3 hours.

The risk (as an odds ratio, OR) of injury or responsibility for a RTA for drivers who tested positive for morphine was between OR: 8.20 and OR: 32.0 compared to those who did not have a positive test result.

In cancer patients at steady-state receiving 209 mg morphine/day blood concentrations of morphine were on average measured at 66 µg/L whilst a single intramuscular dose 8.75 mg/70 kg resulted in a peak 70 µg/L serum concentration 10 to 20 minutes after dosing.

In individuals (from different studies) suspected of or proven to have been driving under the influence of morphine: the range of means varied from 38 µg/L morphine to 81 µg/L.

A threshold was recommended taking into consideration both therapeutic concentrations and concentrations found in drug-drivers.

There was insufficient evidence to recommend a threshold for codeine.

Box 9.2: Basis for the recommendation of the heroin threshold

Heroin is a semi-synthetic opioid. It is an illicit drug with a powerful euphoriant effect: regardless of the route of administration it decreases alertness and motor activity.

In the UK during the period from April 2011 to March 2012, 197,110 adults were in treatment contact with substance-misuse services, with the majority using heroin (81%).

A third of these used illicit opioids alone, with the remaining two thirds combining heroin with cocaine.

In England and Wales in 2010/11, for those who reported driving under the influence of illegal drugs at least once or twice in the previous 12 months, 19% had used heroin within that last year.

The quantity of heroin used varies widely from person to person: regular use requires increased dosing to achieve the same 'sought after' effect and doses in excess of 1g per day are not unusual in dependent addicts.

Heroin breaks down very quickly in the body, with a half-life between 2 and 5 minutes. It is broken down to 6-monoacetylmorphine (6-MAM) a potent metabolite. 6-MAM is also short lived (half-life 6-25 minutes). The main metabolic breakdown product of 6-MAM and thus heroin is morphine.

Recreational use of heroin is unlikely to be detected in biological samples because of its rapid onset of action and metabolism to 6-MAM. The presence of morphine in blood can be indicative of either medicinal (diamorphine or morphine) or illicit opioid (heroin). According to European researchers, the risk (as an odds ratio, OR) of serious injury or death for those drivers who tested positive for Illicit opiates was between OR: 2 and OR: 10.

A threshold was recommended for morphine reflecting its presence in the body as a metabolite of heroin.

There was insufficient evidence to recommend thresholds for dihydrocodeine, oxycodone and hydrocodone.

Box 9.3: Basis for the recommendation of the methadone threshold

Methadone is a synthetic opioid, used in the treatment of heroin dependence, but also as an analgesic (pain killer) and antitussive (cough suppressant).

In England in 2004, 1,954,700 individual items of methadone were prescribed to approximately 200,000 individuals for opioid dependence: there is no reliable data on the number of those prescribed methadone that drive.

It is a requirement that patients prescribed methadone self-declare to the Driver and Vehicle Licensing Agency (DVLA); they are subject to annual medical review in order to keep their driving licence entitlement. There is considerable discrepancy between estimates of numbers of people on methadone programmes and the number of declarations to the DVLA.

In England and Wales in 2011/12 it was estimated that 0.3% of 16 to 59 year olds (CSEW survey) had used heroin and/ or methadone in the previous year (a level that has generally remained stable for many years).

In epidemiological studies examining populations involved in RTAs or apprehended for drug-driving methadone was the third most frequently detected drug and was the fifth most frequent in RTA cases in Europe.

Methadone is a long-acting drug and adverse effects include sedation, cognitive impairment, respiratory depression and somnolence. The half-life of methadone is 34-46 hours.

The risk estimate (OR) of serious injury or death in a RTA for those drivers who tested positive for medicinal opioids (including methadone) was between OR: 4.8 and OR: 9.2 compared to drivers who did not have a positive test result.

The mean blood concentration of methadone found in individuals suspected of, or proven to have been, driving under its influence was 180µg/L.

MMT patients with plasma concentrations of the drug between 90µg/L and 132µg/L achieved scores necessary to pass a driving test.

A therapeutic concentration in MMT patients is commonly reported to be 400 µg/L (doses >60 - 80 mg/day).

A high threshold was recommended in relation to methadone detected alone: at low concentrations risk to driver safety is inconclusive. The Panel also acknowledged the role of the medical branch of the DVLA in assessing patients prescribed methadone and wishing to drive (Box 2.4).

MMT patients are not always compliant: the use of methadone obtained illicitly to supplement prescribing and the use of other drugs known to be of considerable risk for safe driving such as alcohol, cannabis and cocaine is commonplace.

A further threshold was recommended when methadone is detected concurrently with alcohol (<80 mg/100 ml blood) on the basis that the concomitant use of alcohol will contribute to unsafe driving.

There was insufficient evidence to recommend thresholds for buprenorphine and fentanyl.

Recommendations

- Based on the evidence available to the Panel (summarised above), it is recommended that a threshold in whole blood for morphine is set at 80 µg/L.

- In addition, a threshold is recommended for morphine when detected in the presence of alcohol. It is recommended that the threshold in this circumstance be set for morphine at 40 µg/L and the alcohol level be set at 20 mg alcohol per 100 mL blood
- Based on the evidence available to the Panel (summarised above), it is recommended that a threshold in whole blood for methadone is set at 500 µg/L.
- In addition, a threshold is recommended for methadone when detected in the presence of alcohol. It is recommended that the threshold in this circumstance be set for methadone at 250 µg/L and the alcohol level be set at 20 mg alcohol per 100 mL blood

It is also recommended that:

- Strengthened medical information be provided that warn individuals prescribed medicinal opioids (methadone), medicinal opiates (morphine) and illicit opiates (heroin) about the risks of consuming the drug and driving particularly if alcohol had also been consumed concurrently.
- Healthcare providers and practitioners should be properly informed and fully conversant with the potential risks associated with the use of opioid drugs and driving.
- Special attention is paid by healthcare professionals to those >65 years of age who are prescribed one or more opioid/opiate medicines and intend to drive
- Special attention is paid by healthcare professionals to those on methadone maintenance treatment and who are also prescribed one or more benzodiazepine and intend to drive
- Clear information should be made available for prescribers, pharmacists and patients about which medicines are not compatible with driving or are only compatible if used in particular circumstances and quantities.

10. DRUG SPECIFIC FINDINGS: BENZODIAZEPINES

Background

Benzodiazepine (BZ) drugs are widely prescribed and their general clinical effects are well known. They have been most commonly used for either the treatment of insomnia (and are sometimes classified on this basis as hypnotics whose primary function is to induce sleep (Gottesmann, 2002)) at night, or for the treatment of anxiety and classified as anxiolytics (Ballenger (2001) or (minor) 'tranquilliser' whose primary function is to lessen anxiety (Bond & Lader, 2012). Many benzodiazepines have anti-convulsive properties and are licensed for treatment of epilepsy, and others can be muscle-relaxing.

Besides medicinal use, benzodiazepines are commonly misused in combination with illicit or licit substances and less frequently misused as a drug of first choice. Seizures of benzodiazepines by law enforcement agencies have increased by more than 50 per cent between 2005 and 2009 according to the World Drug Report (2011). The use of benzodiazepines is common among drug users in treatment, particularly those receiving methadone substitution therapies. Today, the non-medical use of benzodiazepines is widespread, where prescription drugs are sold outside the control of the health authorities often through illegally-operating internet pharmacies. Benzodiazepines, specifically alprazolam and diazepam, are among the most often diverted and abused medicines (United Nations, 2010). However, there remains an absence of information on overall patterns of benzodiazepine use, making estimation of the extent of non-medical benzodiazepine drug use difficult.

Epidemiological prevalence

Several surveys demonstrate that benzodiazepines are the most widely misused prescription medicine in the United Kingdom. For 2011/12 the CSEW, a general household survey of adults aged 16 and over, estimated last year use of tranquillisers⁵² at 0.5% in adults aged 16-59 years.

⁵²The CSEW estimates illicit drug use. Respondents are asked questions about 'Tranquillisers (not prescribed by a doctor)'. The exact tranquilliser used by respondents is not known, and may include both benzodiazepines and barbiturates.

