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Work performed, main results and recommendations

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DRUID partner (see the list of partners pp. 6-7)

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Annex A1 – List of deliverables

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List of abbreviations and definitions

AC	Additional Cost Model
AGL	Amendment Guidelines to FP6 contracts
ATC	Anatomical Therapeutic Chemical
BAC	Blood Alcohol Concentration
CA	Consortium Agreement
CC	Core Contract (Contract No TREN-05-FP6TR-S07.61320-518404-DRUID)
COOR	DRUID Co-ordinator
CPHM	Committee for Medicinal Products for Human Use
DG MOVE	Directorate General Mobility and Transport
DR	Driver Rehabilitation
DRET	Driver Rehabilitation Evaluation Tool
DRUID	Driving Under Influence of Drugs, Alcohol and Medicines
DUI	Driving Under Influence
DUID	Driving Under Influence of Drugs
EAB	Ethical Advisory Board
EC	European Commission
EMA	European Medicines Agency
EU	European Union
FC	Full Cost Model
FCF	Full Cost Model with flat rate
GFI	Guidelines to Financial Issues
GRPF	Guidelines for request for payments form
HCP	Health Care Provider
HFI	Handbook of Financial Issues
HS	Hospital studies
ICADTS	International Council on Alcohol, Drugs and Traffic Safety
ICT	Information and Communication Technologies
IP	Integrated project
OR	Odds ratio
ORs	Odds ratios
OECD	Organisation of Economic Cooperation and Development
OF	Oral Fluid
PIL	Patient Information Leaflet
PL	Package leaflet
PM	Project Management
QA	Quality Assurance
QAB	Quality Assurance Board
QAP	Quality Assurance Plan
QM	Quality Management
QMS	Quality Management System
QRD	Quality Review of Documents
PhVWP	EMA Pharmacovigilance Working Party
PT	Proficiency Test
RH	Rehabilitation
RRT	Round Robin Test (same as PT)
RSS	Road side surveys
SC	Steering Committee
SDLP	Standard Deviation of Lateral Position
SpC	Special Clauses
SmPC	Summary of Product Characteristics
TL	Task Leader
WG	Working Group
WI	Work Instruction
WP	Work Package
WPL	Work Package Leader

Publishable Executive Summary

The DRUID Final Report presents main results of the project and evidence based conclusions relevant for EU and Member States policy makers. The basis for recommendations included in the Final Report is the content of 50 DRUID deliverables (available under www.druid-project.eu) in which research outcomes of the seven project Work Packages (WP) are described in detail.

The Final Report is divided into four main sections: (1) introduction, (2) main research results, (3) conclusions and (4) recommendations.

Section 1 gives an overview of the project objectives, the DRUID consortium and the architecture of project activities.

Section 2 contains the **main research results** of the efforts undertaken within seven DRUID Work Packages. These results are divided in two groups:

- 1) A description of the **problem situation** (results of studies and experiments of the WP1 and WP2) with regard to DUI/ DUID:
 - The data on prevalence of psychoactive substances in the general driving population that was generated within roadside surveys conducted in 13 European countries according to a uniform study design. For this purpose samples of body fluids of approximately 50,000 randomly selected drivers have been analyzed (WP2). The data on prevalence of psychoactive substances in drivers in accidents that was generated from studies in hospitals in six European countries and from data on killed drivers in four countries according to a uniform study design. For this purpose samples of body fluids of approximately 3,600 seriously injured drivers and 1300 killed drivers have been analyzed (WP2)
 - Risk estimates for driving under influence of psychoactive substances have been derived from the case-control studies in which data of the roadside surveys was compared to the data of approximately 4,500 drivers seriously injured or killed in an accident (WP2)
 - Characteristics of drivers tending to drive under the influence of psychoactive substances (WP2)
 - A description of the current state of research on the impact of alcohol, illicit drugs and medicines on driving is given based on DRUID meta-analyses and reviews (WP1)
 - The results of driving tests conducted to close knowledge gaps on major illicit drugs and medicines (WP1)
- 2) Information on **countermeasures** appropriate to combat driving under influence of psychoactive substances (results of activities of the WP3 - WP7):
 - Results of evaluation of oral fluid screening devices and checklists for identifying clinical signs of impairment (WP3)
 - Results of the cost-benefit analysis of increased drug-driving enforcement through traffic police (WP3)
 - A four level classification and labeling system for medicines regarding their influence on driving performance (WP4)

- The most comprehensive database on European rehabilitation schemes and measures as well as on quality assurance measures for rehabilitation programs (WP5)
- A compilation of practices of driving license withdrawal in European countries and recommendations concerning best practice for withdrawal/ licensing strategies (WP6)
- Guidelines for health care professionals on prescribing and dispensing medicines taking into account their impact on driving performance (WP7)
- Recommendations on how to disseminate the DRUID results to different target groups, i.a. general public, young drivers, patients, health care professionals, policy makers (WP7)

Section 3 contains conclusions drawn from the outcomes of DRUID described in the Section 2, including cross-references between different WPs.

Section 4 presents recommendations based on the scientific outcomes of the project. As DRUID focuses on the effects of driving under the influence of alcohol, illicit drugs and psychoactive medicines, recommendations are given with regard to each of these three groups of substances. By describing a countermeasure, target groups that should be addressed by this countermeasure are described as well. Further on, recommendations are given concerning appropriate legal regulations, enforcement strategies, rehabilitation measures and strategies for driver's license withdrawal. Finally, objectives for future research activities are recommended.

Section 1 - Introduction

In order to attain the EU target of significantly reducing fatalities in road traffic, it was necessary to address risks associated with all components of the road transport system: vehicles, roads, infrastructure, and driver performance.

With regard to the latter, an evidence based consensus exists that consumption of psychoactive substances is one of the major factors affecting driving performance and causing accidents. The scientific discussion on this topic was dominated before by the problem of drunk driving. Whereas public concerns with regard to illegal drugs and medicines in traffic were growing, our knowledge five years ago was insufficient to address these concerns.

DRUID was conceived aiming to close this knowledge gap and was implemented as a comprehensive and integrative effort, absorbing all research results achieved in the past and conducting pioneering studies addressing new challenges. DRUID embraced all psychoactive substances, alcohol as well as medicines and drugs. The intention was to analyse all facets of the problem: consumption, impairing effects, accident risk, enforcement and licence withdrawal strategies, rehabilitation and prevention. This approach was substantially new as all prior research studies concentrated on particular problem areas and/or on particular substance groups.

- **Project objectives**

The overall objective of DRUID was to provide scientific support to EU road safety policy makers by making scientific based recommendations concerning combating driving under the influence of psychoactive substances.

DRUID tried to differentiate between problems common for all psychoactive substances and consumers and those typical for a group of substances (or for a single one) or for different target groups. Consequently, measures to combat DUI/DUID that will be developed on the basis of DRUID recommendations, could be either general or targeted, taking into account characteristics of consumers and substances. Special attention was paid to patients consuming medicines.

The first task that DRUID participants decided to implement was a comprehensive state-of-the-art review of research results in the domain of DUI/DUID. It was foreseen to upgrade this pre-existing knowledge with the results of DRUID own original studies and experiments. Project partners planned to establish a brand new theoretical and methodological framework to be used as a platform on which the pre-existing knowledge and results of manifold DRUID studies should be integrated and evaluated.

Epidemiological and experimental studies in DRUID were designed aiming to win new insights in the real scale and danger of consumption of psychoactive substances in traffic across Europe and to try to assess accident risks caused by consumption of most prevalent substances.

The project aimed at assessing possibilities to determine blood concentration thresholds for various drugs analogically to alcohol blood concentration thresholds applied in European countries to combat driving under the influence of alcohol. A major problem to be solved was linking the impairment to the accident risk. Calculating accident risks from epidemiological data is a straightforward approach with face validity. If epidemiological data is sufficient, this approach enables researchers to calculate accident risks related to substance concentrations in body fluids. In case the data is poor (as it is common for most illegal substances and medicines), the impairment approach must be chosen.

One of the DRUID important tasks was practical and scientific evaluation of oral fluid screening devices for drug detection used for enforcement purposes. The project consortium intended to evaluate different enforcement strategies and to conduct cost-benefit analysis of

these strategies aiming to recommend procedures that would facilitate decision making concerning drug enforcement policy.

An important objective of DRUID was to develop an empirically based classification and categorisation system which allows a consistent labeling of medicines with respect to their impact on driving performance and to enable physicians and pharmacists to use this system. The approach is characterised by developing so called 'generic' manual for training health care professionals, based on experiences in Belgium, Spain and the Netherlands.

Rehabilitation programmes for consumers of psychoactive substances were systematically documented and evaluated, taking into account prior experiences. DRUID implemented the most comprehensive study of drivers' rehabilitation systems across Europe, evaluated them and recommended "best practices".

Accompanying the research on prevalence and risk, special emphasis was given to the legal situation in the different European countries, their efforts of combating DUI/DUID and their experience with countermeasures and prevention. It was intended to reveal "best practice" procedures to be recommended to the Member States.

Health care professionals need to be informed about the potential risk associated with the use of any kind of psychoactive substance (illicit drugs, medicines, alcohol). DRUID intended to develop guidelines to make health care professionals aware of their role and to provide them with relevant information. Further on, it was proposed to develop professional standards to address the role of physicians and to involve European professional organisations of physicians in this activity. Adequate training activities were supposed to be designed and tested.

Information about medicines that are likely to affect driving performance, and thus entail a higher risk of being involved in an accident, must be communicated to patients in a manner that ensures the information is fully understood. With this purpose DRUID aimed to evaluate methods of developing information leaflets, public campaigns and web-sites. An important objective was to find ways to apply ICT using the DRUID knowledge in computerised prescribing and dispensing systems.

- **DRUID consortium**

The DRUID consortium united the following 37 partners from 17 member States and Norway:

##	Participant name	Short Name	Country
1	Bundesanstalt für Straßenwesen	BASt	DE
2	TÜV Rheinland Consulting GmbH	TRC	DE
3	Technical University of Denmark	DTU	DK
4	Centre for research and technology Hellas	CERTH-HIT	EL
5	National Institute for Transport and Safety Research	IFSTTAR	FR
6	Université de Caen – Basse Normandie	UNICAEN	FR
7	Motor Transport Institute	ITS	PL
8	Institute of Forensic Research	IES	PL
9	Universiteit Gent	UGent	BE
10	SWOV Institute for Road Safety Research	SWOV	NL
11	KLPD	KLPD	NL
12	Maastricht University, Faculty of Psychology	UMaas	NL

##	Participant name	Short Name	Country
13	University of Groningen, Pharmacy	RUGPha	NL
14	University of Groningen, Psychology	RUGPsy	NL
15	Universidad de Valladolid	UVa	ES
16	Netherlands Organisation for Applied Scientific Research TNO	TNO	NL
17	Statens Väg- och Transportforskningsinstitut	VTI	SE
18	Centrum dopravního výzkumu	CDV	CZ
19	Centre Regional de Pharmacovigilance	UGren	FR
20	Bayerische Julius-Maximilians-Universitaet Wuerzburg	UWUERZ	DE
21	Kuratorium für Verkehrssicherheit	KfV	AT
22	Jefatura central de trafico	DGT	ES
23	Società Italiana di Psicologia della Sicurezza Viaria	SIPSiVi	IT
24	Institute of Transport Economics	TOI	NO
25	University of Turku	U. Turku	FI
26	Norwegian Institute of Public Health	FHI	NO
27	Direkcija Republike Slovenije za ceste ¹	DRSC	SI
28	National Institute for Health and Welfare	THL	FI
29	Institut Belge pour la Sécurité Routière asbl	IBSR	BE
30	Ludwig-Maximilians-Universitaet Muenchen	LMU	DE
31	Universtaetsklinikum Heidelberg	UKL-HD	DE
32	University of Copenhagen	UKBH	DK
33	Institut für Therapieforschung	IFT	DE
34	University of Szeged	USZ	HU
35	U.O.C. Tossicologia Forense e Antidoping – Azienda Ospedaliera-Universita di Padova	TFA-UNPD	IT
36	Centre of Post-Graduated Studies in Legal Medicine of the National Institute of Legal Medicine of Portugal	CPS-NILM	PT
37	Institute of Forensic Medicine, Mykolas Romeris University	TMI	LT
38	Javna agencija Republike Slovenije za varnost prometa	AVP	SI

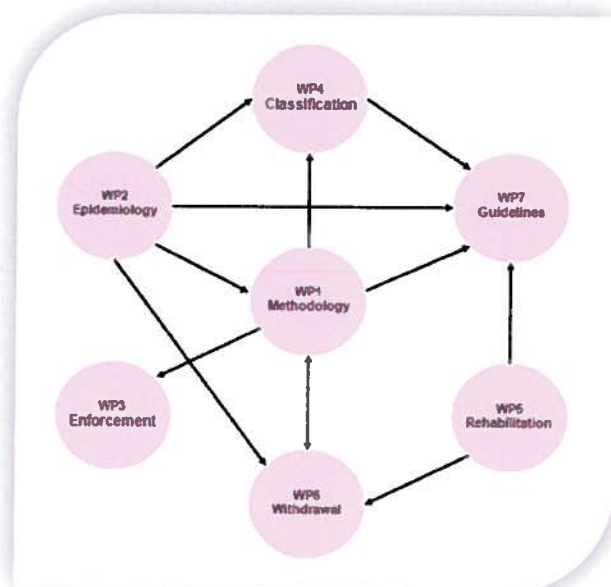
¹ As of 31.08.2010 Javna agencija Republike Slovenije za varnost prometa (AVP) took over rights and responsibilities of the DRSC. For administrative reasons, DRSC stayed an official partner following Commission's request. Thus, AVP became the 38s DRUID partner.

- **DRUID implementation structure**

DRUID was structured objective oriented and aiming to address the following requests of the European Commission:

EC requirements	Work package	Work package content description
To enable policy makers to refer to a substance blood concentration threshold defined for driving a power-driven vehicle	WP 1	Methodology and Experimental Research
To deliver reference studies of the impact on fitness to drive for alcohol, illicit drugs and medicines	WP 2	Epidemiological Studies, Relative Risk Calculation
To evaluate mobile drug detection devices and to implement cost-benefit analysis of enforcement strategies	WP 3	Enforcement: Methods and Devices, Enforceable Legislation
To introduce classification and labeling system for medicines with regard to their influence on driving performance	WP 4	Developing a Classification System for Medicinal Drugs
To provide authorities with recommendations concerning effective drivers rehabilitation schemes, adapted to individual driver's situation	WP 5	Rehabilitation – Good Practice
To recommend strategies of driving bans, which are compatible with the road safety objectives and at the same time respect the need for mobility	WP 6	Withdrawal – Existing Practices and Recommendations
To define responsibility of health care professionals vis-à-vis dangerous patients consuming psychoactive substances and the role they can play with regard to road safety. To develop information and dissemination instruments for different target groups	WP 7	Dissemination and Guidelines, Training Measures

The diagram below shows the input-output and cooperation links between Work Packages:



Section 2 – Work performed and main research results

The DRUID project was an integrative effort to reduce the danger of alcohol, illicit drugs and medicines in traffic. It investigated which problems and countermeasures are common for psychoactive substances as a whole and which problems must be tackled differently with respect to the characteristics of consumers and substances.

In the following section the work performed within five years is summed up. The main results are described. Section 2 is divided into two parts: Part 1 describes the problem situation, which mainly refers to the results of the epidemiological (WP 2) and experimental research (WP 1); part 2 presents countermeasures with respect to enforcement (WP 3), classification of medicines (WP 4), rehabilitation of offenders (WP 5), withdrawal of driving license (WP 6), and dissemination of information to different target groups (WP 7).

1. Problem situation (WP1 & WP2)

The consumption of alcohol, illicit drugs and medicines influences cognitive and motor skills relevant for safe driving and thereby can alter fitness to drive. It was the objective of DRUID to collect all available data on the effects of the different substances on fitness to drive. Data were gathered in epidemiological and experimental studies.

WP1 and WP2 aimed at assessing the situation regarding the prevalence and accident risk of the use of alcohol, illicit drugs, and (psychoactive) medicines of drivers in Europe. Therefore in WP2, two of the major attempts to obtain these insights were the DRUID roadside surveys (D2.2.3) and the DRUID hospital studies on seriously injured and killed drivers (D2.2.5). Of both data on prevalence are available. In order to get risk estimations, both data sources were brought together in the DRUID case-control study (D2.3.5). Based on the prevalence of psychoactive substances in the driving population and of the prevalence of these substances in the ed killed and injured accident victims, risk estimates "odds ratios" of getting seriously injured or killed by driving with psychoactive substances were derived. Results of psychoactive substances already available from published studies were summarized in meta-analyses. This was done for alcohol (D1.1.2a), for major illicit drugs and medicines (D1.1.2b; D1.1.2c) and for opioids used in substitution treatment (D1.1.2c). In addition driving tests were conducted on several illicit drugs (D 1.2.1) and medicines (D1.2.2) in real traffic, in driving simulators and on closed circuits.

Figure 1 gives an overview about the different sources of data used in DRUID in order to derive risk estimations: epidemiological data, experimental data, and meta-analyses.

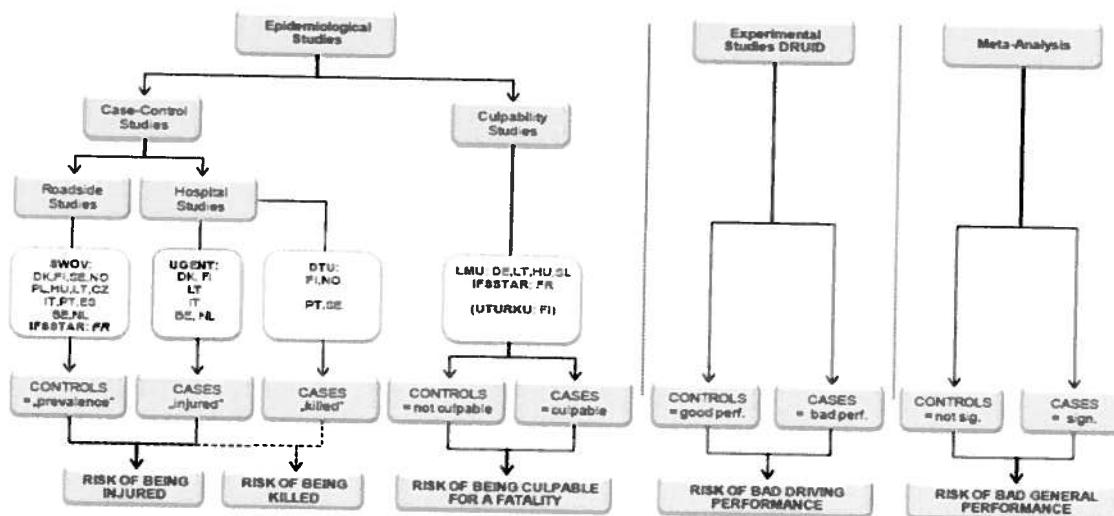


Figure 1: Available sources of data in DRUID (D1.3.1, p. 24).

A methodological framework was developed in DRUID that allowed integration of these different sources of data. It is described in detail in D1.1.1. Its main features are:

- 1) Impairment by alcohol is used as reference. Therefore the current state of research on the effects of alcohol on driving and skills related to driving was summarized in a meta-analysis. In addition in all driving tests an alcohol comparison was done in order to be able to compare all substance effects to those caused by 0.5g/L BAC.
- 2) Odds-ratios are used as common risk measures. Epidemiological studies provide odds ratios as risk measures. All results of experimental studies as well as the results of the meta-analyses were transferred to ORs, too (see D1.1.1 for more details). By doing so ORs could be used as common reference for the comparison of the results of different types of studies.
- 3) Standardization of procedures. In order to be able to integrate the results of studies conducted by different partners, they have to be conducted as similar as possible. Therefore mandatory protocols were developed for the experimental studies (D1.1.1) as well as for the epidemiological studies (D2.1.2). All meta-analyses were also conducted according to a comparable methodology to allow the integration of results.

1.1. Epidemiology

Before DRUID only a few surveys have been carried out in Europe as well as in Australia regarding the prevalence of psychoactive substances in the driving population. These studies were based on saliva samples and indicated similar results for drivers of passenger cars. About 1 % took illicit drugs, primarily cannabis/stimulants. About 4-6 % took licit drugs, primarily stimulants, hypnotics or anxiolytics, or medicines without impairing effects. Recent studies have been carried out in Denmark, Norway, the Netherlands and the United Kingdom, the latter three studies were part of the project IMMORTAL of the 5th Framework Program.

1.1.1. Objectives

The major aim of WP 2 was to assess the increased risk for drivers being involved in a traffic accident after consumption of various psychoactive substances including alcohol. These results were mainly obtained by means of case-control studies. Thus, the results reflect both the most common psychoactive substances in the driving population (prevalence studies) and the accident risks (case-control studies) while impaired by alcohol and other psychoactive substances and/or various combinations. The following objectives were defined:

- **Prevalence of alcohol and other psychoactive substances**
 - in the general population
 - in drivers in traffic in general (road side surveys; RSS), including differences in the patterns of psychoactive substance use between EU countries.
 - in drivers who have been injured/killed in traffic accidents (hospital studies; HS)
- **The relative risk**
 - for a car driver of getting seriously injured or killed in a road accident while positive for alcohol and other psychoactive substances
 - for a responsible car driver of getting involved in a fatal car accident while positive for alcohol and other psychoactive substances
 - for patients using psychotropic medicines of getting involved in an accident

- **Characteristics**

- of drivers impaired by alcohol and other psychoactive substances in the general driving population
- of accident involved drivers
- of general drug users
- of drink and drug drivers

1.1.2. Methodology

In total 25 partners from 15 countries took part in the epidemiological work package, as shown in Figure 2.

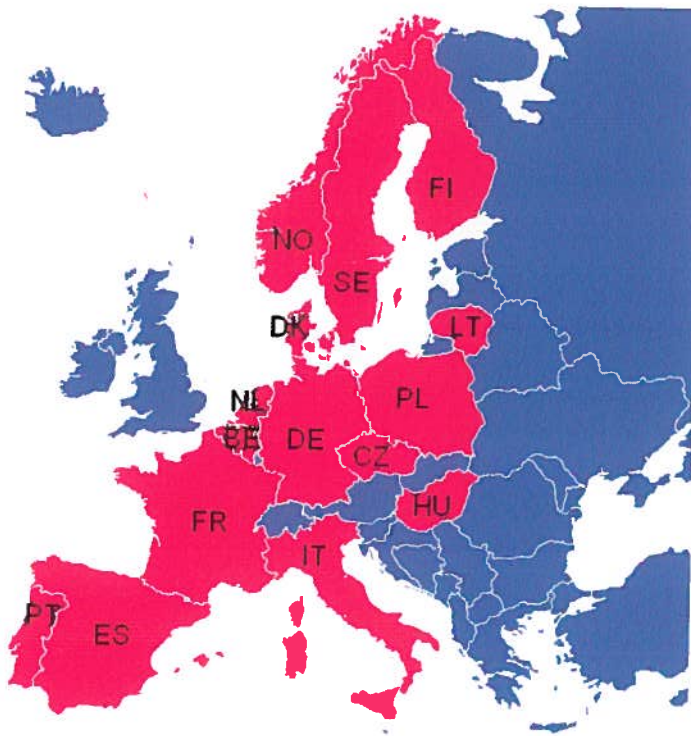


Figure 2: Countries participating in the epidemiological work package.

1.1.2.1. Methodology of the studies on prevalence of alcohol and/or other psycho-active substances

Prevalence of alcohol and/or other psycho-active substances was surveyed in the following populations:

a) The general population

Information on the prevalence of consumption of some frequently used medicines with effects on the central nervous system (i.e. opioids, antipsychotics, anxiolytics, hypnotics and sedatives, antidepressants, drugs used in addictive disorders, and antihistamines for systemic use) in a non-hospitalised EU population was collected over the years 2000 to 2005. In the same way, information on the use of illicit drugs in Europe (i.e. cannabis, amphetamines, ecstasy, LSD, cocaine and crack cocaine, and opioids) was collected of retrospective data from the years 1994 until 2006 (D2.1.1).

b) The general population of car drivers

The prevalence of alcohol and other drugs in the driving population was assessed in thirteen European countries (Belgium, Hungary, Poland, Czech Republic, Italy, Portugal, Denmark, Lithuania, Sweden, Spain, the Netherlands, Finland, Norway) based on road side surveys (D2.2.3). The roadside surveys (RSS) were conducted according to a general design between January 2007 and July 2009.

Participants, i.e. drivers of passenger cars and vans, were randomly selected using a stratified multistage sampling design. In the first stage, one or more regions per country were selected. These regions were meant to be representative for the country with regard to substance use and traffic distribution. Within the selected regions smaller research areas were selected, and within these areas, survey locations were selected, where subjects were stopped at random, and were requested to participate in the study.

Due to voluntary participation non-response and non-response bias are common problems in epidemiological studies. Non-response bias occurs in the case that not responding people differ from those who do respond with regard to drug and/or alcohol use. Since only in Italy the drug tests were mandatory researchers in other countries had to cope with non-response rates. If drivers under influence would be more likely to refuse participation, results of the roadside surveys would underestimate the prevalence rate of psychoactive substances. Underestimation of the prevalence rate among controls will result in overestimation of the risk associated with psychoactive substance use. In order to exclude a selective non-response bias the response and the non-response group were compared for other variables in order to show their comparability.

With regard to days of the week and times of the day, the study population sample was stratified into eight time periods over the week, for each of the survey areas. The time periods did not overlap and covered all the days of the week and all times of the day. The distribution of the study population sample by time periods was not proportionate to the distribution of the general driving population over these periods. This was unavoidable since in many of the thirteen countries the researchers had to take into account the preferences of the police. Police was needed to stop the drivers from moving traffic. Weight factors were applied to correct for this disproportion based on the ratio by time period between the distribution of traffic and the distribution of the participants.