European data: benzodiazepines and driving

In most European countries, benzodiazepines are the most common medicines detected in driving populations involved in RTAs but there is high national variability. Significant scientific evidence is also available with regard to the role of the benzodiazepines in RTAs such that individual drugs within this class feature in road traffic legislation in countries such as Norway (Table 10.1). The DRUID project estimates the prevalence of benzodiazepines in the general European driving population at 0.9%. In Denmark, benzodiazepines were found in 38% -47% of the samples collected from apprehended drivers with clonazepam being the most frequently-detected (17% -25%) followed by diazepam (9% -17% of the cases).

Table 10.1: Drug thresholds in Norwegian legislation: benzodiazepines (Norwegian Institute of Public Health, 2012)

Benzodiazepines	Impairment limit (µg/L)	Limit for graded sanctions (µg/L)	Limit for graded sanctions (µg/L)
	Comparable to 1.2g/L BAC	Comparable to blood alcohol of 0.5g/L BAC	Comparable to blood alcohol of 1.2g/L BAC
Alprazolam	3	6	15
Diazepam	57	143	342
Fenazepam* (Phenazepam)	1.8	5	10
Flunitrazepam	1.6	3	8
Clonazepam	1.3	3	8
Nitrazepam	17	42	98
Oxazepam	172	430	860

* Fenazepam is not legally available in the UK

Among killed drivers in the DRUID studies, the presence of benzodiazepines was the second most frequent toxicological finding after alcohol (DRUID, D2.2.5, 2010). In

European drivers, benzodiazepines⁵³ were often not used in combination with other psychoactive substances: the proportion of benzodiazepine use in combination with other drugs was around 15%. However, in Italy, almost half of all benzodiazepines were found in combination with other drugs. Research conducted on drivers in Scotland during the early 2000s suggested that benzodiazepines were the most prevalent drug group, with blood samples of over 80% of drivers suspected of being impaired by substances other than alcohol due to drugs having blood samples testing positive for a benzodiazepine (Officer, 2009).

With regard to drivers in the UK the CSEW has a self-completion module that includes questions relating to drug use and drug driving. In 2010/11, for those who reported driving under the influence of illegal drugs at least once or twice in the previous 12 months, 31% had used tranquillisers within the previous 12 months. Oliver *et al.* (2006) analysed biological samples from drivers apprehended under suspicion of impaired driving and found that 75% of biological samples analysed from this group (n=283) tested positive for drugs. Benzodiazepines were the most commonly detected drug group, followed by opioid drugs: polydrug use was found in 56% (n=86) of blood samples. The Panel considered prevalence data from laboratory analysis of 3,616 blood samples taken in suspected cases of drug-driving which screened positive (by ELISA) for one or more drugs. The data, which is predominantly from England and Wales and was collected between January 2008 and October 2012, showed that benzodiazepines were present in 41% of drug positive samples.

Patterns of use

Benzodiazepines are widely prescribed. With the exception of epilepsy (clonazepam, clobazam) there are no licensed indications for the prescription of benzodiazepines beyond short-term use, although it has been estimated that at least 1 million people were prescribed benzodiazepines long-term in the United Kingdom (Ashton, 2005) and a proportion is thought likely to develop dependence (O'Brien, 2005). However, the size of the problem is difficult to determine. Patients who are prescribed benzodiazepines for problems with anxiety or sleep do not usually escalate their doses even when

⁵³The benzodiazepine group consists of diazepam, nor diazepam, oxazepam, lorazepam, alprazolam, flunitrazepam, and clonazepam.

prescribed the drug long-term. However, high-dose benzodiazepine use has been reported for lorazepam with doses up to 95 mg/day (Martinez-Cano et al, 1996; Bond & Lader, 2012). The usual doses of different benzodiazepines in various preparations for therapeutic use are given below:

- Diazepam: usually 5 – 15 mg daily
- Nitrazepam: usually 5-10 mg daily
- Flurazepam (Hypnotic): 15 - 30 mg daily
- Flunitrazepam: 0.5 - 2 mg daily
- Temazepam: 10 – 20 mg daily
- Oxazepam: 30 mg maximal daily dose
- Lorazepam: usually 4 mg maximal daily dose

Benzodiazepines are also frequently misused recreationally but users may not become dependent. When used in this way, benzodiazepines are sometimes inhaled intranasally or injected; these routes achieve the desired effect much more rapidly than use by the oral route. Quantity of use varies widely from person to person and may reach levels of consumption well in excess of the usual therapeutic regimens. Recreationally, irregular use is likely to produce acute intoxication especially if used in combination with other substances: illicit use of benzodiazepine drugs has been shown to be associated with more poly-drug use behaviour compared to those who do not use these drugs. benzodiazepines are purchased as tablets, capsules, injections or suppositories: some such as fenazepam (phenazepam) (although not licensed in the UK as a medicine) can be obtained as a 'legal high', or sold as 'fake Valium' in powder or liquid form in doses of 1 gram (Talk to Frank, 2012) and has been used as a recreational drug (Dargan et al, 2012), as has flunitrazepam (Abanades et al, 2007).

Pharmacokinetics (PK) and blood-drug concentrations

Benzodiazepines are predominantly consumed by the oral route and tend to be readily absorbed. The acute intake of benzodiazepines is followed by a concentration-dependent deterioration of performance in controlled experimental studies. In Norway, physicians were able to demonstrate that the same was true in

impaired drivers who had significantly higher blood concentrations of diazepam, oxazepam and flunitrazepam compared to unimpaired drivers (Norwegian report, 2010). They are often categorised according to their pharmacokinetic profile into three groups (Table 10.2):

- Short half-life (<3-4 hours);
- Medium half-life (8-24 hours);
- Long half-life (>24 hours).

Table 10.2: Half-life of Benzodiazepine drugs (Moffat et al, 2011)

Official name	Used as Anxiolytic (A) or Hypnotic (H)	Half-life(hours)
Short half-life: Triazolam	H	2-4
Medium half-life: Oxazepam Temazepam Lorazepam Loprazolam Flunitrazepam	A H A H H	4-15 8-11 9-24 12-16 16-35
Long half-life: Nitrazepam Clonazepam Diazepam Flurazepam	H A/ treatment of epilepsy A H	18-38 30-40 20-100 20-100

The specific pharmacokinetics for some common benzodiazepines is given below:

Clonazepam: This benzodiazepine is rapidly and completely absorbed after oral administration and maximal plasma concentrations are reached within 1 to 4 hours. The plasma elimination of clonazepam is typically between 30 to 40 hours (Riss et al, 2008).

Diazepam: This is fairly-quickly absorbed following oral administration as a tablet or liquid and peak plasma concentrations are seen after 15-90 minutes. The drug persists in the body for some time – the elimination half-life of diazepam is 30 hours, but can range from 20 to 100 hours. Diazepam is metabolised in the liver to N-desmethyldiazepam (nordiazepam), and other compounds such as oxazepam and temazepam (Wolff et al, 1997): these have similar properties to diazepam and are prescribed in their own right. Nordiazepam has a half-life ranging from 30 to 200

hours. Toxic effects of these compounds may be observed when blood concentrations are greater than 1,500 µg/L diazepam (Moffat et al, 2011). Over a two-year period (2001-2002), 94 cases of individuals suspected of drug-driving with unusually high blood-diazepam concentrations ($\geq 1,100$ µg/L diazepam) were recorded (Bramness, 2002). From these cases, the mean (median) and maximum concentrations of diazepam were 2,000 µg/L (1,700 µg/L) and 7,800 µg/L, and the corresponding nordiazepam concentrations were 1,500 µg/L (1,000 µg/L) and 7,600 µg/L, respectively.

Flunitrazepam: This benzodiazepine is extensively metabolised to the mildly pharmacologically active desmethyl flunitrazepam and 7-aminoflunitrazepam, which is inactive (Moffat et al, 2011). Peak plasma concentrations occur in the body after about 1 hour following a single-dose (Moffat et al, 2004) or 3 hours after daily dosing for a month. Blood or plasma flunitrazepam concentrations are usually in a range of 5-20 µg/L in patients receiving the drug therapeutically as a hypnotic at night-time, and between 10-50 µg/L in those arrested for impaired driving. (Jones et al, 2007; Robertson & Drummer, 1998; Baselt, 2008) In drug-driving fatalities that involved flunitrazepam alone, a concentration of 480 µg/L flunitrazepam was reported. A dose response effect has been observed.