All countries have used a StatSure Saliva Sampler device for saliva collection, except for the Netherlands, where saliva was collected by means of ordinary spit cups. Blood samples were collected in Belgium, Italy, the Netherlands and Lithuania. All four countries used glass tubes for the collection containing sodium fluoride and potassium oxalate.

Extraction of the substances was based on liquid-liquid (LLE) or solid phase (SPE), chromatographic separation was performed by gas chromatography (GC) or Liquid chromatography (LC), detection was done by mass spectrometry.

In total 23 substances were included in the "core substance list". For each substance an analytical cut-off was selected based on the lowest limit of quantitation (LOQ) that could be measured by all toxicological laboratories that were involved in the analysis of the substances. LOQ's reflect the lowest concentrations for substances at which quantitative results can be reported with a high degree of confidence. For the final results presented in this report, equivalent cut-offs, and not the LOQ's, have been used for analysis of the core substances to correct for differences in concentrations of substances in blood and in saliva. Blood was collected in some of the countries (Italy and Lithuania), both blood and/or saliva in two countries (Belgium and The Netherlands), and saliva in the remaining nine countries. Equivalent concentrations for blood and saliva were developed within the DRUID project to be used for the decision on whether a sample was positive for a substance or considered negative (D1.4.2). This means that concentrations of both blood and saliva could be included into the calculations. These equivalent concentrations have not been known before and therefore were developed in DRUID WP2 (Table 1). Equivalent concentrations are an important finding, that solved the problem of two different specimen being collected in the road side surveys.

Table 1: Recommended equivalent cut-offs for DRUID core substances.

Equivalent cut-offs		
Substance	Whole blood (ng/mL)	Oral fluid/saliva (ng/mL)
Ethanol	0.1 (g/L)	0.082 (g/L)
6-AM	10	16
Alprazolam	10	3.5
Amphetamine	20	360
Benzoylcegonine	50	95
Clonazepam	10	1.7
Cocaine	10	170
Codeine	10	94
Diazepam	140	5.0
Flunitrazepam	5.3	1.0
Lorazepam	10	1.1
MDA	20	220
MDEA	20	270
MDMA	20	270
Methadone	10	22
Methamphetamine	20	410
Morphine	10	95
Nordiazepam	20	1.1
Oxazepam	50	13
THC	1.0	27
Zolpidem	37	10
Zopiclone	10	25
Tramadol	50	480
7-amino-clonazepam	10	3.1
7-amino-flunitrazepam	8.5	1.0

In total more than 50,000 drivers of passenger cars and vans from the driving population in the participating countries gave a saliva sample, a blood sample or both samples.

c) Seriously injured and killed car drivers

A cross-sectional survey was conducted to determine the prevalence of alcohol and other drugs in injured (sampled between October 2007 and May 2010) and killed (sampled between January 2006 and December 2009) drivers in 9 European countries. Studies in hospitals of seriously injured car drivers were conducted in six countries (Denmark, Finland, Lithuania, Italy, Belgium, and The Netherlands); studies of killed car drivers took place in four countries (Finland, Norway, Sweden, and Portugal). In order to be able to compare the different studies a uniform design was developed for all participating countries. Obligatory inclusion criteria were: Driver of a motorized vehicle, injured in an accident on a public road or in the direct vicinity of a public road, only primary admissions to the hospital (no referrals), because of traumatological reasons with a time interval between the accident and sampling of less than 3 hours and an injury severity being MAIS 2 or higher. Each country could decide upon additional national criteria.

Drug concentration was analyzed from blood samples. Extraction was based on liquid-liquid (LLE) or solid phase (SPE) extraction, chromatographic separation was performed by gas chromatography (GC) or liquid chromatography (LC): High Performance (HPLC) or Ultra Performance (UPLC). Detection was done by mass spectrometry (MS) or nitrogen/phosphorus detection (NPD). Commonly defined DRUID cut-offs were used to define positivity (Table 2).

Table 2: Whole blood cut-offs for DRUID core substances.

Substance	Whole blood (ng/mL)
Ethanol	0.1 (g/L)
6-AM	10
Alprazolam	10
Amphetamine	20
Benzoyllecgonine	50
Clonazepam	10
Cocaine	10
Codeine	10
Diazepam	20
Flunitrazepam	2
Lorazepam	10
MDA	20
MDEA	20
MDMA	20
Methadone	10
Methamphetamine	20
Morphine	10
Nordiazepam	20
Oxazepam	50
THC	1
THCCOOH	5
Zolpidem	20
Zopiclone	10
Tramadol	50
7-amino-clonazepam	10
7-amino-flunitrazepam	2

Substance concentrations are depending on the pharmacokinetics of the drugs. Therefore the time lag between e.g. the accident and blood sampling has high impact on substance concentration in the sample. In the injured drivers, the maximum delay between the accident and blood sampling was three hours (median = 1.17 hours). The maximum time interval between accident and taking of the blood sample in killed drivers was 24 hours. Since substance concentration diminishes over time the measured concentrations will be lower than the concentration at the time of the accident or at the stop.

Because of the very large interindividual variation in drug metabolism, no back-calculation of the concentration of the drug for the time of the accident was done. In killed drivers, at the time of death, metabolism slows down or stops. But post-mortem redistribution can occur. In order to minimize the risk of post-mortem redistribution, blood was taken from peripheral sites like the femoral vein. This was done if possible by all the centers that participated in the killed driver study.

Fluoride was added to the tubes in order to slow down the degradation of instable drugs like cocaine. A total of 3570 seriously injured drivers and 1293 killed drivers were sampled in this study.²

1.1.2.2. Methodology of the studies on accident risk for driving with alcohol and/or psychoactive substances

Relative risk is defined as the ratio of two risks, the risk of an event occurring in the group of exposed subjects and the risk of the event occurring in the group of non-exposed subjects. The relative risk estimates were approximated to odds ratios, and calculated by means of logistic regression.

Within DRUID, the accident risk while driving under influence of alcohol and other drugs was surveyed in the following populations:

a) The relative risk for a car driver of being seriously injured or killed in a road accident while positive for alcohol and other drugs

The relative risk for a driver of getting seriously injured in an accident while positive for a given substance was approximated to the odds ratio between the odds for a driver of getting seriously injured in an accident while positive for a given substance and the odds of getting seriously injured while negative (D2.3.5). The data from the hospital studies of seriously injured drivers were used as cases. The data from the road side surveys were used as controls (D2.3.5).

As the information whether a subject was exposed to a substance or not came from toxicological analyses of samples from both blood and saliva, it was crucial for this study that equivalent cut-offs for blood and saliva were developed. The risk estimates have been based on blood samples of the injured or killed drivers and on blood and saliva samples collected of the controls in the RSS. Samples were considered positive if the concentration was at or above the equivalent cut-off either in blood or saliva (Table 1). Six countries contributed to the study on the relative risk for getting seriously injured: Denmark, Finland, Lithuania, Italy, Belgium and the Netherlands.

The relative risk as approximated to the odds ratio between the odds for a driver of getting killed in an accident while positive for a given substance and the odds for a driver of getting killed in an accident while negative was calculated by means of logistic regression for the same substance groups as were used in the study of relative risk for seriously injured drivers. Like for the study on the relative risk for drivers of getting seriously injured, the relative risk estimates for killed drivers were based on blood samples collected of killed drivers and on blood and saliva samples collected of the controls in the RSS. Samples were considered positive if the concentration was at or above the equivalent cut-off either in blood or saliva. Four countries contributed to the study on the relative risk of getting killed in an accident: Finland, Norway, Portugal and Sweden.

b) The relative risk of responsibility for a fatal accident while positive for alcohol and other drugs

Relative risk estimates of impaired car drivers involved in fatal accidents were calculated based on a responsibility study in France (D2.3.2). Blood samples from car drivers involved in fatal accidents in the period October 2001 – September 2003, whether killed, injured or non-injured were confirmation analyzed for alcohol and illicit drugs. In total, 7455 car drivers

² See D2.2.4 for more information

were included in the study. The DRUID cut-offs (Table 2) were used as indication for a sample of being positive for a drug. The reference group was car drivers with alcohol concentration below 0.1 g/L. The relative risk estimates were approximated to odds ratios. The relative risk explains the difference in risk of responsibility between sober car drivers (relative risk for the reference group=1) and responsible car drivers who were positive for a substance. The odds ratios were adjusted for age and gender. Similar studies were carried out in other countries (D2.3.3 and D2.3.4)

c) The relative risk for patients using psychotropic medicines of being involved in an accident

The aim of this study was to assess the association between the risk of a traffic accident and the exposure to psychotropic medication by means of a case-control study, a so called pharmaco-epidemiological study. The study was performed in the Netherlands and was based on the linkage of databases regarding pharmacy prescriptions, police registered traffic accidents, hospital records and driving licence data (D2.3.1). The case population was defined as adults, who had a traffic accident between 2000 and 2007 and were driving, and received medical assistance. The control population was defined as adults, who had a driving license and had no traffic accident during the study period. In total, 3963 cases and 18828 controls were selected for the case-control analysis.

1.1.2.3. Methodology of the studies on characteristics of drink and drug impaired drivers

Characteristics of drink and drug impaired drivers were investigated in the following populations:

a) Characteristics of drivers in the general driving population

Results from the road side surveys (D2.2.3) showed for which age groups and gender of drivers various substances were most prevalent. In addition to this, the study includes information on the prevalence by time of the day and week.

b) Characteristics of accident involved drivers

Results from the hospital studies of seriously injured drivers and the studies of killed drivers (D2.2.5) showed for which age groups, gender and time of the day and week various substances were most prevalent in injured drivers.

c) Characteristics of general drug users

The main aim of the study that was carried out in Germany (D2.2.2) was to estimate the prevalence of drugs in drivers in traffic. Instead of detecting drugs in the driving population – like road-side surveys do – 200 illegal drug users and 100 matched control persons (non-users of drugs) were queried for four weeks about their driving and drug consumption behavior by a questionnaire deployed on smart-phones. The questionnaire was filled in daily for 28 days by the persons involved in the study.

The data about drug use and driving not only assessed the frequency of drug driving and other information on the trips, so as time, day, distance and passengers, but also data about situations that led to refraining from driving under the influence of drugs. Finally, the study included information on person-related characteristics, so as socio-demographic variables, previous experience and attitudes. Therefore, also individual factors associated with drug driving could be revealed.

d) Characteristics of drink and drug drivers

Qualitative interviews on motives to drink and drug driving were carried out in Sweden and Hungary (D2.2.1) based on a uniform interview guide. But due to very limited possibilities of recruiting drug drivers in Hungary, the results on drug driving are limited to Sweden.

1.1.3. Results

The presented results refer to the prevalence, the relative risk and the characteristics of drink and drug impaired drivers. Only major results are described.

1.1.3.1. Results of the studies on prevalence of alcohol and/or other psychoactive substances

Prevalence studies were addressed to different populations:

a) The general population

In the general population an increase in the use of medicinal psychotropic drugs and drugs with central nervous system side-effects could be observed. This increase is in line with the results of former studies. The major increase was seen in the consumption of antidepressants and drugs used in addictive disorders. For the other classes of interest either a slight increase or no increase was noted. Illicit drugs are most prevalent among the population in the Southern European countries whereas medicines are most prevalent in the Nordic countries. These data serve as background information for a better understanding of the European problem of illicit drug use and, subsequently, for comparison with the prevalence of illicit and medicinal drug use in the driving population.

b) The general population of car drivers

The prevalence of alcohol and other drugs in the driving population was calculated in thirteen European countries based on roadside surveys. Highest prevalence in general was found for alcohol, with highest prevalence in the southern countries of Europe (Spain, Italy, Portugal). There were big differences between the prevalence in the various countries.

The same tendency for the prevalence in the driving population as for the prevalence in the general population was observed: Higher prevalence of medicinal drugs in the Nordic countries (Denmark, Norway, Sweden, Finland) and higher prevalence of illicit drugs in the southern countries of Europe. However, regarding the prevalence of medicine in the Northern Europe, there were differences in the prevalence between the four countries for the various types of medicines.

In Eastern Europe (Czech Republic, Hungary, Poland, Lithuania) the prevalence of both alcohol, illicit as well as medicinal drugs was relatively low compared to the other European regions whereas drug use in Western Europe (Belgium, the Netherlands) was more or less on the European average. Combined use of alcohol and drugs and multiple drug use was more common in the southern countries of Europe.

For illicit drugs cannabis (THC) was the most frequently detected drug in traffic, followed by cocaine. Amphetamines and illicit opiates were less frequently detected. Illicit drugs were in general mainly detected among young male drivers, during all times of the day but mainly during the weekend.

Medicinal drugs were in general mainly detected among older female drivers during daytime hours. Benzodiazepines were the most prevalent medicinal drug in traffic, z-drugs were less prevalent. However, considerable differences between countries were observed.

On a European level alcohol was estimated to be found in 3.48% of the drivers, illicit drugs by 1.90% of the drivers, medicinal drugs in 1.36% of the drivers, drug-drug combinations in 0.39% of the drivers and alcohol-drug combinations in 0.37% of the drivers. However there were big differences between the means in the four European regions (North, South, West, East). There were high prevalence rates of alcohol, cocaine, cannabis and combined use in Southern Europe, partly also in Western Europe, whereas z-drugs and medicinal opioids were more common, although still low prevalent, in the northern countries.

c) Seriously injured and killed car drivers

The prevalence of alcohol alone was between app. 15 and 30% except for Portugal (40%). Alcohol in combination with other drugs was found in 12% of the samples in Belgium down to about 2% in Lithuania. Furthermore, the following remarks characterize alcohol use: For seriously injured drivers, the highest percentage of positive drivers was found in Belgium (alcohol alone in app. 30% and alcohol combined with other drugs in app. 12.5% of the drivers). For killed drivers, the highest percentage of positive drivers was found in Portugal (alcohol alone in app. 40% and alcohol combined with other drugs in app. 6% of the drivers). Among the positive drivers – both seriously injured and killed, the majority had a blood alcohol concentration equal to or above 0.5g/L.

The prevalence of illicit drugs varied between the countries with considerable combined use of various substances. Amphetamine use appeared to be more common in Northern Europe, both for seriously injured and killed drivers. In Portugal, no killed drivers were positive for amphetamines. Cocaine use seemed to be more prevalent in Southern Europe, except for killed drivers in Sweden. In Finland neither any seriously nor killed drivers were positive for cocaine. The percentages of cannabis (THC and THCCOOH) positive drivers varied, with the highest percentage in seriously injured drivers in Belgium (app 10% alone and in combination with other drugs) and the lowest in Lithuania (below 1% alone and in combination with other drugs). For killed drivers the highest percentage was found in Norway (app 6% alone and in combination with other drugs) and the lowest in Finland (app 1.3% but only found combination with other drugs). No illicit opiates were found in the killed drivers.

Regarding medicines a few countries had outstanding high prevalence, that is for benzodiazepines alone in seriously injured drivers in Finland (app. 10%) and for medicinal opioids alone in Lithuania in seriously injured drivers (close to 6%). Furthermore, the following remarks characterize medicinal drug use: Benzodiazepine use appeared to be more common in Northern Europe, both for seriously injured and killed drivers, with a maximum for Finland both for seriously injured drivers (app. 10%) and for killed drivers (app. 5%). In the Netherlands no seriously injured drivers were positive for benzodiazepines. Z-drug use was mostly found in Northern Europe. No positive findings for Z-drugs were recorded in Italy, Lithuania and Portugal. Medicinal opioids were found in all countries, with a maximum for seriously injured drivers in Lithuania (app 6% alone and 2% in combination with other drugs) and a minimum in the Netherlands (app 0.5%, only found alone). In Lithuania the percentage of seriously injured drivers who were positive for medicinal opioids was twice as big as in the other five countries. Similar, in Sweden the percentage of killed drivers who were positive for medicinal opioids was twice as big as in the other three countries.

1.1.3.2. Results of the studies on accident risk for driving under the influence of alcohol and/or psychoactive substances

The results of the studies on accident risk for driving under the influence of alcohol and/or psychoactive substances refer to three different types of risk estimates. The relative risk estimates were adjusted by age and gender (when there was enough data); if there was not enough data the crude odds ratio were calculated.

a) The relative risk for a car driver of being seriously injured or killed in a road accident while positive for alcohol and other drugs (D2.3.5)

The data from the hospital studies of seriously injured/killed drivers were used and as cases. The data from the road side surveys were used as controls (D.2.3.5). The relative risk for alcohol varied considerably between countries. The relative risk of getting seriously injured was not significantly different from 1 for alcohol concentrations between 0.1-0.49g/L. For killed drivers, the relative risk was already from 0.1g/L significantly above 1. All estimates in

this section are based on data from all countries using the results of the analyses with adjusted odds ratios. The estimate based on data from all countries indicated a risk of getting seriously injured of 1.18 (CI: 0.81-1.73) and the risk of getting killed in an accident of 8.01 (CI: 5.22-12.29). For alcohol concentrations in the interval 0.5-0.79g/L, the relative risk of getting seriously injured was significantly increased for some of the countries (Denmark, Finland and the Netherlands) and for killed drivers in Norway and Portugal. The estimate based on data from all countries indicated a risk of getting seriously injured of 3.64 (CI: 2.31-5.72) and a risk of getting killed of 45.93 (CI: 23.02-91.66). For alcohol concentrations at 0.8g/L and above all risk estimates except for Italy were significantly above 1. For alcohol concentrations between 0.8-1.19g/L, the estimate based on data from all countries indicated a risk of getting seriously injured of 13.35 (CI: 8.15-21.88) and a risk of getting killed in an accident of 35.69 (CI: 15.68-81.22). For alcohol concentrations from 1.2g/L and above, the estimate based on data from all countries indicated a risk of getting seriously injured of 62.79 (CI:44.51-88.58) and a risk of getting killed of 500.04 (CI: 238.07-inf).

Amphetamines alone were too rare in some of the countries to enable the calculation of the relative risk of getting seriously injured or killed. However the relative risk of death in an road accident was considerable increased for Finland, Norway and Sweden. The estimates based on data from all countries indicated a risk of getting seriously injured of 8.35 (CI: 3.91-17.83) and a risk of killed drivers of 24.09 (CI: 9.72-59.71). The variations in the risk estimates reflect sparse data with positive concentrations. The results should therefore be handled with care.

For cocaine alone there were only few positive samples, and the risk estimates for the single countries varied to a high degree without being significantly above 1. On the contrary, this was the case when calculating the risk based on all countries with the estimate indicating a risk of getting seriously injured of 3.30 (CI: 1.40-7.79) and of getting killed of 22.34 (CI: 3.66-136.53).

The relative risk estimates for cannabis (THC), based on single countries were only significantly increased for some of the countries but varied between countries to a high degree. However, based on data from all countries the relative risk of getting seriously injured and killed while positive for cannabis were not significantly above 1 with a risk of getting seriously injured of 1.38 (CI: 0.88-2.17) and the risk of getting killed of 1.33 (CI: 0.48-3.67). But this result should be handled with care because of the very different single country estimates.

Positive samples were few for illicit opiates, and therefore the risk estimates should be handled with care. Risk estimates significantly above 1 for the single countries were only found for fatal injured drivers. The estimate based on data of all countries indicated a significantly increased risk of killed drivers (crude odds ratio) of 10.04 (CI: 2.04-49.32). The estimate based on data from all countries of getting seriously injured of 2.47 (CI: 0.50-12.10) was not significantly increased. The variations in the risk estimates reflect sparse data with positive concentrations.

The estimates of the relative risk of getting seriously injured or killed while positive for medicines were not very different between most of the participating countries. However, the confidence intervals were very large for some of the estimates.

Some of the risk estimates based on calculations of data from single countries were significantly above 1. However, based on aggregated data of all countries, both the relative risk of getting seriously injured and the relative risk of getting killed were significantly above 1 for benzodiazepines, Z-drugs and for medicinal opioids. The estimate for benzodiazepines and Z-drugs of getting seriously injured was 1.99 (CI: 1.36-2.91) and of getting killed 5.40 (CI: 3.90-7.46) based on data from all countries. The estimate for medicinal opioids of getting seriously injured was 9.06 (CI: 6.40-12.83) and of getting killed 4.82 (CI: 2.60-8.93) based on data from all countries.

The estimates of the relative risk of getting seriously injured or getting killed while positive for combinations of alcohol and/or drugs were considerably increased in nearly all countries. Based on aggregated data of all countries, the relative risk of getting seriously injured or killed while positive for alcohol and drugs was substantially increased. The same was the case for multiple drug use. The estimate of getting seriously injured while positive for alcohol and drugs was 28.82 (CI: 18.41-45.11) and of getting killed 31.52 (CI: 16.83-59.05) based on data from all countries. The aggregated estimate of getting seriously injured while positive for multiple drugs was 8.01 (CI: 5.34-12.01) and of getting killed was 18.51 (CI: 10.84-31.63) based on data from all countries.

Based on risk estimates calculated of aggregated data of all countries involved and the risk estimates calculated for the single countries, an overall assessment of the magnitude of the relative risk was done. The result by substance group is shown in Table 3.

Table 3: Relative risk level of getting seriously injured or killed in an accident for various substance groups.

Risk level	Risk	Substance group
Slightly increased risk	1-3	0.1 g/L ≤ alcohol in blood < 0.5 g/L Cannabis
Medium increased risk	2-10	0.5 g/L ≤ alcohol in blood < 0.8 g/L Cocaine Illicit opiates Benzodiazepines and Z-drugs Medicinal opioids
Highly increased risk	5-30	0.8 g/L ≤ alcohol in blood < 1.2 g/L Amphetamines Multiple drugs
Extremely increased risk	20-200	Alcohol in blood ≥ 1.2 g/L Alcohol in combination with drugs

Cannabis and amphetamines: due to very different single country estimates, the risk estimate must be treated with caution.

Benzoyllecgonine, cocaine and illicit opiates: due to few positive cases and controls, the risk estimates must be treated with caution.

The highest risk was associated with high blood alcohol concentration and alcohol combined with other psychoactive substances. Other problem groups were medium alcohol concentrations, multiple drug use and driving with amphetamines. Medium increased risk was assessed for alcohol concentrations between 0.5 and 0.8g/L, for cocaine and for the medicines included in the study. The risk associated with cannabis was assessed to be similar to the risk of driving with a low alcohol concentration. However, it should be noted that the risk estimates for illicit drugs were based on small numbers of positive samples and should therefore be handled with care.

b) The relative risk of responsibility for a fatal accident while positive for alcohol and other drugs (D2.3.2)

For amphetamine, cocaine and opiates, adjusted odds ratios of responsibility were not significantly different from 1. This means that the risk of responsibility for positive drivers was not significantly different from that of sober drivers.

Among car drivers, positive cannabis detection was found to be associated with increased risk of responsibility. A significant concentration effect was identified. The effect of cannabis remained significant after adjustment for age, gender and alcohol: adjusted odds ratio was 1.89 (CI: 1.43-2.51).

For alcohol (≥ 0.1 g/l), adjusted odds ratios of responsibility were much higher than those associated to cannabis: adjusted odds ratio for alcohol was 8.39 (CI: 6.95-10.11).

No interaction was statistically significant between alcohol and cannabis. This means that the odds ratio of responsibility associated to being positive to both cannabis and alcohol is merely the product of the respective odds ratios of cannabis and alcohol alone.

c) The relative risk for patients using psychotropic medicines of being involved in an accident (D2.3.1)

The pharmacoepidemiological study that was performed in the Netherlands showed an increased accident risk for drivers exposed to at least one psychotropic medication of 1.28 (CI: 1.1 - 1.5). The risk was found to be higher for drivers in combination therapy, namely 1.55 (CI: 1.2 - 2.0) and users of modern antidepressants, namely 1.76 (CI: 1.4 - 2.2). The highest risk groups were new users, intermediate and long half-life benzodiazepine users, female users, and young/middle-aged users, although only some of the trends in elevated risk were statistically significant.

The increased relative risks found in this study indicate that psychoactive medications can constitute a problem in road safety. Therefore, both health care providers and patients should be properly informed and aware of the potential risks associated with the use of these medications.

1.1.3.3. Results of the studies on characteristics of drink and drug impaired drivers

Characteristics of drink and drug impaired drivers were investigated in the four following populations:

a) Characteristics of drivers in the general driving population

Results from the road side surveys (D2.2.3) showed for which age groups and gender of drivers various substances were most prevalent. Additionally information on the prevalence by time of the day and week were given.

As expected, the prevalence of alcohol was significantly higher for male drivers than for female drivers. In most countries the prevalence of alcohol-positive drivers was highest for the two oldest age groups (35-49 and ≥ 50 years). This was both the case for male and for female drivers.

For alcohol concentrations equal to and above 0.1 g/L, the prevalence was significantly different in different time periods. As expected, the highest prevalence was on weekend nights whereas the lowest was on weekend days. But surprisingly, there was no difference in prevalence of concentrations at and above 0.5 g/L over the various time periods.

Amphetamines were mainly used by drivers younger than 35 years. In some countries this drug was more prevalent among male drivers and in other countries more prevalent among female drivers. The distribution of amphetamines by time period differs between countries.

Cocaine was mainly found in male drivers and in general, the prevalence of cocaine was very low, but varied significantly by age and country. Cocaine was most prevalent among male drivers aged 25-34 years, and least prevalent in the age group 50 and above. Cocaine was detected during all time periods.

Cannabis seemed to be a weekend drug mainly used by young male drivers. There was a significant difference in the prevalence of cannabis in different time periods, most prevalent in weekend days and least prevalent in weekend mornings. However, cannabis was found during all days and hours of the week in most countries.

Illicit opiates were most often used by male drivers aged 35 to 49 years, except for Belgium where most users were younger than 25. Illicit opiates were not detected among drivers from northern European countries (Denmark, Finland, Norway and Sweden) and from eastern European countries (Czech Republic, Lithuania, Poland and Hungary).

Benzodiazepines were in general most prevalent in drivers aged 50 and above and significantly more prevalent than in the youngest age group (18-24 years) where they were least prevalent. However, in Italy most benzodiazepines were used by young drivers aged 18-24. In contrast to cannabis, benzodiazepines were drugs that were mainly prevalent in mature female drivers and during daytime. Thus, prevalence was significantly different over the time periods; it was most prevalent in the daytime during weekdays and least prevalent in the evenings of the weekdays.