Flurazepam: This benzodiazepine is extensively metabolised (up to 70 % of a dose) during the first pass through the liver. Concentrations in blood are thus low and decrease quickly. Peak plasma concentrations have been reported in the range 0.5 µg/L to 30 µg/L and blood concentrations greater than 200 µg/L may be toxic (Moffat et al, 2004). The major metabolites in blood are N¹-desalkylflurazepam and N¹-(2-hydroxyethyl) flurazepam, which are both pharmacologically active. Peak plasma concentrations obtained at 3 hours following a single-dose for two subjects were 1 µg/L to 5 µg/L flurazepam (Moffat et al, 2011).

Lorazepam: This benzodiazepine is metabolised to the inactive glucuronide conjugate and approximately 50% of a dose is excreted in urine in about 24 hours. Toxic effects may be observed when blood concentrations are greater than 1500 µg/L (Moffat et al, 2011). Toxic effects were observed in subjects who were estimated to have consumed between 100-200 mg lorazepam: plasma concentrations were measured at between 300 µg/L and 600 µg/L.

Nitrazepam: This benzodiazepine is metabolised to 7-aminonitrazepam and the 7-acetamido derivative. The therapeutic range is usually 30-70 µg/L and blood concentrations greater than 200 µg/L may produce toxic effects (Moffat et al, 2011). A dose-response effect has been shown for nitrazepam.

Oxazepam: Oxazepam is largely metabolised to its glucuronide form. Oxazepam is a metabolite of several other benzodiazepines including chlordiazepoxide, diazepam, desmethyldiazepam (nordiazepam) and temazepam. Based on a comprehensive meta-analysis of 26 pharmacokinetic studies of plasma-concentration time studies and other pharmacokinetic parameters carried out, DRUID researchers reported that the concentration in plasma of oxazepam that was equivalent to impairment at 50 mg alcohol per 100 ml blood was 330 µg/L oxazepam (range 300 µg/L to 390 µg/L, oxazepam).

Temazepam: Temazepam is a metabolite of several benzodiazepines, including diazepam and temazepam, and is itself demethylated to oxazepam. The therapeutic serum concentration ranges from 300 to 900 µg/L and toxic effects are thought to occur when serum concentrations rise above 1000 µg/L.

Collection of specimens for evidential analysis

Different biological specimens have been used in clinical and forensic toxicology to detect benzodiazepine drugs. Hair testing has been used in many European countries to confirm abstinence from illicit drugs in persons whose driving licences have been suspended for drug-impaired driving because hair testing provides a much longer window of detection than urine testing. However, acidic drugs such as the benzodiazepines bind less well to hair and usually have lower concentrations than more basic compounds (such as the amfetamines).

The greatest application of oral fluid has been screening for illicit drug use in drug-dependent populations and it has been widely used to screen for illicit drug use in drivers (Verstraete, 2005). Oral fluid is often seen as an alternative to blood and provides evidence of recent drug use. However, oral fluid cannot confirm that the individual is currently likely to be suffering from impairment due to drug ingestion; only a blood sample can confirm this satisfactorily (Drummer, 2009).

Blood sampling is considered to be the most effective way to measure the concentration of a drug in the body. However, benzodiazepine concentrations in whole blood differ from those determined in plasma (Table 10.3)

Table 10.3: Blood: plasma ratio data for different BZ (DRUID main findings, 2012)

Drug	Blood/plasma ratio	Reference
Diazepam	0.55 - 0.70	Skopp, 2004; Moffat et al, 2011
Nordiazepam	0.59	Moffat et al, 2011
Alprazolam	0.63 – 0.8	Skopp, 2004
Oxazepam	0.9 – 1.0	Iten, 1994
Flunitrazepam	0.75	Skopp, 2004
Clonazepam	0.65	Moffat et al, 2011

Toxicological analysis to determine blood/plasma ratios for different benzodiazepine drugs have been determined by different researchers and are presented above for information (Table 10.3). Whole blood was therefore considered to be the most appropriate biological fluid for setting thresholds and because it relates best to the scientific evidence in relation to driving. Laboratory limits of detection (LOD) for common benzodiazepines for confirmatory evidential tests are shown in Table 10.4.

Table 10.4: Analytical cut-offs and laboratory limits of detection in blood for common benzodiazepines (Logan and Osselton, 2011)

Substance	LOD in Blood (µg/L) when using GC-MS
Diazepam	20
Nordiazepam	20
Lorazepam	10
Oxazepam	50
Temazepam	50

Pharmacodynamics (PD)

Benzodiazepines are a drug class with a series of common effects: these include a lessening of anxiety and induction of sleep. In bringing about sedation, partial amnesia may occur which 'clouds the consciousness' (O'Brien, 2005), with or without ataxia (unsteadiness). Naive users of the drug may appear disinhibited and demonstrate a lack of control. Reviews of pharmacodynamic studies with healthy volunteers have generally shown that benzodiazepines can cause severe impairment in tests designed to measure psychomotor and driving performance (Van Laar 1998; Vermeeren 2004; Verster et al 2004). The peer-reviewed literature generally indicates that benzodiazepines cause a reduction in overall speed of information-processing and motor response. In addition, performance may be adversely affected the morning after drug ingestion: this is known as the 'hangover' or 'residual' effects of benzodiazepines. The magnitude of impairment is dependent on various factors, including dosage, pattern of use and time of intake (Orriols et al, 2011). However, overall, the significant issues for drivers relate to the sedative effects of benzodiazepine drugs.

Diazepam, a widely prescribed benzodiazepine, is prescribed for many reasons: as a hypnotic (for insomnia); an anxiolytic; an anti-epileptic, for the acute treatment of seizures; as a muscle relaxant and in the management of alcohol withdrawal. It is commonly misused. Numerous studies have addressed the relationship between the time of administration of diazepam and its effects on cognitive function. Chronic dosing with diazepam usually leads to tolerance for some adverse and therapeutic effects (such as sedation) but it is unclear whether tolerance develops to the performance-impairing effects of the drug. Performance seems most affected following doses ranging from 5mg - 10 mg, 1-3 hours after administration (Yamazaki et al, 2007; Bond & Lader, 1982). When diazepam was administered (5mg) three times a day for eight days, poor cognitive function was recorded after the first dose and persisted for the entire dosing schedule (Bond, Lader, & Shrotriya, 1983).

It is known that the degree of tolerance that an individual develops is not the same for all effects and that loss of tolerance occurs after a period of abstinence; however, the intrinsic capacity of the individual to metabolise the drug together

with the likelihood of concomitant prescription of other drugs or use of other licit (alcohol) or illicit psychoactive substances suggest that the prescription of benzodiazepines should be accompanied by clear information about the potential for driver impairment. This is particularly the case for older individuals (>65 years of age) who are frequently prescribed hypnotics since the older patient tend to be more sensitive to drug effects.

Benzodiazepines and driving: the scientific evidence

There is a substantial literature investigating the relationship between benzodiazepine use and RTAs. Research has taken many forms including case-control studies, cohort, case control and 'culpability' studies, police and/or emergency studies and simulated or actual driving tests with drivers consuming benzodiazepines. The research has shown that the use of benzodiazepines leads to increased risk of motor vehicle accidents (Smink et al, 2010; Rapoport et al, 2009; Gibson et al, 2009; Gustavsen et al, 2008; Ray et al, 1993; Engeland et al, 2007; Movig et al, 2004; Mura et al, 2003; Longo et al, 2000). Specific scientific evidence has been published citing evidence of road traffic effects for clonazepam (Linnoila et al, 1990; Vester et al, 2002; Leufkens et al, 2007), lorazepam (Volkerts et al, 1992; flunitrazepam (Vermeeren et al, 1995; Bramness, 2002) (which has an increased risk of RTA compared to other benzodiazepine (OR: 4.11, P <0.05), and oxazepam (Volkertset al, 1992) and diazepam (Bramness, 2002; Barbone, 1998).