Z-drugs were not found in Southern Europe. Most drivers positive for Z-drugs were 50 years and older, except for Hungary where all drivers were between 25 and 34 years old. Z-drugs were most often detected during daytime hours at weekdays. In none of the countries Z-drugs were found in weekend nights.

Medicinal opioids were distributed in a similar way as benzodiazepines: their prevalence differed significantly with age, being most prevalent in the age group 50 and above and least prevalent in the youngest age group (18-24). Like benzodiazepines, they were significantly more prevalent among female than male drivers. In general, the highest prevalence was detected during daytime hours.

Alcohol in combination with drugs had a significantly different prevalence among age groups; the age group of 25-34 years had the highest prevalence and the age group of 50 and above the lowest. In general the prevalence for alcohol-drug combinations for male drivers was higher than for female drivers. There was a significant difference in prevalence over the time periods; thus the combination of alcohol and drug(s) was most prevalent in daytime of the weekend and least prevalent in daytime of the weekdays.

Multiple drug prevalence was significantly different among countries; it was most prevalent in Spain and Italy and least prevalent in Denmark, Poland and Sweden. Drug-drug combinations were most frequently detected among younger drivers. The distribution over the four age groups varied largely between countries. In general multi-drug use was more common among male than among female drivers. There was no significant difference in prevalence over time periods.

b) Characteristics of accident involved drivers

Results from the hospital studies of seriously injured drivers and the studies of killed drivers (D2.2.5) showed for which age groups, gender and time of the day and week various substances were most prevalent.

As for time periods, in both studies, higher percentage of positives were normally found among drivers involved in accidents that occurred at night time, either during the week or the weekend, compared to percentages of positive drivers found among subjects involved in accidents during daytime. Lithuania was the only country in which the lowest percentage of positive drivers was found during week nights.

A significant difference was found between gender both for seriously injured drivers and for killed drivers. In general, the prevalence in male drivers was higher than in female drivers.

Both for male drivers in the group of seriously injured drivers and in the group of killed drivers, the group aged 25-34 was the one that had the highest percentage of positive subjects, except for seriously injured drivers in Lithuania and killed drivers in Finland.

Alcohol was mostly found in the younger age groups of males for seriously injured drivers, whereas in the sample of killed drivers, alcohol was also present in mature drivers.

Cannabis was most prevalent in the younger age groups of male drivers, both for seriously injured drivers and killed drivers.

Amphetamines, cocaine and illicit opiates were most prevalent in younger age groups of male seriously injured drivers, whereas the three substance groups were also common in mature killed drivers.

Benzodiazepines were mostly present in male drivers in the sample of seriously injured drivers, but were prevalent for all age groups, both for seriously injured drivers and killed drivers. The diffusion of this substance group among both gender and all age groups may be explained by the various therapeutic uses, different benzodiazepines being prescribed, among others, for the treatment of anxiety disorder, sleeping disorders and epilepsy.

Z-drugs appeared to be more common in Northern Europe. They are not used at all in Southern Europe. Use of these medications was recorded in both genders, and apparently more frequent in the older age groups starting from 35 years.

Medicinal opioids were also most prevalent in the northern countries. However, there was no clear picture regarding age and gender.

c) Characteristics of general drug users

The smart-phone study (D2.2.2) revealed that 20.5% of the drug users' drives were under the influence of drugs, with cannabis as the most prevalent drug, followed by alcohol. Other stimulants or multiple drug use only counted for small percentages.

The results showed various differences between drug users and non-users, e.g. the time they went to bed, was at a later time of the evening for drug users than for non-users, and in the same way drug users got up later in the morning compared to non-users. In the evenings, drug users stayed out more often at private locations (i.e. at friends) whereas the non-users more often visited public locations.

In general, drug users were more mobile at night compared to the non-users, who were more mobile at usual rush-hour times indicating a daily working routine. But, compared to non-users that were less mobile during night time, the drug users had less night time trips by car than the non-users. The drug users seemed to compensate by using alternative modes of transportation at these hours.

Regarding alcohol consumption, the drug users consumed alcohol more frequently and in higher doses than the non-users and had the double prevalence of drink driving than the non-users.

High consumption frequency proved to be a striking predictor for frequent drug driving and highly impaired driving in general, since most substance-positive drives and drives with high blood concentrations were made by excessive substance users compared to moderate or heavy drug users.

For alcohol, the subjective feeling of impairment increased with increasing blood alcohol concentration, whereas for cannabis this relation was only found for moderate to heavy cannabis users. This indicates that especially moderate substance users are able to judge their intoxication more realistically. They can be described as being responsible-minded concerning drugs in traffic. This assumption was derived from a lower number of drives under the influence, lower blood concentrations on drug drives and a subjective feeling of impairment depending on the actual intoxication in those users.

Other influencing factors were the perceived risk of detection by the police, the distance to drive, the availability of alternative transport modes and the presence of companions. The results also indicated that male drivers less often drive under the influence in case they have female companions.

Finally, based on German criminal records and self-reported dangerous traffic situations within the study period, it was demonstrated that the drug users did not seem to be more at risk than the non-users. So, except from driving under the influence, there was no evidence that the drug-users showed risky driving behaviour in traffic.

d) Characteristics of drink and drug drivers

The qualitative interviews on motives to drink and drug driving were carried out in Sweden and Hungary (D2.2.1). The results showed that the interviewees belonged to a very specific group of people who were addicted to alcohol and or other drugs. Normal sanctions did not prevent their driving while intoxicated and this applied to participants from both Sweden and Hungary, partly because they perceived themselves to have very little control over their behavior, partly because they did not believe that they would be stopped by the police. Those who had been stopped pointed out that this had happened because the police were carrying out a routine control, and not because they had driven in an unsuitable way.

The interviewees did not believe that alcohol or drugs would impair their driving and therefore they did not perceive any real risks of driving. However, one important difference between drugs and alcohol was that drugs were believed to make them a *better* driver whereas alcohol did not make them any worse. Thus, drug driving was not regarded as an offence in the same way as drink driving.

Following this, respondents who had been caught for drink driving expressed more feelings of shame than those who had been caught for drug driving. This was partly because of the offence itself but, as mentioned before, it had more to do with having to admit to others that they had been drinking and driving and could not control their drinking. Feelings of shame appeared not to be related to a feeling that the act itself could result in an accident but somewhat related to if their friends and relatives disapproved. The same feelings were not expressed by the drug drivers, only later when they were under treatment and they looked back at their life did the feeling of shame and anguish emerge.

The participants whose drinking and driving was related to problems with alcohol would argue that losing the license or even to be imprisoned would not have helped them to stop re-offending. Instead, it was the treatment program which had helped them by providing a greater insight into their own problems.

1.2. Experimental studies and Meta-analyses

A second approach to explore the problem situation of impaired driving was to conduct experimental studies and meta-analyses. In addition to the epidemiological research which helps to provide a broad overview of the situation experimental research examines specific problems in more detail (e.g. effects of a specific psychoactive substance used by a specific group of subjects in determined driving situations).

1.2.1. Objectives

Experimental studies and meta-analysis were conducted in WP1. The objectives of this Work Package were³:

1. Providing an overview about the state-of-the-art of research results in the domain of DUI/DUID with a special focus on impairment caused by alcohol;
2. Closing existing research gaps by conducting driving tests by using a standardized procedure that allows the comparison of the research results;

1.2.2. Methodology

The experimental work and the meta-analyses were conducted according to a standardized procedure.

a) Meta-analyses

When a sufficient number of published studies on a certain psychoactive substance is available, those studies can be summarized by a meta-analysis. In DRUID this was done for alcohol, major illicit drugs and medicines.

The **meta-analysis on alcohol** (D1.1.2a) comprises experimental studies published until 2007. A total number of 450 papers in which 5,300 findings concerning alcohol effects on (driving) performance, social behavior or mood are described were included. For every finding the presence or absence of a significant alcohol effect is coded. From a meta-analytic perspective, this procedure belongs to the method of vote counting. This means the significant findings of effects are summarized for each group of dependent measures for the same range of BAC. The impairment function derived from the meta-analysis (Figure 3) is used to determine the concentration of psychoactive substances causing the same impairment as certain BAC levels. Therefore the percentage of significant findings in those studies, derived from the meta-analyses of medicines and major illicit drugs, is compared to that of alcohol (Figure 4). By doing so the substance concentration can be determined at which the same percentage of significant findings exists as for the different BAC levels.

In the **meta-analysis of medicines and illicit drugs** (D1.1.2b) 605 publications with a total number of 13 191 findings were included, that fulfilled certain quality criteria. Only experimental studies with single oral administration to healthy subjects were included into this meta-analysis, because studies with either multiple administration to healthy subjects or with administration to patients are very rare and therefore cannot be analyzed in a meta-analytic approach. This meta-analysis provides information about the impact of antipsychotics, anxiolytics, hypnotics, sedatives, antidepressants, antihistamines, and major illegal drugs (see the detailed list of agents in Table 4) on driving and skills related to driving.

³ The methodological framework is outlined at the beginning of section 2. An integrated summary of all outcomes of DRUID is given in section 3. Recommendations from a scientific point of view are given in section 4. Therefore the focus here will be on the experimental studies and the meta-analyses.

For opioids mainly used in substitution treatment for opioid addicts (morphine, methadone, and buprenorphine), narcoanalgetics, and hallucinogens too few published studies were available. Therefore it was not possible to summarize those results by a meta-analysis. Instead a **review** was done for the effects of these agents on driving and skills related to driving (D1.1.2c).

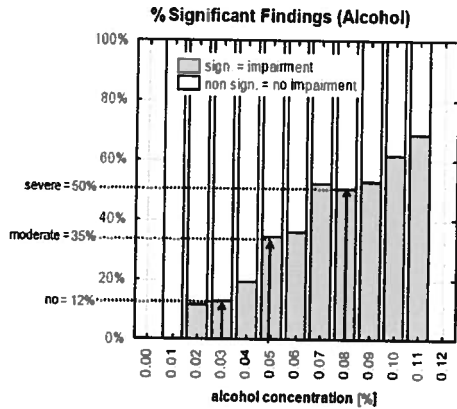


Figure 3: Using BAC levels (e.g. 0.3g/L, 0.5g/L and 0.8g/L) to determine categories of impairment by fixing the percentage of significant findings in the meta-analysis.

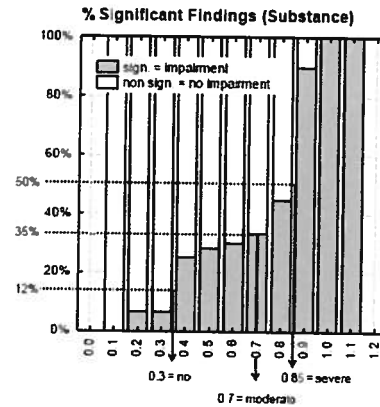


Figure 4: Application of the impairment categories for alcohol (no = 0.3g/L, moderate = 0.5g/L and severe impairment = 0.8g/L) to determine the substance concentrations causing an equivalent effect as the three BAC levels.

Table 4: Meta-analytically evaluated psychoactive substances in D1.1.2b (sorted by number of studies per substance group in descending order; D1.3.1 p. 51).

Class	Substance Name	n studies	n effects	n effects/n studies	
Anxiolytics	diazepam	103	2104	20.4	
	lorazepam	68	1244	18.3	
	oxazepam	26	377	14.5	
	alprazolam	21	354	16.9	
	meprobamate	17	313	18.4	
	bupropion	16	341	21.3	
	clobazam	16	287	17.9	
	bromazepam	9	202	22.4	
	chlordiazepoxide	9	101	11.2	
	Hypnotics & Sedatives	triazolam	46	1305	28.4
nitrazepam		44	417	9.5	
zopiclone		31	857	27.6	
temazepam		30	895	23.2	
flunitrazepam		29	491	16.9	
flurazepam		22	203	9.2	
zopiclone		21	331	15.8	
Antidepressants	lormetazepam	13	161	12.4	
	zaleplon	12	350	29.2	
	brotizolam	6	78	13	
	Anti-psych.	promethazine	11	236	22.8
		haloperidol	10	228	21.5
		subprinde	8	88	10.6
	Antidepressants	amitriptyline	32	475	14.8
		imipramine	13	210	16.2
		mianserin	8	145	18.1
		trazodone	8	146	18.3
paroxetine		6	118	19.7	
fluoxetine		5	150	30	
Antihist. amines		diphenhydramine	58	982	17.2
	terfenadine	16	259	16.2	
	triprolidine	14	233	16.6	
	loratadine	13	213	16.4	
	fenofenadine	5	170	34	
Drugs	THC smoking	234	2664	11.4	
	THC oral admin	63	1448	23	
	d-amphetamine ²²	20	416	20.8	

Dose related information is highly relevant for healthcare providers as well as for patients because they need to know for certain agents which dose might have an impact on driving ability. Therefore the effects were evaluated with respect to the dosages and the corresponding impairments found in the studies. An approximation procedure was applied and the following parameters were calculated:

- dosage that causes the maximum impairment,
- time span after application when the impairment is highest,
- BAC that is equivalent to the maximum impairment,
- duration of the impairment,
- degree of impairment.

In order to relate the impairment to the concentration of the substance in blood, a meta-analysis of pharmacokinetic studies was done. This led to approximated concentration curves in time course for different substances and different substance concentrations. Using this approximation the blood plasma concentration of a substance could be estimated by knowing the dose of the substance administered and the duration between the time the substance was administered and the time the performance test was done.

b) Driving test (Experimental studies)

13 driving tests were conducted (Table 5) according to a standardized procedure.

Table 5: Overview of psychoactive substances examined in the driving tests (WP1).

No.	Substance / Participants
1	Mdma (100 mg) with and without alcohol (0.5.g/kg)
2	Dexamphetamine (10mg) with and without alcohol
3	Mdma (25, 50 and 100mg) before and after a night of sleep deprivation
4	Dexamphetamine (10 and 40 mg) before and after sleep deprivation
5	Zopiclone in patients and controls
6	Medicated vs. unmedicated insomnia patients
7	Alprazolam (0.5 mg) in anxious patients
8	Treated vs. untreated sleep apnea patients (CPAP)
9	Codiliprane and zolpidem in elderly drivers: alone and in combination
10	Codiliprane in healthy volunteers
11	Dronabinol in light and heavy users of THC
12	Opioid analgesics in chronic pain patients
13	Risperidone/paliperidone in patients diagnosed with psychosis

All studies on the impact of illicit drugs were conducted according to placebo controlled, double-blind, within-subjects study designs. All studies employed representative subject samples, i.e. recreational users of MDMA, patients who went through a strict medical screening and selection procedures. Most of the studies employed cross-over designs which were preferred for their efficiency while providing maximal statistical power with relatively small sample sizes. Most studies were conducted in real traffic, some in advanced driving simulators. Due to the national legal and ethical restrictions, one experiment had to be conducted in a closed circuit.

Driving tests on the effects of illegal drugs were conducted at Tmax, i.e. when drug concentrations were maximal and, in case of sleep deprivation, also in morning after a night of sleep loss. More details on study designs, screening, subject characteristics, and in- and exclusion criteria can be found in the study reports in D1.2.1 and D1.2.2.

All studies were adhered to a set of mandatory settings of which the most important were:

- Number of subjects: the minimum number of subjects was 16. The choice for a subjects' sample-size was always corroborated by a statistical power analysis.
- Subject selection: studies with MDMA and dexamphetamine only included recreational users of these drugs. Drug-naive, healthy volunteers were excluded.
- Drug screens: subjects were always tested for drugs in urine prior to testing
- Alcohol screens: subjects were always tested for alcohol (breath) prior to testing
- Driving experience: subjects needed to have a driver's license
- Training sessions: all subjects received training sessions of actual driving tests, simulator driving tests and/or laboratory performance tests in order minimize learning effects. Training was performed by all subjects to achieve a stable performance level prior to study entrance.
- Subjective measures: e.g. alertness, mental effort, etc.
- Ethics: all partners obtained study approval from their local (and national) ethics review boards and conducted their study according the declaration of Helsinki and Good Clinical Practice.
- Alcohol calibration: For all parameters alcohol effects on driving were used as a standard reference to quantify the amount of impairment. Therefore all partners conducted a placebo-controlled alcohol study in order to calibrate their primary driving parameters for the effects of BAC 0.5 g/L. Any drug induced performance change > performance change induced by BAC 0.5 g/L was qualified as a clinical relevant drug effect. Drug effects equal to those produced by a BAC of 0.5 g/L were also considered to define the "threshold" of impairment for an individual drug. Drug effects were tested for comparability to BAC 0.5 g/L effects by means of equivalence testing.
- Toxicology: in all studies whole blood, serum and blood spots were collected for determining concentrations of the investigated active agent.
- Statistics: the statistical analyses consisted of 2 steps: 1) assessment of overall treatment effect by means of superiority testing; 2) equivalence testing of drug effects relative to the alcohol criterion.
- Standard set of driving parameters and driving scenarios. These driving parameters basically covered 3 core levels of driving behaviours: Automated behaviours – well-learned (over-learned) skills, controlled behaviours – controlled manoeuvres in traffic, executive, strategic behaviours - interactive functions with ongoing traffic, planning, risk taking.

Road tracking scenario

The road tracking scenario was based on the Road Tracking Tests that has been used in the Netherland in over 100 studies for measuring drug effects on driving (O'Hanlon et al., 1982). Participants were required to drive a 100km course maintaining a constant speed of 95 km/h and a steady lateral position in traffic lanes. The primary driving measure was the standard deviation of lateral position or SDLP. SDLP is an index of road tracking error or weaving, swerving and overcorrecting.

SDLP was measured using an electro-optical device mounted on the rear of the vehicle which continuously records lateral position relative to the traffic lane. An increase in SDLP, measured in centimetres, indicated driver impairment, as the driver's ability to hold the car in a steady lateral position diminished.

Car-Following scenario

The Car Following task was developed to measure attention and perception performance, as errors in these areas often lead to accident causation. In this task participants were required to match the speed of a lead vehicle and to maintain a constant distance from the vehicle as it executes a series of deceleration and acceleration manoeuvres. The primary dependant variable was reaction time to lead vehicle's speed decelerations. This test assessed a driver's ability to adapt to manoeuvres of other motorists (Brookhuis & de Waard, 1993; Ramaekers & O'Hanlon, 1994).

Risk taking scenario

Risk taking scenarios were only embedded in studies using a driving simulator. Standard parameters applied: gap acceptance, number of crashes, number of red light crossings and number of crashes during sudden event scenarios.

Laboratory tests

In addition, all partners including a number of **laboratory tests** measuring skills related to driving. These test included tracking tasks, attention tasks, reaction tasks and cognitive tasks. Performance parameters associated with these laboratory tests were considered secondary outcome measures.

1.2.3. Results

In the following the results of the meta-analyses and the experiments are described.

1.2.3.1. Meta-analysis of alcohol

In Figure 5 the percentage of significant findings for all performance categories is shown. Since this percentage increases to the same degree as the BAC, a linear function is fitted to the empirical values of the general performance data. The general impairment function comprises 2914 performance findings. At a BAC of 0.5g/L, 30% of the findings are significant, while at a BAC of 0.8g/L about 50% of the findings are significant. More detailed information about the impairment caused in different categories of performance and mood is available in the Deliverable 1.1.2a.

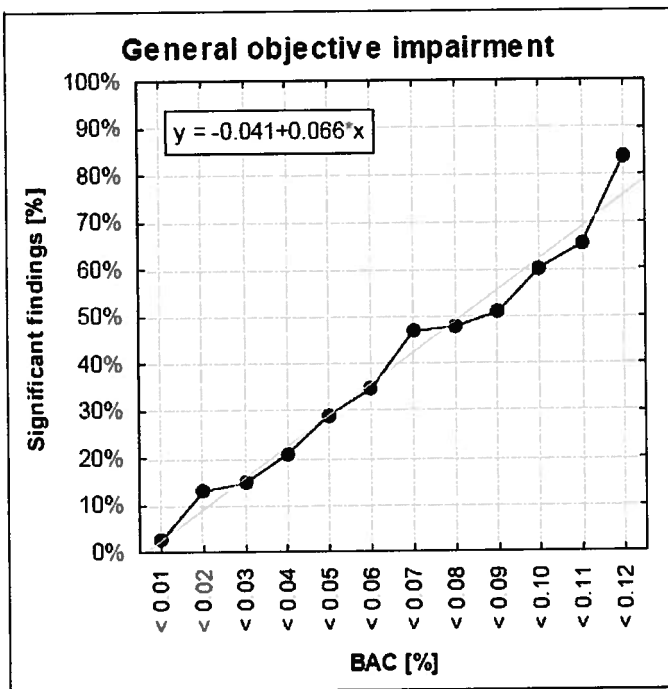


Figure 5: General impairment caused by alcohol (regarding all performance categories) – percentage of significant findings for each BAC category, based on the meta-analysis of alcohol (D1.1.2a, p. 71).

1.2.3.2. Meta-analysis of medicines and illicit drugs

Table 6 shows the impairment caused by certain dosages of medicines based on the meta-analysis of medicine and illicit drugs. Highly impairing are/is:

- the **anxiolytics** alprazolam (1 mg), and high dosages of oxazepam (30 mg), diazepam (20 mg), and lorazepam (2 / 2.5 mg),
- the **antidepressants** mianserin (10 mg), and amitriptyline (25 / 50 mg),
- the **hypnotics/sedatives** flunitrazepam (2 mg), triazolam (0.5 mg), zopiclone (7.5 mg), and zolpidem (20 mg), and
- the **antipsychotic** promethazine (27 mg), and
- THC (24.5 mg, oral administration).

Neither antihistamines nor illicit drugs cause a comparable high impairment. For more details see D1.1.2b.

Based on the meta-analyses of experimental studies no negative influence of stimulants on the fitness to drive could be stated. In general, there were more findings of performance improvements than of performance impairments. D-amphetamine is the agent on which most studies were available (dosage 1mg to 36 mg). Recent studies focused on the impact of designer amphetamine MDMA (ecstasy) on performance. In those studies more improvements than impairments were found, too. Accordingly, there was no performance decrement during the time of action after consumption of "normal" doses (40mg to 125mg).

Cocaine showed similar effects as amphetamines. From the meta-analysis of experimental studies no negative influence on the fitness to drive could be stated. Only some case-reports and non-experimental publications revealed negative effects. But there was a lack of studies focusing on the impairment during the post acute phase.

The literature review on **opioids used in substitution therapy** revealed that substitutes may cause impairments even at low dosages when implicated in a single dose to healthy subjects. There was no clear evidence if patients treated chronically were able to drive, as there were big differences in performance decrements between individuals. Many patients in substitution therapy are using other substances in addition to their medication. Therefore it is recommended that a screening for other drugs should always be done before a decision is made if a patient should be allowed to drive.

1.2.3.3. Experimental studies

All studies investigating the effects of **stimulants on driving** (MDMA and dexamphetamine) did not reveal impairing effects or increased risk taking caused by the drug consumption itself (see Table 8 and Table 9 for an overview of the results). In general, low doses of stimulant drugs produce neutral or even stimulating effects on a range of psychomotor functions. However there are some studies showing that stimulants may also produce detrimental effects on specific cognitive functions and increase risk taking behaviours.

Sleep deprivation alone caused impairments equivalent to those observed under the influence of 0.5 g/L BAC. Only in case of additional alcohol consumption an increased risk taking behavior could be observed. Stimulant effects of MDMA and amphetamine were not sufficient to overcome or compensate for driving impairments produced by concomitant alcohol use or sleep deprivation. No clear relation could be found between drug concentrations in blood (and plasma) and driving impairment for MDMA and dexamphetamine.

The pharmacological effects of stimulants and the effects of drug use setting (e.g. poly-drug use, concomitant alcohol use and sleep deprivation) were intertwined and significantly contributed to driver impairment. Moreover, users of stimulating drugs were not aware about post-acute fatigue effects.

A summary of the results of the studies done to investigate the impact of **medicinal drugs** on actual and simulated driving is presented in Table 10, Table 11 and Table 12.

Zopiclone (7.5mg) and alprazolam (0.5mg) produced significant driving impairment in patients as well as in healthy controls. Zolpidem (10mg) produced significant driving impairment in elderly subjects. Chronic users do not experience subjectively any sedative effects of zopiclone and alprazolam, whereas infrequent users and healthy users reported feelings of reduced alertness and sleep. This lack of awareness of (residual) sedative effects of zopiclone and alprazolam may lead insomnia and anxious patients to believe that car driving is safe during treatment with these drugs.

Results from the insomnia study showed that driving performance and driving related psychomotor performance did not differ between medicated insomniacs, unmedicated insomniacs and normal sleepers (i.e controls). These results indicate that driving performance of insomniac patients does not differ from that of normal sleepers,

even in insomniacs that had been prescribed hypnotic medication. The lack of driving impairment in medicated insomniacs could however be predicted from the type of hypnotics that patients were using. About 2/3 of the patients received short acting hypnotics or low doses of hypnotics that previously shown not to produce any residual impairment in driving test (e.g. zolpidem, temazepam). Sleep apnoea turned out to be strongly correlated to driver impairment.

Combinations of codeine and paracetamol in general did not produce driving impairment when administered to healthy volunteers even at higher doses. However, driving impairment became apparent after the lowest dose when administered to elderly subjects. Thus the results indicate that the impairing potential of codeine/paracetamol varies with age.

Dronabinol (Marinol®) impaired driving performance in occasional and heavy users in a dose-dependent way. Equivalence tests demonstrated that dronabinol induced increments in SDLP were bigger than impairment associated with 0.5 g/L BAC in occasional and heavy users, although the magnitude of driving impairment was generally less in heavy users.

The results of the driving tests with patients suffering from chronic pain under long-term treatment with opioid analgesics revealed that driving performance of patients was comparable to that of healthy controls. Nevertheless neuropsychological tests assessing skills related to driving revealed that pain patients performed worse compared to healthy controls on a number of tests.