The risk of a RTA following benzodiazepine use has been demonstrated in several studies in both older and young population groups (Leung, 2011). The use of benzodiazepines has been estimated to increase the risk of having an accident by 62% compared with non-use (Barbone et al, 1998). Analysis of benzodiazepines by half-life revealed that those drugs with a long half-life (Table 10.2) were associated with an increased risk of a RTA (OR: 2.03, 1.41-2.93); for anxiolytics with a long half-life, the OR was 2.22 (range OR: 1.47 – 3.37) and for hypnotics, the OR was 0.88 (range OR: 0.41 to 1.87, 95% CI) (Brabone et al, 1998), suggesting a greater need for attention to driver-safety for long acting anxiolytics such as temazepam and nitrazepam. Orriols (2011) investigated the association between the use of benzodiazepines and the risk of RTAs from three French national databases, with

more than 72,000 drivers involved in injury-related road traffic accidents, from 2005 to 2008. The risk of being responsible for a traffic accident in this research for those who had hypnotic benzodiazepines detected in blood (OR: 1.39) was less than that observed for the anxiolytic benzodiazepines. Other evidence linking benzodiazepines and RTAs found an **increase in traffic accidents among people with three or more benzodiazepine prescriptions.**

Reviews estimate that the increased risk of a RTA in those consuming benzodiazepines compared to non-users ranged from 61% (Rapoport et al, 2009) to 290% (Engeland, Skurtveit, & Morland, 2007). The most recent review (Smink, 2010) considered data from 66 separate studies: all studies reviewed found an association between use of benzodiazepines and risk of a traffic accident, death or injury. The association between benzodiazepines and road traffic accidents was thought to be related to their deleterious effect on cognitive function, including reaction times.

A meta-analysis of 21 epidemiological studies and 69 experimental studies between 1966 and 2010 confirmed the findings of other research and found that benzodiazepines (hypnotics, anxiolytics and sedatives) were associated with a 60% (for case-control studies: pooled odds ratio [OR] 1.59; 95% CI 1.10, 2.31) to 80% (for cohort studies: pooled incidence rate ratio 1.81; 95% CI 1.35, 2.43) increase in risk of a traffic accident: accident risk was higher in drivers older than 65 years of age. It was also observed that anxiolytics (single or multiple doses) during the daytime affected driving performance independent of drug half-life (Dassanayake et al, 2011). Whilst in 18 healthy drivers (mean age 64.3 years) prescribed 20 mg temazepam, the magnitude of adverse effects was comparable to those found previously in younger volunteers on standardized highway driving tests between ten and eleven hours after administration of the drug (Moffat et al, 2011).

There is other evidence that suggests that benzodiazepines may lead to deleterious driving behaviour in the older patient (Leveille et al, 1994; Ray et al, 1993). In hospitalised, motor vehicle crash victims aged ≥ 60 years, benzodiazepines were associated with a greater risk of a crash resulting in hospitalisation than others not-prescribed benzodiazepines (Meuleners et al, 2011), as shown in Table 10.5. This suggests that blood concentrations of benzodiazepine within the therapeutic range may also impact on driver safety.

Thomas (1998) found the risk of being involved in an RTA for drivers older than 65 years was higher when longer-acting and larger quantities of benzodiazepines were consumed. The risk of an RTA, if over 65 years of age, whilst driving under the influence of benzodiazepine drugs was OR: 5.3 and ranged from OR: 4.0 (for chronic condition) to OR: 6.0 (without chronic condition) (table 10.5). This is a significant risk and the Panel recommends that special attention is given to the prescription of benzodiazepine for drivers over 65 years of age.

Table 10.5: BZ medication and risk estimate (as an OR) of a RTA requiring hospitalisation (n = 616) in drivers aged ≥60 years (adapted from Meuleners et al, 2011)

Benzodiazepine	Odds-Ratio (95% Confidence interval) P-value
All exposed subjects	OR: 5.3 (3.6 – 7.8) p<.001
Male	OR: 6.2 (3.2 – 12.2) p<.001
Female	OR: 4.9 (3.1 – 7.8) p<.001
Chronic condition: No	OR: 6.0 (3.8 – 9.5) p<.001
Chronic condition: Yes	OR: 4.0 (2.9 – 8.1) p<.001

Both Ray (1992) and Bramness (2002) suggest that any benzodiazepine use increases two-fold the risk of a RTA in a concentration-dependent fashion: risk is significantly higher when blood concentrations are above the normal therapeutic range (OR: 3.75, 1.46 – 9.63). An overview of the risk estimates as an odds ratio (OR) for involvement in, responsibility for or injury as the result of a traffic accident when driving under the influence of benzodiazepine drugs is shown in Table 10.6.

With hypnotics, converging evidence from experimental and epidemiological studies indicates that diazepam, flurazepam, flunitrazepam and nitrazepam significantly impair driving, at least during the first 2-4 weeks of treatment (Dassanayake et al, 2011). A meta-analysis that looked at best estimates of risk of accidents for a range of drugs including benzodiazepines found small or moderate increases in accident risk associated with their use (ELvik, 2012). These findings map

onto the European research carried out by DRUID (Report on main findings, 2010) that estimated overall that the increased risk as an odds ratio (OR) for involvement in, responsibility for, or injury as the result of a traffic accident when driving under the influence of benzodiazepines ranged between OR: 2-10.

Table 10.6: An overview of the relative risks as an odds ratio (OR) for involvement in, responsibility for, or injury as the result of a traffic accident when driving under the influence of benzodiazepines

Substance	Odds Ratios (OR)	Reference and basis for OR
Diazepam	OR: 1.61 (N=411; p<0.001)	Bramness 2002
Oxazepam	OR: 3.65 (N=73; P<0.05)	Impairment in apprehended drivers in Norway
Flunitrazepam	OR: 4.11 (N=211;p<0.05)	
Different BZ combined*		*Adjusted for all background variables
Mildly >Therapeutic Range-TR	OR: 1.60 (0.84 - 3.05)	
Moderately > TR	OR: 3.71 (1.34 - 10.27)	
Highly elevated>TR	OR: 3.75 (1.46 – 9.63)	
Long half-life (diazepam)	OR: 1.45 (1.04-2.03)	Hemmelgarn 1997
Continued use up to 1 yr	OR: 1.26 (1.09-1.45)	Drivers in injurious accidents Age 67-84 yrs
Short half-life (oxazepam)	OR: 1.04 (0.81-1.34)	
Continued use up to 1 yr	OR: 0.91 (0.82-1.01)	
Hypnotics (2-4 weeks)	OR: 6.5 (1.9-22.4)	Neutel 1995
Flurazepam/Triazolam	OR: 3.9 (1.9-8.3)	Saskatchewan study Accidents severe enough to require hospitalisation
Anxiolytics (2-4 weeks)	OR: 5.6 (1.7-18.4)	
Diazepam, Lorazepam, Oxazepam	OR: 2.5 (1.2-5.2)	
BZ + positive breath test	OR; 8.15 (2.06-32.34)	Barbone 1998
Anxiolytics (long half-life)	OR: 2.22 (1.47 – 3.37)	UK Tayside police 19,386 drivers first RTA: 1731 used drugs
Hypnotic (long half-life)	OR: 0.88 (0.41-1.87)	
BZs	OR:0.9 to 2.4	Thomas, 1998; Review case control studies
BZs	RR [^] : 1.5 (1.2-1.9)	Ray 1992; 1993.
≥ 20 mg diazepam	RR [^] : 2.4 (1.3-4.4)	65-84 years, RTA drivers
BZs and Z-drugs		Bernhoft, 2011,
Seriously injured	OR: 1.99 (1.36-2.91)	DRUID epidemiology study conducted in 9 EU countries of being seriously injured or killed
Killed drivers	OR: 5.40 (3.90-7.46)	

*Seriously injured based on aggregated data, ** fatally injured based aggregated data,

[^]relative risk

Benzodiazepines, drug concentrations and driving

The risk of driver impairment was shown to increase significantly with increasing benzodiazepine blood-drug concentrations, with odds ratios of being assessed impaired as OR: 1.61 for diazepam ($p = 0.001$), OR: 3.65 for oxazepam ($p = 0.05$) and OR: 4.11 for flunitrazepam ($p = 0.05$) respectively (Bramness et al, 2002). In order to address the lack of any clear definition for “impairment” in most European countries, other information such as blood-drug concentrations, clinical and other observations are used to determine driver impairment for legislative purposes.