Patients using risperidone drove with a lateral position that was comparable to that observed in controls. However the standard deviation of lateral position and reaction time to sudden events were significantly increased in patients and comparable or bigger than those observed in controls with 0.5 g/L BAC. The present data thus seems to indicate that patients under the influence of risperidone do have some impairment that should be considered of clinical relevance.

Table 8: Summary of MDMA and dexamphetamine effects on primary and secondary driving parameters (improvement, no effect or impairment) as well as subjective measures of arousal and sleep, alone and in combination with alcohol.

	Study 1: MDMA-alcohol study			Study 2: Dexamphetamine – alcohol study		
	MDMA	Alcohol	MDMA + Alcohol	Dexamphetamine	Alcohol	Dexamphetamine + Alcohol
Road tracking	Decrease SDLP	Increase SDLP	Increase SDLP Relevance of impairment undecided (95%CI drug effect includes BAC 0.5 as well as 0)	No effects	Increased SDLP	Increased SDLP Relevance of impairment undecided (95%CI drug effect includes BAC 0.8 as well as 0)
Car Following	No effect	No effect	No effect	No effect	No effect	No effect
Risk Taking	No effect	No effect	No effect	No effect	Shorter gap acceptance; increased red light crossings and number of crashes	Shorter gap acceptance; increased red light crossings and number of crashes Relevance of impairment undecided (95%CI drug effect includes BAC 0.8 as well as 0)
Laboratory measures of skills related to driving	Not assessed	Not assessed	Not assessed	No effect	Impairment of attention, tracking and RT	Impairment of attention, tracking and RT
Subjective measures	Decreased sleepiness	Increased sleepiness	Increased sleepiness	Decreased sleepiness	No effect	Decreased sleepiness

Table 9: Summary of MDMA and dexamphetamine effects on primary and secondary driving parameters (improvement, no effect or impairment) as well as subjective measures of arousal and sleep, alone and in combination with alcohol.

	Study 3: MDMA – sleep deprivation study			Study 4: Dexamphetamine study – sleep deprivation study		
	MDMA	Sleep deprivation	MDMA + Sleep deprivation	Dex-amphetamine	Sleep deprivation	Dexamphetamine + Sleep deprivation
Road tracking	No effect	Increased SDLP; Impairment > BAC 0.8 g/L	Increased SDLP; Impairment > BAC 0.8g/L	No effect	Increased SDLP Impairment > BAC 0.5 g/L	Increased SDLP (Relevance of impairment undecided)
Car Following	No effect	No effect	No effect	Dose related improvement of phase delay	Impairment of phase delay	impairment of phase delay
Risk Taking	Not assessed	Not assessed	Not assessed	Improvement RT to crossing cars	Impairment of phase delay	Improvement RT to crossing cars
Laboratory measures of skills related to driving	Neutral on most measures, Improvement on rapid information processing	Impairment of attention and impulse control	Impairment of attention and impulse control	Not assessed	Not assessed	Not assessed
Subjective measures	Increased arousal	Decreased arousal	Decreased arousal	Decreased sleepiness	Increased sleepiness	Increased sleepiness

Table 10: Summary of treatment and sleep disorder effects on primary and secondary driving parameters as well as subjective measures of arousal or sleep (ZOP=zopiclone; PLA=placebo; BAS=baseline and ALP=alprazolam).

	Study 5: Residual effects of zopiclone 7.5 mg			Study 6: Insomnia patients	Study 7: Alprazolam 0.5 mg in anxious patients			Study 8: Sleep apnoea patients
	Chronic hypnotic users ZOP vs. PLA	Infrequent hypnotic users ZOP vs. PLA	Healthy controls ZOP vs. PLA	Medicated insomnia patients vs. unmedicated insomnia patients vs. healthy controls	Medicated anxious patients ALP vs. BAS	Unmedicated anxious patients ALP vs. BAS	Healthy controls ALP vs. BAS	Patients with CPAP vs. patients with no CPAP vs. controls
Road tracking	Increased SDLP; Impairment > BAC 0.5 mg/mL	Increased SDLP; Impairment > BAC 0.5 mg/mL	Increased SDLP; Impairment > BAC 0.5 mg/mL	No difference between groups	Increased SDLP; Impairment > BAC 0.5 mg/mL	Increased SDLP; Impairment > BAC 0.5 mg/mL	Increased SDLP; Impairment > BAC 0.5 mg/mL	Increased SDLP in both patients groups relative to controls No difference between patient groups
Car-Following	No effect	No effect	No effect	No difference between groups	Increased brake reaction time and increased time driven at close distance to leading vehicle	Increased brake reaction time and increased time driven at close distance to leading vehicle	Increased brake reaction time and increased time driven at close distance to leading vehicle	Increased brake reaction time and increased time driven at close distance to leading vehicle in both patient groups
Risk Taking	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed
Laboratory measures of skills related to driving	Impairment of memory, tracking, divided attention, inhibitory control	Impairment of memory, tracking, divided attention, inhibitory control	Impairment of memory, tracking, divided attention, inhibitory control	No group differences in verbal memory, divided attention, vigilance and inhibitory control.	No effect	No effect	Decreased reaction time	No difference between groups
Subjective measures (sleepiness/alertness)	Increased next day alertness	No effect	Decreased next day alertness	No group differences in sleepiness and alertness	No effect	Decreased alertness	Decreased alertness	Decreased alertness in patient groups

Table 11: Summary of treatment and pain disorder effects on primary and secondary driving parameters as well as subjective measures of arousal or sleep (COD= codillprane; PLA=placebo; ZOL = zolpidem; DRO=dronabinol).

	Study 9: Codillprane and zolpidem in elderly: alone and in combination			Study 10: Codillprane in healthy volunteers	Study 11: Dronabinol in THC users		Study 12: Opioid patients
	COD vs. PLA	ZOL vs. PLA	COD+ZOL vs. PLA	COD vs. PLA	Occasional THC users DRO vs. PLA	Heavy THC users DRO vs. PLA	Patients treated with opioids vs. controls
Road tracking	Increased SDLP	Increased SDLP	No effect	No effect	Increased SDLP: Impairment DRO 10mg > BAC 0.5 mg/mL Impairment DRO 20mg > BAC 0.8 mg/mL	No overall superiority effect of DRO on SDLP Big individual variation in change SDLP after DRO 10 and 20mg : 95% CI includes zero as well as alcohol criterion value	No difference between groups
Car-Following	No effect	No effect	No effect	Not assessed	Decreased Time to Speed Adaption	No effects	No difference between groups
Risk Taking	Increased number of crashes	No effect	No effect	Not assessed	Not assessed	Not assessed	Not assessed
Laboratory measures of skills related to driving	Not assessed	Not assessed	Not assessed	No effects	No effect on Standard Filed Sobriety Tests	No effect on Standard Filed Sobriety Tests	Patient perform worse than controls on some isolated tests
Subjective measures (sleepiness/alertness)	Not assessed	Not assessed	Not assessed	Small increase of sleepiness	Increased sedation	Increased sedation	No difference between groups

Table 12: Summary of risperidone/paliperidone effects on primary and secondary driving parameters as well as subjective measures of arousal or sleep.

	Study 13: Risperidone/paliperidone
	patients diagnosed with psychosis and receiving risperidone vs. controls during placebo and alcohol
Road tracking	Increase in SDLP of patients > increase in SDLP of controls during alcohol (BAC=0.5 mg/mL). Alcohol also affected lateral position. The latter was not affected in patients
Car-Following	Not assessed
Risk Taking	RT to sudden events increased in patients and controls during alcohol relative to controls during placebo. Increase in RT in patients was comparable/bigger than BAC=0.5 mg/mL
Laboratory measures of skills related to driving	9 out 11 patients passed the Vienna driving evaluation test
Subjective measures (sleepiness/alertness)	Not assessed

1.3. Synopsis of problem situation based on epidemiology

Referring to the epidemiological studies of DRUID the main results can be summed up like this:

Prevalence of alcohol and/or other psychoactive substances in relation to road safety:

- Alcohol had the highest prevalence in the driving population (up to app. 4%), but with the majority of the alcohol positive drivers below 0.5g/L as well as in seriously injured and killed drivers in all countries (up to 15-25%), with the most of the alcohol positive drivers above 0.5g/L
- There was a higher prevalence of illicit drugs in the southern part of Europe both in the population and in the driving population.
- There was a higher prevalence of medicines in the northern part of Europe both in the population and in the driving population.
- Combined use of alcohol an/or other drugs was more common in accident involved drivers than in the driving population.
- There was no clear picture of the distribution of illicit drugs and medicines among injured and killed drivers, however, combined use of alcohol and/or other drugs was much more prevalent in drivers involved in accidents than in the driving population.

Accident risk for driving with alcohol and/or psychoactive substances:

- The risk of getting seriously injured or killed drivers when positive for alcohol of 0.5-0.8 g/L was medium increased of the magnitude of 2-10 times the risk for sober drivers. The risk increased exponentially by alcohol concentration, for alcohol concentrations of 1.2 g/L and above the risk was extremely increased of the magnitude of 20-200 times the risk for sober drivers.
- The risk of getting seriously injured or killed drivers when positive for most of the illicit drugs and medicines was medium increased of the magnitude of 2-10 times the risk for sober drivers.
- The risk of getting seriously injured or killed drivers when positive for multiple drugs was highly increased and considerably higher than the risk when positive for a single drug.
- The risk of getting seriously injured or killed drivers when positive for alcohol in combination with other drugs was extremely increased and comparable to the risk when positive for high alcohol concentrations.
- Killed drivers, who were responsible for the accident and positive for high alcohol concentrations, had a highly increased risk compared to the risk of killed responsible drivers, not positive for alcohol.
- Responsible drivers, positive for alcohol, involved in fatal accidents had a risk of about 8 times that of responsible drivers, not positive for alcohol. Those positive for cannabis had a risk of about twice that of drivers not positive for cannabis.

Characteristics of drink and drug impaired drivers:

- Drivers do not think that alcohol impairs their driving, and they think that drugs improve their driving.
- Drink drivers feel more ashamed than drug drivers. They are mainly worried that their friends disapprove their behavior.
- Drug drivers do not feel ashamed, but after treatment, they would look back with shame.
- Rehabilitation reduces recidivism.
- Drink driving with high concentrations and drug driving seems to be associated with addicted users, whereas moderate users are more responsible.
- Although drug drivers go up later in the morning and go to bed later in the night than those who do not take drugs, the drug users drive less than other driver groups in the late hours.

2. Countermeasures

2.1. Enforcement

2.1.1. Objectives

DRUID WP 3 dealt with the evaluation of enforcement strategies whereas enforcement was implemented by traffic police applying oral fluid mobile screening devices for drugs detection.

The following main objectives were pursued:

- a) Large scale practical evaluation of onsite oral fluid screening devices for detecting of psychoactive substances in drivers.
- b) Large scale scientific evaluation of onsite oral fluid screening devices for detecting of psychoactive substances in drivers and checklist for clinical signs of impairment.
- c) A cost-benefit analysis of drug driving enforcement by the police.

2.1.2. Methodology

a) Practical evaluation of oral fluid screening devices

13 manufacturers participated in practical evaluation of their screening devices⁴. They provided information on devices and prepared training materials for police teams.

Evaluation was implemented in six European countries (Germany, Belgium, Ireland, Finland, Spain and the Netherlands) by trained teams of police officers under real conditions in compliance with a uniform experiment design and applying a uniform protocol.

The practical evaluation has been focussed on:

- Successful performance
- Duration of collecting a sufficient oral fluid sample
- Duration of sample analysis
- Hygienic aspects
- DPO's⁵ impression of reliability of the obtained indication
- DPO's opinion on the simplicity of the test.

Test persons were asked for their opinion on the tests they performed and the relevance of enforcement legislation.

b) Scientific evaluation of oral fluid screening devices and a checklist for clinical signs of impairment

Tests were performed on eight (out of initially 13) devices that have been assessed as the most promising. Analytical evaluation of oral fluid screening devices and preceding selection procedures was carried out in the Netherlands, Belgium and Finland from

⁴ See DRUID Deliverable 3.1.1 for more details.

⁵ DPO – Dedicated Police Officer

October 2007 to December 2009. Tested substance classes were amphetamine(s), methamphetamine, MDMA, cannabis, cocaine, opiates, benzodiazepines and PCP.

A checklist for clinical signs of impairment (CSI) was evaluated in order to see if visible signs of impairment can be used as preceding selection criteria for performing an on-site test. The checklist was based on several existing checklists, e.g. one developed for the German police and previously used in the European IMMORTAL (Impaired Motorists, Methods of Roadside Testing and Assessment for Licensing) project.

Study populations consisted of randomly selected drivers from the DRUID roadside surveys, drivers suspected of driving under the influence of drugs, patients of treatment centres and rehabilitation clinics and customers of coffee-shops.

Oral fluid was collected as the reference sample. For some cases, in the Netherlands, whole blood samples were also collected.