Bramness (2002) compared the OR (95% CI) for being determined “impaired” on different elevated levels of diazepam blood concentrations compared to the therapeutic range. When adjusted for all background variables, the OR for mildly, moderately and highly elevated above expected therapeutic blood diazepam concentrations was OR 1.60 (0.84-3.05), OR 3.71 (1.34-10.27, $p < 0.05$) and OR 3.75 (1.46-9.63, $p < 0.01$) respectively. It was concluded that cut-off thresholds for driver risk could be established for benzodiazepines to avoid a zero-tolerance approach: this would help exclude compliant patients on low-dose benzodiazepine treatment inadvertently found involved, but not at fault, with regards to RTAs (Bramness et al, 2002). However, Jones et al (2004) reported that polydrug use (including alcohol, other medications and illicit drugs) was often observed in those who used benzodiazepines and thought an estimation of risk for a single benzodiazepine might not be meaningful. Nevertheless, others have taken this approach (Andreasen et al, 2011).

The National Institute of Forensic Toxicology (NIFT) (which analyses all blood samples from Danish drivers suspected of driving under the influence of alcohol or drugs) has established that medicinal drugs are detected at supra-therapeutic concentrations in blood (see table 10.7 below). Essentially, impaired drivers (unless older drivers) usually have higher blood concentrations of benzodiazepines than seen in individuals taking benzodiazepines as prescribed. In a sample of 818 drivers suspected of driving under the influence of drugs, those found to be impaired had significantly higher blood concentrations of benzodiazepine (Bramness et al. (2002). These differ from those reported by Jones & Holmgren (2012) who selected 1000 cases of driving under the influence of drugs (DUID) over a 12 month period

based on the presence of diazepam and nordiazepam in the blood samples. They found (assuming a plasma/blood ratio of 1.8:1) that the mean concentration detected for diazepam was 370 µg/L. In 90 cases (9%) the concentration of diazepam in blood exceeded 830 µg/L. The time period between driving incident and blood sampling may have been the reason for the different observations, for reasons explained previously.

Table 10.7: Range, median and average blood concentration for the most frequently detected drugs in drivers suspected of driving under the influence of drugs in Denmark (Andreasen et al, 2011)

Substance	Average Conc (µg/L)	Median (µg/L)	Range (µg/L)
Clonazepam	60	34	8-1003
Diazepam	732	455	150-6500
Nordiazepam	688	405	150-11, 000

Setting threshold concentrations at specific concentrations in blood for benzodiazepine (potentially above the normal therapeutic range) would be a different approach from the zero-tolerance principle that has been applied elsewhere. The zero-tolerance approach which makes it illegal to drive with any concentration of benzodiazepines in the blood (set at the laboratory limit of detection) has the disadvantage of making it very difficult (if not impossible) for unimpaired patients compliant on therapeutic dosages to drive without fear of possible repercussions.

Blood concentration data for diazepam, nordiazepam and temazepam obtained from cases which were submitted to the FSS DUID unit, in England between 2004 and 2007 where drivers provided a blood sample when apprehended by the police for suspected of drug-driving and who had not tested positive for alcohol are presented in Table 10.8. Between 2004 –2007, of the total cases screened for drugs, 184 cases were positive for benzodiazepines (4.4%).

Table 10.8: Blood concentration data for diazepam, nordiazepam and temazepam obtained from cases which were submitted to the FSS between 2004 and 2007

Substance	No cases	Mean (µg/L)	Median (µg/L)	Range (µg/L)	Therapeutic range (µg/L)	Toxic range (µg/L)
Diazepam	260	530	420	29-2330	125-3000	>5000
Nordiazepam	252	370	250	28-2220	200-1800	
Temazepam	49	1130	868	192-3600	300-9000	>10,000

The Panel also noted data from 2,995 blood samples taken between January 2008 and October 2012 and analysed by GC-MS and which contained one or more drugs. The data, which is predominantly from cases in England and Wales, relates to cases of Road Traffic Accidents (RTA) or impairment witnessed by the police, followed by assessment by a forensic physician. The data is shown in table 10.9. The Panel noted that the time between any witnessed impairment and sample collection was unknown and likely to be variable making comparison between this and other datasets difficult.

Table 10.9: Blood concentration data for different BZs detected in cases of drug-driving submitted to a forensic laboratory for analysis between January 2008 and October 2012

Substance	No cases	Mean (µg/L)	Median (µg/L)	Range (µg/L)	Therapeutic range (µg/L)	Toxic range (µg/L)
Diazepam	48	146	100	20-620	100-1,000*	>5,000
Diazepam + other BZ	636	614	400	0-10,000	Na	
Nordiazepam	11	97	55	20-240	200-1,800	
Nordiazepam + other BZ	250	754	350	10-10,000	Na	
Temazepam	17	352	300	30	860	>10,000
Temazepam + other BZ	207	342	90	0 – 9,000	Na	

Lorazepam	10	61	35	20	240	
Lorazepam+ other BZ	8	131	60	40 - 490	Na	

*Moffat et al, 2004

Although the blood concentration data for the different benzodiazepine drugs differ, this is to be expected where conditions such as the time period between the driving incident and the collection of the blood sample are not controlled. The median blood concentration data from the UK (Table 10.8) and from Denmark (Table 10.7) is remarkably similar for diazepam: the lower concentrations observed in Table 10.9 may reflect a longer period of time between dosing and sample collection. The Panel has taken the decision to recommend a threshold reflecting the increased risk of RTA with increasing benzodiazepine blood-drug concentrations. A similar rationale was used for temazepam. A threshold was not set for chlordiazepoxide, nitrazepam, alprazolam and flurazepam because of a lack of scientific evidence in terms of risk estimates for RTAs.

The risk of driver impairment was shown to increase with increasing benzodiazepine blood-drug concentrations, with odds ratios of being assessed impaired as OR: 1.61 for diazepam, OR: 3.65 for oxazepam and OR: 4.11 for flunitrazepam. For this reason and based on the evidence (summarised above) available to the **Panel, the threshold recommended in whole blood for diazepam is 550 µg/L**. At this concentration, impairment in driving and RTAs have been found to occur compared to drivers who had not consumed the drug. Recommendations are also made for **oxazepam (recommended threshold is 300 µg/L); flunitrazepam (recommended threshold is 300 µg/L); lorazepam (recommended threshold is 100 µg/L); clonazepam (recommended threshold is 50 µg/L); and temazepam (recommended threshold is 1,000 µg/L)** since these compounds have also been shown to increase the risk of a RTA in a concentration-dependent fashion: risk is significantly higher when blood concentrations are above the normal therapeutic range.

Benzodiazepines and alcohol in relation to driving

There is evidence that the use of any benzodiazepine with alcohol significantly increases the risk of a RTA. For instance, when concentrations of alcohol greater than 20 mg per

100 ml blood (0.2g/L) were found in those who also had any benzodiazepine detected, the odds of a RTA were increased (Benzodiazepine Driving Collaboration Group (1993), this was also the case where there was a positive breath test in the UK (OR: 8.15, 2.06-32.34) (Barbone et al, 1998). A meta-analysis of 21 epidemiological studies and 69 experimental studies between 1966 and 2010 found that benzodiazepines were associated with a 60% to 80% increase in risk of a traffic accident; when combined with alcohol; this risk increased 7.7 fold (Dassanayake et al, 2011).

For this reason and based on the evidence available to the Panel (summarised above) a dual threshold is recommended that takes account of the additive effect of alcohol and benzodiazepine use combined. The threshold in whole blood recommended **in the presence of alcohol for diazepam is 275µg/L; for oxazepam is 150 µg/L; for flunitrazepam is 150 µg/L; clonazepam is 25 µg/L; lorazepam is 50 µg/L and for temazepam is 500 µg/L.** The presence of a benzodiazepine in combination with alcohol significantly increases the risk as an odds ratio (OR) for involvement in, or injury as the result of a road traffic accident. And the threshold recommended in whole blood for alcohol when detected in combination with any of the above benzodiazepine is 20 mg alcohol per 100 mL blood. The measurement of alcohol at this threshold already exists in legislation concerning aviation in this country.

Box 10.1: Basis for the recommendation of the benzodiazepine thresholds

Benzodiazepine (BZ) drugs are widely prescribed and their general clinical effects are well known. They are most commonly used for the treatment of insomnia at night (hypnotics), or for the treatment of anxiety (anxiolytics).

Benzodiazepines are also frequently used recreationally but users may not become dependent. The quantity used varies widely from person to person and may reach levels of consumption well in excess of the usual therapeutic regimens.

Several surveys have demonstrated that benzodiazepines are the most widely-misused prescription medicine in the United Kingdom. In 2011/12 previous year use of tranquillisers was estimated to be 0.5% in adults aged 16-59 years.

In 2010/11, for those who reported driving under the influence of illegal drugs at least once or twice in the previous 12 months, 31% had used tranquillisers within that time period.

The acute intake of benzodiazepines is followed by a concentration-dependent deterioration of performance in controlled experimental studies. In Norway, physicians were able to demonstrate that impaired drivers had significantly higher blood concentrations of diazepam, oxazepam and flunitrazepam compared to unimpaired drivers

The risk estimate (OR) of a RTA requiring hospitalisation in drivers aged ≥ 60 years whilst driving under the influence of benzodiazepine drugs was OR: 5.3 (3.6 – 7.8, $p < .001$).

Any benzodiazepine use increases two-fold the risk of a RTA in a concentration-dependent fashion: risk is significantly higher when blood concentrations are above the normal therapeutic range (OR: 3.75, 1.46 – 9.63).

When adjusted for all background variables, the OR of a RTA for diazepam for blood concentrations moderately and highly elevated above the expected therapeutic blood concentrations was OR: 3.71 (1.34-10.27, $p < 0.05$) and OR: 3.75 (1.46-9.63, $p < 0.01$) respectively.

A threshold was recommended in relation to the mean blood concentrations of diazepam (from different studies), found in individuals suspected of, or proven to have been, driving under its influence: the range of mean diazepam concentrations varied from 146 $\mu\text{g/L}$ to 830 $\mu\text{g/L}$.

A threshold was recommended in relation to the mean blood concentrations of temazepam (from different studies), found in individuals suspected of, or proven to have been, driving under its influence: the range of mean temazepam concentrations varied from 352 $\mu\text{g/L}$ to 1,130 $\mu\text{g/L}$.

A threshold was recommended for oxazepam based on the knowledge that this drug is a common metabolite of other benzodiazepines and taking into consideration the mean blood concentrations of oxazepam found in individuals suspected of or proven to have been driving under its influence: blood concentrations observed ranged from 300 $\mu\text{g/L}$ to 390 $\mu\text{g/L}$.

A threshold was recommended in relation to the blood concentrations of flunitrazepam found in individuals proven to have been driving under its influence: blood

concentrations ranged from 10 µg/L to 50 µg/L and the therapeutic range reported in persons receiving the drug therapeutically as a night-time hypnotic was reported to be 5 µg /L to 20 µg/L).

A threshold was recommended in relation to the mean blood concentrations of clonazepam (60 µg/L) found in individuals suspected of, or proven to have been, driving under its influence.

A threshold was recommended in relation to the mean blood concentrations of lorazepam (61 µg/L) found in individuals suspected of, or proven to have been, driving under its influence.

A further threshold was recommended when the above drugs are detected concurrently with alcohol (<80 mg/100 ml blood) on the basis that the effects of concomitant alcohol use are intertwined and significantly contribute to unsafe driving.

There was insufficient evidence to recommend thresholds for nitrazepam, chlordiazepoxide, alprazolam and flurazepam.

Recommendations

Based on the evidence available (summarised above) to the Panel, the following threshold in whole blood that specifically reflect increased road safety risk and increased likelihood of a RTA for the **following benzodiazepines are recommended:**

- It is recommended that a threshold in whole blood for diazepam is set at 550 µg/L
- It is recommended that a threshold in whole blood for oxazepam is set at 300 µg/L
- It is recommended that a threshold in whole blood for flunitrazepam is set at 300 µg/L
- It is recommended that a threshold in whole blood for clonazepam is set at 50 µg/L
- It is recommended that a threshold in whole blood for temazepam is set at 1000 µg/L

- It is recommended that a threshold in whole blood for lorazepam is set at 100 µg/L
- In addition, a threshold is advised for the above benzodiazepine when detected in the presence of alcohol. It is recommended that the threshold in this circumstance be set for benzodiazepine in whole blood at half the threshold established for the individual benzodiazepine alone, and the alcohol level be set at 20 mg alcohol per 100 mL blood

In addition the Panel recommends that:

- Special attention is paid by healthcare professionals to those >65 years of age who are prescribed one or more benzodiazepine and intend to drive
- Special attention is paid by healthcare professionals to those on methadone and buprenorphine maintenance treatment and who are prescribed one or more benzodiazepine and intend to drive

Clear information should be made available for prescribers, pharmacists and patients on which benzodiazepine medicines are proscribed for driving.

11. DRUG SPECIFIC FINDINGS: MISCELLANEOUS DRUGS

The Panel is aware that there are drugs with similar pharmacological mechanisms of action to those discussed in this report and which, by analogy, are likely to pose similar impairing effects on driving performance. However, because of their relatively recent introduction, or their current relatively low usage in the UK, there is often incomplete knowledge of their pharmacokinetics and, especially, insufficient evidence regarding their possible involvement in traffic accidents. This did not allow odds ratios (ORs) to be estimated or limits to be proposed.

These drugs would include the so-called 'legal highs' available on the internet and designed to mimic the effects of illicit drugs but sufficiently different in chemical structure to avoid being controlled under the Misuse of Drugs Act (1971). Some such drugs have subsequently been controlled under the Act. Recent examples include methoxetamine, a close chemical analogue of the Class A drug phencyclidine and the Class C drug ketamine and, somewhat earlier, naphyrone and mephedrone both now Class B drugs as are the related, and previously controlled cathinone derivatives. Examples of some of these substances are briefly discussed below.

Mephedrone

Background

Synthetic cathinones are manufactured derivatives of cathinone, one of the psychoactive compounds present in the plant *Catha edulis* (khat). There are at least 12 different types of synthetic cathinones: methedrone and 3, 4-methylene, dioxypyrovalerone (MDPV) being most common (Mas-Morey et al, 2012). Others being used as recreational drugs include butylone, dimethylcathinone, ethcathinone, ethylone, 3- and 4-fluoromethcathinone, methylenedioxypropylvalerone (MDPV), methylone, and pyrovalerone (Prosser & Nelson, 2012).

Epidemiological prevalence

Mephedrone (4-methylmethcathinone) became available online in 2007 and is consumed in many European countries (EMCDDA, 2009). In the UK, by the end of July

2010, mephedrone was identified in at least 38 drug-related fatalities (Ghodse et al, 2010). New measures of drug use added to the CSEW for drugs recently classified under the Misuse of Drugs Act show that last year use of mephedrone (1.4%) was at a similar level as ecstasy use (1.4%) among those aged 16 to 59 (the third most used drug within this age group). For those aged 16 to 24, mephedrone use (4.4%) was at a similar level of use as powder cocaine (4.4%; the second most used drug amongst young people).

Patterns of use

Synthetic cathinones, particularly mephedrone have recently emerged and grown to be popular drugs of abuse. They are often considered "legal highs" and sold as "bath salts" or "plant food" and labelled "not for human consumption" to circumvent illicit drug use legislation (Prosser & Nelson, 2012). Further research is needed to understand the mechanisms of action, and the clinical and psychological effects of these compounds on driving behaviour.

Gamma-hydroxybutyrate (GHB) and Gamma-butyrolactone (GBL)

GHB and GBL are closely related drugs with similar sedative and anaesthetic effects. GBL is not active in its own right; it is a pro-drug and is converted into GHB in the body. GHB has been employed, generally informally, for a variety of purposes including the treatment of sleep disorders, anxiety and depression, and for symptomatic treatment of alcohol and opiate withdrawal (Sumnall et al, 2008). GHB is also associated with the recreational drug scene (Nicholson and Balster, 2001) and is commonly known as 'liquid ecstasy'.

Epidemiological prevalence

Reports in Australia and Europe have suggested that the use of GHB is on the increase (Espinosa et al., 2001; Degenhardt et al., 2005). A Swiss study reported that the percentage of people presenting to accident and emergency with GHB intoxication doubled from 2001 to 2003 (Liechi et al., 2006). Estimates of the prevalence of GHB use in adult populations are much lower than for the misuse of cocaine or ecstasy but in targeted surveys among visitors to large-scale parties in the Netherlands (in 2009) a prevalence of GHB of 4.6% was reported (UK Focal Point on Drugs, 2011).

Patterns of use

The drug is sold as a white crystalline powder and recreational doses of GHB range from 500 mg to 3000 mg. Sumnall et al, (2008) found that GHB was taken primarily at home rather than in clubs. Respondents to this study reported using GHB for relaxation and fun and to aid sleep. Most GHB users were polysubstance users.

Pharmacokinetics & Pharmacodynamics

The effects desired by GHB users include euphoria, relaxation and increased sensuality and disinhibition (Liechi et al., 2006). However, with higher blood concentrations use results in cognitive impairment, ataxia and a lack of awareness of surroundings. Indeed, Galicia, Nogue & Miro (2011) found in cases of poisoning or overdose admitted to an emergency department that the most common clinical observation was reduced consciousness, whilst Degenhardt et al, (2002) observed that 50 % GHB users had experienced an episode of loss of consciousness and an inability to be woken up. It is this hyper somnolence and the risk of sudden sleep onset that makes driving after taking GHB or GBL far from safe. Further research is needed to understand the patterns of use behaviour associated with GHB particularly in combination with other drugs such as alcohol.

Lysergic Acid Diethylamide (LSD)

The Panel also considered 'older' drugs like LSD (LSD-25 is an early code name) and psilocin which, together with other tryptamine derivatives, can be described as hallucinogens and which might, therefore, be expected to negatively affect driving performance. Their current usage in the UK is not high and therefore, data are not available to enable the Panel to propose limits.

Background

LSD is a white powder or a clear, colourless liquid manufactured from lysergic acid which occurs naturally in the ergot fungus that grows on wheat and rye. It is a Schedule I controlled substance, available in liquid, powder, tablet and capsule form. The liquid is often applied to blotter paper squares (frequently with colourful designs). There is no

known medicinal use of the drug and recreationally is used as a hallucinogen and for its ability to alter human perception and mood.

Epidemiological prevalence

Among young adults (15-34 years), lifetime prevalence estimates of LSD use in Europe range from zero to 5.5% (UK Focal Point on Drugs, 2011).

Pattern of Use

The strength of illicit LSD ranges from 20 µg to 80 µg per dose. Experienced users typically consume 100µg to 200µg for a 'good high'. LSD produces significant psychedelic effects with doses as little as 25µg to 50µg. LSD impairs reaction time (auditory and visual), choice reaction time, and visual acuity for up to 4 hours. Impaired divided attention, ataxia, and grossly distorted perception have also been reported following LSD use.

Pharmacokinetics

LSD has a plasma half-life of about 2.5 to 4 hours. Metabolites of LSD include N-desmethyl-LSD, hydroxy-LSD, 2-oxo-LSD, and 2-oxo-3-hydroxy-LSD. These metabolites are all inactive. Onset of effects is rapid following intravenous administration (10 minutes). Following oral ingestion, onset of the first effects is experienced in 20-30 minutes, peaking at 2-4 hours and gradually diminishing over 6-8 hours. Residual effects may last longer. Flashbacks may occur suddenly, often without warning, and may occur within a few days or more than a year after use. Threshold toxic dose in humans has been reported with 100-200µg with associated blood concentrations of 2-30 µg/L. Intravenous doses of 1-2µg/kg have been associated with blood concentrations of 1-5 µg/L LSD. Single oral doses of 160 µg resulted in peak plasma concentrations of 9 µg/L LSD.

Pharmacodynamics

Effects are unpredictable and will depend on the dose ingested, the user's personality and mood, expectations and the surroundings. Hallucinations, increased colour perception, altered mental state, thought disorders, temporary psychosis, delusions,

body image changes, and impaired depth, time and space perceptions. Users may feel several emotions at once or swing rapidly from one emotion to another. “Bad trips” may consist of severe, terrifying thoughts and feelings, fear of losing control, and despair.

The use of LSD is not likely to be compatible with the skills required for driving due to its severe psychomotor, cognitive and residual effects. LSD usage in the UK driving population is unknown and therefore data are not available to enable the Panel to propose limits.

Psilocybin and psilocin

Psilocybin (phosphorylated 4-hydroxyethyltryptamine) is a hallucinogenic alkaloid or active ingredient that occurs naturally in a variety of mushrooms (commonly referred to as ‘magic mushrooms’). Psilocin is also contained in the mushrooms but in smaller quantities than psilocybin. Psilocin is also the primary metabolite of psilocybin and is considered to be the primary source of hallucinogenic effects (Niesink et al, 1996). Both substances are chemically related to LSD, but they are approximately 200 times less potent.

The Panel recommends that surveillance procedures should be in place to monitor information regarding the usage and the possible involvement in RTAs of newer drugs appearing on the scene as well as older drugs which may increase in popularity. The possibility should exist of introducing these into the legislation by adding them to the list of drugs which, if present in the blood above a specified limit, would constitute a driving offence.

Recommendations

- To establish surveillance procedures for monitoring information regarding the usage and the possible involvement in RTAs of newer drugs appearing on the scene as well as older drugs which may increase in popularity.

- To collect biological material on a more systematic basis from those involved in RTAs that would enable comprehensive screening for the newer, older and seasonally available drugs being used recreationally.

12. SUMMARY AND CONCLUSIONS

The expert Panel on drug driving was asked by the Department for Transport in April 2012 to make recommendations about which drugs should be included in regulations for the purposes of a new offence of driving with a specified controlled drug in the body. It was also asked to consider what thresholds for these drugs should be set in regulations to improve road safety. The extent of the road safety problem associated with drug driving was recently presented in the 2010 North report. The House of Commons Transport Select Committee (2010) published a report on its inquiry into drink and drugs driving law. The committee recommended that the Government develop a five-year strategy for tackling drug-driving and the Panel endorsed the development of a strategy which should also encompass the review of drugs for which thresholds might be set in forthcoming legislation.

In its report the expert Panel has considered the scientific evidence related to drug driving in the UK: the prevalence of drug use amongst drivers, the prevalence among road traffic accident drivers and the risk to road safety and other factors that might influence the problem. The Panel has considered how different drugs affect drivers in the general population and in particular the risk of a road traffic accident whilst driving under the influence of these substances. The findings of epidemiological and experimental studies formed a large part of the Panel's discussion about threshold concentration limit in blood. To justify a limit, risk estimates (calculated as odds ratios) were considered alongside the known pharmacokinetics and pharmacodynamics of the drugs. Contextual data on the concentrations of drugs in drivers apprehended in the UK for suspected and witnessed impairment or when involved in a RTA was also available to the Panel.

In most cases, the Panel's recommendations are restricted to the parent drugs and/or active metabolites: so that the presence of a drug above the cut-off concentration generally means that the person will be unfit to drive. However, in some cases, it is necessary to focus on the metabolite, e.g. when the parent drug is unstable and is metabolised very rapidly, e.g. heroin has a half-life of 3 – 6 minutes and its active metabolite 6-acetylmorphine also has a short half-life and is unstable in blood. In that case, morphine is used, but it is also pharmacologically active. Cocaine is also unstable in

blood even when preserved with fluoride, and in this case a threshold for the inactive metabolite benzoylecgonine is suggested in addition to the threshold in cocaine.

The medicinal drugs were a particularly challenging issue. Characterisation of these drugs for drug-driving purposes is conceptually difficult because several different user groups, who use the medication in different circumstances, are involved, including those who legitimately use licensed psychoactive medication; those prescribed psychoactive medication for treatment of drug/alcohol dependence and; those who obtain prescribed psychoactive medication illicitly and use it alone or with other drugs for recreational purposes. When considering thresholds, the Panel looked for clear scientific evidence of risk estimates (expressed as odds ratios) for RTAs. This has included using epidemiological evidence and meta-analysis to assess road safety risk. The Panel has also considered the issue of patients becoming tolerant to psychoactive medication when on long-term stable doses. However, in some cases, for example with regards to benzodiazepines, there is scientific evidence that even compliant patients prescribed benzodiazepine drugs are at increased risk of an RTA when compared to drivers who are not under the influence of these drugs. Risk is especially high during the first 4 weeks of treatment and is particularly increased when medicines are consumed in combination with alcohol. It is important to recognise this and take steps to reduce this risk.

The effects of the 'Z-drugs', so called because they are a group of hypnotic agents which each begins with 'Z' and are used solely in the treatment of insomnia, were also explored by the Panel. Zaleplon was found to be infrequently prescribed and so epidemiological data are limited. The Panel were satisfied that the drug has not been linked to an increased risk of RTA in the scientific literature. On the other hand there is some indication that zolpidem may affect driving behaviour particularly during the first 4 weeks of use and this drug should be kept on the radar for future recommendations. Zopiclone however is a cause for concern. Although not controlled under the Misuse of Drugs Act (1971) and thus outside of the Panel's remit, zopiclone has been reported to have a high RTA risk in epidemiological studies and a meta-analysis reported increased risk estimates (as an odds ratio) for fatal injury (OR: 2.6) and injury (OR:1.6) for zopiclone. The Panel believes that there is sufficient evidence to suggest a need for a threshold to be set for zopiclone as a road safety measure.

In considering what thresholds should be set for common prescription medication, the Panel has looked at the blood concentrations found in those using doses of the drug within a normal therapeutic range used in prescriptions compared to concentrations found in addicts misusing medicines. Where there is a lack of consensus with regard to blood concentrations that pose a risk to driver safety the Panel also looked at concentrations of blood measured in individuals suspected and known to have been driving under the influence of drugs. In relation to morphine, for example, the Panel has recommended a limit which is significantly above the average steady-state concentrations of morphine in blood found in cancer patients prescribed morphine long term doses.

The Panel noted that there had been a considerable increase in poly-drug use by drivers and the road safety risk associated with driving after consuming drugs and alcohol at one time is extremely high. Based on this evidence, the Panel is also recommending that a lower limit should be set for certain drugs where they are found in combination with alcohol, as this combination leads to much greater accident risk when driving than a low concentration of the drug on its own. These lower drug limits are recommended when blood alcohol concentrations above 20 milligram per 100 millilitres (20 mg/100ml) of blood is also detected.

The Panel are aware of the fact that there are drugs with similar pharmacological mechanisms of action to those discussed in this report and which, by analogy, are likely to pose similar impairing effects on driving performance. These drugs include the so-called 'legal highs' designed to mimic the effects of illicit drugs but sufficiently different in chemical structure to (initially) avoid being controlled under the Misuse of Drugs Act. The prevalence of 'legal highs' among drivers or the effects of newer 'designer drugs' on road safety remains unknown and because of their current relatively low usage in the UK, there is often incomplete knowledge of their pharmacokinetics and, especially, insufficient evidence regarding their possible involvement in RTAs. To date odds ratios (ORs) for road traffic accident risk have not been estimated for these compounds. The Panel was unable to establish threshold limits for some newly controlled drugs such as mephedrone.

The Panel strongly endorses the North Report (2010) recommendation that laboratories undertaking forensic work should be encouraged to screen routinely for a

wider range of psychoactive substances so as to establish a more accurate picture of the type of substances prevalent in those suspected of driving under the influence of drugs.

The Panel makes the following recommendations for threshold limits for drug driving:

Drug (short description)	Recommended threshold limit in blood (µg/L)	Recommended threshold limit in blood (µg/L), where more than 20 mg alcohol is also present in 100 ml blood
THC tetrahydrocannabinol (the main active ingredient of cannabis)	5 µg/L	3 µg/L
Cocaine (an illicit drug)	80 µg/L	40 µg/L
BZE benzoylecgonine (the main breakdown product of cocaine in the body)	500 µg/L	<i>no limit recommended for combination with alcohol</i>
Amphetamine (an illicit drug, which is sometimes also prescribed for example for the treatment of Attention Deficit and Hyperactivity Disorder)	600 µg/L	300 µg/L
Methamphetamine (an illicit drug)	200 µg/L	100 µg/L
MDMA 'Ecstasy' (an illicit drug mainly used in a clubbing environment)	300 µg/L	150 µg/L
ketamine (an anaesthetic also misused in a clubbing environment)	200 µg/L	100 µg/L
Morphine (To note: morphine is a breakdown product of heroin)	80 µg/L	40 µg/L
Methadone (a drug with medical uses, prescribed for heroin dependence)	500 µg/L	250 µg/L

Diazepam (a hypnotic drug prescribed for anxiety)	550 µg/L	275 µg/L
Oxazepam (a hypnotic drug prescribed for anxiety)	300 µg/L	150 µg/L
Flunitrazepam (a hypnotic drug prescribed for insomnia)	300 µg/L	150 µg/L
Clonazepam (a hypnotic drug prescribed for anxiety)	50 µg/L	25 µg/L
Lorazepam (hypnotic drug prescribed for anxiety)	100 µg/L	50 µg/L
Temazepam (a hypnotic drug prescribed for anxiety and insomnia)	1000 µg/L	500 µg/L

Whilst it is clear that data on drug-driving does exist there appears to be a lack of routine about its collection, extraction and analysis such that a complete, current picture in the UK has failed to emerge. The Secretary for State should consider adopting a similar system to that in Norway, where blood samples are routinely collected at all RTA following standardised collection procedures and analysed against a universal list of substances: results should be held in a national database. This system would facilitate the evaluation of drug prevalence from a road safety perspective and provide much needed evidence of the consequences of drug-driving.

The Panel are also concerned about the extent of the general public's knowledge and awareness of the risks of driving under the influence of drugs and are therefore also recommending that it is important to strengthen medical information that warns individuals about the risks of consuming drugs and driving, particularly if alcohol had also been consumed concurrently. There should also be efforts undertaken to ensure that healthcare practitioners are better informed about these risks and in turn inform those under their care.

The Panel make the following additional recommendations with regard to drug driving:

Area of interest	Recommendation
Blood sampling	Blood sampling should be undertaken as soon as possible after the incident and an appropriate preservative should be used
Long distance driving (amfetamine-type drugs)	Particular attention should be paid to driver safety initiatives in long distance drivers who may not be aware of the deleterious effects of amfetamine-type drugs
Medical Information (opioids/opiates)	Medical information be provided that informs individuals prescribed medicinal opioids (methadone), medicinal opiates (morphine) and illicit opiates (heroin) about the risks of consuming the drug and driving, particularly if alcohol has also been consumed concurrently
Medical Information (benzodiazepines)	Medical information be provided that informs individuals prescribed benzodiazepines about the risks of consuming the drug and driving, particularly if alcohol has also been consumed concurrently
Medical Information (amfetamines)	Medical information be provided that informs individuals prescribed amphetamines for ADHD about importance of compliance with the dosing regimen particularly if intending to drive and the increased risk to driver safety when alcohol is consumed concurrently
Healthcare providers	Healthcare providers and practitioners should be properly informed and fully conversant with the potential risks associated with the use of controlled medicines and driving
Healthcare professionals	Special attention is paid by healthcare professionals to those on methadone maintenance treatment and who are also prescribed one or more benzodiazepine drugs and intend to drive
Event's organisers	Harm-reduction initiatives are organised to ensure that those attending clubbing/dance/rave/festival events recognise that ketamine, MDMA and other recreational drugs are not safe to consume if intending to drive and that combining drug use with alcohol is contraindicated for safe driving.

MHRA	Clear information should be made available for prescribers, pharmacists and patients about which medicines are not compatible with driving or are only compatible if used in particular circumstances and quantities
Healthcare professionals (Prescribers)	Special attention is paid by healthcare professionals to those >65 years of age who are prescribed one or more opioid/opiate medicine and intend to drive
Public awareness	A programme to raise awareness among the general public takes place with regard to drug use and driving and alcohol when used in combination with psychoactive substances
Laboratories	Laboratories engaged in forensic work should be encouraged to screen routinely for a wider range of illicit drugs so as to establish a more accurate picture of the type of substance prevalent in those suspected of driving under the influence of drugs

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