The performance of the tests was assessed based on sensitivity, specificity, accuracy, positive predictive value and negative predictive value for the individual substance tests of the device. These were assessed based on both DRUID and manufacturer cut-offs.

Sensitivity, specificity and accuracy performance values of 80% or more were set as a desirable target value.

c) Cost-Benefit Analysis (CBA)

CBA has a foundation in mainstream (neo-classical) economic theory, whereby economic values are recognised as expressions of individual/household preferences. Road safety can be regarded as an economic good, something that people have a demand for, characterised by a mix of *private* and *public* aspects.

A benefit-cost ratio was estimated according to formula:

$$\text{Benefit-cost ratio} = \frac{\text{Present value of all safety benefits}}{\text{Present value of implementation costs and time use}}$$

In addition to CBA and estimates of net benefits and benefit-cost ratios of increased traffic police enforcement, the study also included cost-effectiveness analysis (CEA).

The CBA should answer two questions: *i)* To what degree is the enforcement of legislation against driving under the influence (DUI) of drugs profitable in economic terms for the society? *ii)* Which of the existing devices for such enforcement are more profitable? For these cost-benefit analyses the following data are needed: *a)* effects of enforcement, i.e. the reduction of accidents, fatalities, injuries and material damage due to this kind of enforcement; *b)* costs of (or positive benefits of preventing) accidents, fatalities, injuries and material damage; *c)* costs (negative benefits) of road user time; *d)* costs of devices/equipment; *e)* costs of police time; *f)* costs of laboratory analyses; *g)* costs of the judicial system. The first three elements are handled on the benefit side, while the latter four enter the cost side of the CBA.

The basic idea of the CBA model is that a particular scenario or group of scenarios will be compared with the reference situation or baseline, which is a continuation of the current situation. Thus, CBA basically compares economic benefits and costs from the implementation of specific policies/projects with a "do-nothing" reference/baseline.

DRUID considered three enforcement (increase) scenarios in CBA, for drug/medicine saliva testing – a low, medium, and high increase (Table 13). Since the CBA was applied to different countries, with different prevalence of different drugs/medicines (and alcohol), also the prevalence effect was taken into account. Regarding alcohol enforcement, one added element in the scenarios was an adjustment of random alcohol breath testing to maintain current enforcement levels / current resource use, that is, transfer some share of the alcohol enforcement towards drug enforcement. Researchers calculated a 10 % reduction in alcohol enforcement, and presented the CBA of this reduction combined with a tripling of drug enforcement.

Table 13: Three different scenarios for increased drug screening in the DRUID Cost-Benefit Analysis.

Low enforcement increase level (50% for drugs/medicines)
Middle enforcement increase level (tripling for drugs/medicines), with and without a 10% reduction in alcohol enforcement
High enforcement increase level (tenfold increase for drugs/medicines)

2.1.3. Results

a) Practical evaluation of oral fluid screening devices

Eight devices were evaluated as “promising”

- Mavand - RapidSTAT
- Securetec - Drugwipe 5+
- Branan - Oratect XP
- Varian - Oralab 6
- Innovacon - OrALert
- Cozart - DDS
- Dräger - Drug Test 5000
- Biosensor – BIOSENS (effective in specific situations in which large number of persons must be tested in a short time, e.g. discos, large concerts, etc.)

Based on the experience of 137 training sessions and 2960 test a number of Police User Requirements and Specifications (PURS) has been formulated. These can be divided in three categories:

- Requirements for training of police officers
- Requirements for operational use of devices
- Requirements for documentation.

Police teams involved in this task developed a set of recommendations concerning combating driving under influence of psychoactive substances from a perspective of police forces. They propose a zero tolerance approach towards illicit drugs and impairment approach towards psychoactive medicines. Police officers deem as necessary to authorize traffic police to implement random tests of drivers on drugs consumption. From their point of view, a refusal of a driver to undergo an alcohol or drugs test should be considered as an offence. Breath sample should be used for detecting alcohol consumption. Oral fluid screening devices should be used for detecting drugs consumption.

b) Scientific evaluation of oral fluid screening devices and a checklist for clinical signs of impairment

Tests were performed on eight (out of initially 13) devices that have been assessed as the most promising. The analytical evaluation of the amphetamine test showed sensitivity varying from 0% to 87 %. Specificity values were from 91% to 100% and accuracy values from 84% to 98%.

For cannabis tests, sensitivities ranged from 11% to 59%. Specificities were between 90% and 100% and accuracies from 41% to 82%.

Cocaine tests scored sensitivities of between 13% and 50%, specificities of 99% to 100% and accuracies from 86% to 100%.

Sensitivities of opiate tests ranged from 69% to 90%. Specificities were between 81% and 100% and accuracies between 75% and 99%.

Benzodiazepine tests had sensitivities from 48% to 67%. Specificities were from 94% to 100% and accuracies from 77% to 100%.

Not enough positive cases were gathered to successfully evaluate any of the methamphetamine, MDMA or PCP tests for the devices in which these were included.

None of the tests reached the target value of 80% for sensitivity, specificity and accuracy for all the separate tests they comprised.

An overall evaluation, wherein any positive drug screening result was viewed as valid providing that the confirmation sample contained one of the DRUID substances analysed, was performed as a measure of the usefulness of the devices in police controls. Three of the devices performed at >80% for sensitivity, specificity and accuracy in the overall evaluation (Figure 6).

Prevalence of drugs in the study population needed to be considered when assessing the evaluation results. In addition, the type and prevalence of drugs within the population for which the device is intended to be used needed to be taken into account when considering the suitability of the device based on the results presented in this report.

All countries took their own approach to the evaluation of the checklist for clinical signs of impairment. The results of the evaluations were not very promising. The indicators proved to be effective mainly for cases of high concentrations or very recent use. Pupil reaction test was best predicting parameter, esp. for AMP and THC. The checklist scored a low sensitivity value (Dutch study), even lower correlation of symptoms and actual presence of drugs (Belgian study) or there were difficulties in correlating the symptoms to actual drug use due to the insufficient data collection (Finnish study).

More experience, better training, and selection of time and locations with high incidence may improve the effectiveness of the CSI checklists.

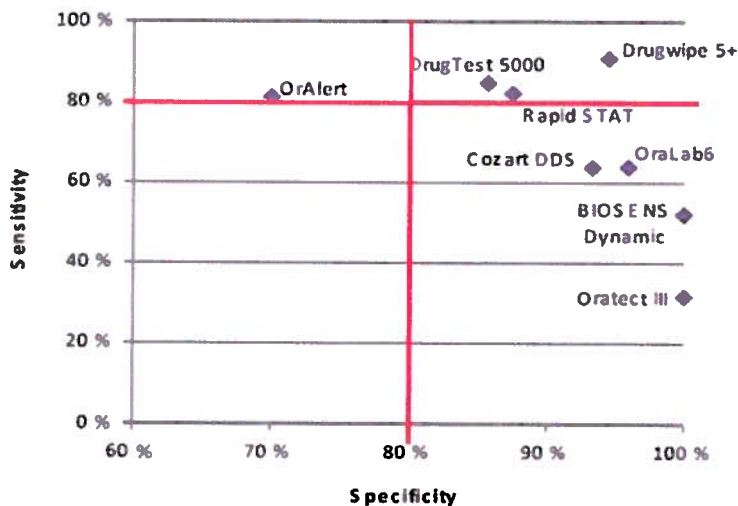


Figure 6: Sensitivity and specificity of the oral fluid screening devices.

c) Cost-Benefits Analysis

Table 14, Table 15 and Table 16 present the results of the economic analyses, for the three main levels of drug enforcement increase. These are calculations for an average of the drug screening devices, where the prevalence-weighted average sensitivity/specificity levels are, respectively, 45.2/96.9% for the Netherlands, 49.8/96.9% for Belgium, and 58.5/96.9% for Finland⁶. In these calculations no change in alcohol enforcement level was assumed. The basic requirement for efficiency of increased drug enforcement is a benefit-cost (BC) ratio of 1.5 or higher (Bickel *et al.* 2006).

Table 14: 50% enforcement increase - Drugs (average device).

	Netherlands	Belgium	Finland
Annual benefits	5,698,297	13,527,835	2,075,422
Annual costs	291,028	1,683,580	1,636,928
Net benefits	5,407,269	11,844,255	438,494
BC ratio	19.6	8.04	1.27
Simulated BC ratio	18	7.7	1.16
simulated St. dev.	11	4.4	0.45
simulated skewness	5.72	8.28	1.50
simulated kurtosis	10.70	4.39	9.24
Costs per convicted	4,825	4,054	4,147
Costs per prevented fatality	408,481	995,247	5,480,361
Tests per 100,000 inhabitants	9	54	218

⁶ The average is based on 10 devices (Sun OraLine and the Ultimed Salivascreen VI), yielding only slightly lower net benefits and BC ratios than averages based on the specified 8 devices.

Table 15: 300% enforcement increase (tripling) - Drugs (average device) (100% alcohol).

	Netherlands	Belgium	Finland
Annual benefits	14,258,846	33,886,725	5,170,513
Annual costs	1,038,106	6,654,135	6,505,710
Net benefits	13,220,740	27,232,590	-1,335,197
BC ratio	13.74	5.09	0.79
Simulated BC ratio	12.79	4.90	0.74
simulated St. dev.	4.28	1.70	0.29
simulated skewness	6.73	9.23	7.47
simulated kurtosis	7.23	2.78	0.37
Costs per convicted	4,303	4,006	4,120
Costs per prevented fatality	582,202	1,569,963	8,703,885
Tests per 100,000 inhabitants	18	108	436

Table 16: 1000% enforcement increase (tenfold increase) - Drugs (average device).

	Netherlands	Belgium	Finland
Annual benefits	22,822,067	54,279,481	8,102,222
Annual costs	4,524,467	29,850,057	29,226,691
Net benefits	18,297,599	24,429,424	-21,124,469
BC ratio	5.04	1.82	0.28
Simulated BC ratio	4.70	1.75	0.25
simulated St. dev.	2.67	0.98	0.13
simulated skewness	17.46	9.33	6.15
simulated kurtosis	2.68	0.99	0.12
Costs per convicted	4,168	3,994	4,113
Costs per prevented fatality	1,584,219	4,391,997	24,415,003
Tests per 100,000 inhabitants	61	360	1.455

The indication from Table 14, 15 and 16 is that increased drug control is most profitable for the Netherlands, and least profitable for Finland. This is logical in terms of baseline enforcement level, since in Finland the drug enforcement level already is 25 times higher than in the Netherlands. In the Netherlands even larger increase might be cost efficient, since the estimated BC ratio is well above 1.5 even for a tenfold increase in enforcement.

When we take into account the different qualities of the drug screening devices, the indication is that the choice of device does make a difference. The quality differences have been assessed in DRUID in D3.1.1 and in D3.2.2. If these quality differences, in addition to affecting the costs (e.g., screening costs and laboratory costs), also are carried forward to the deterrence effect, affecting benefits, the results of the CBA will clearly depend on the quality of the selected drug screening device. Figure 7 shows the difference in BC ratio between the three best rated devices (“above average”), the three in the middle (“average”), and the two worst rated devices (“below average”).

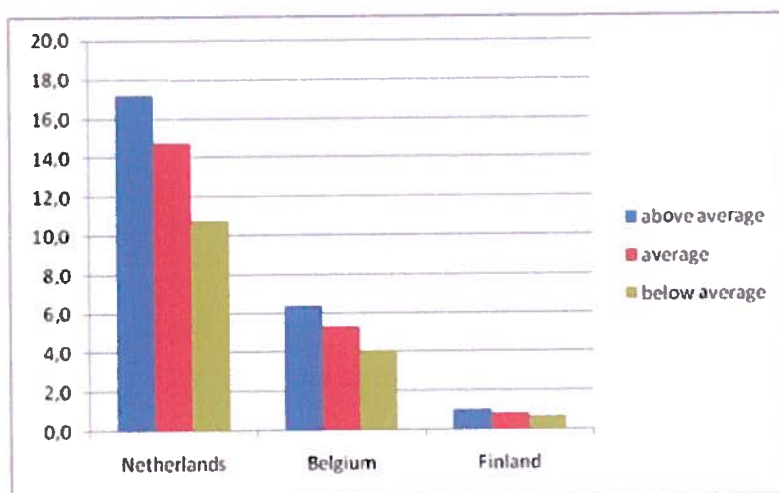


Figure 7: BC ratios for three quality groups of devices; tripling in enforcement.

The final conclusion is that increased drug driving enforcement based on the roadside saliva screening is potentially beneficial, particularly for countries which currently have a low enforcement level. But if the public sector decides to decrease drunk driving enforcement for the sake of financing increased drug driving enforcement (for a given budget), the net benefits of police enforcement will decrease (assuming that drunk driving will increase).

2.2. Classification

2.2.1. Objectives

The overall goals of WP4 (Classification) were:

- To review the existing classification and labeling systems regarding medicinal drugs concerning their impact on driving performance.
- To define the criteria and the methodology on the establishment of European classification and labeling system of medicinal drugs concerning their impact on driving performance.
- To develop a methodology to continuously update classification/categorisation system and labeling system on medicinal drugs concerning their impact on driving performance.
- To classify the relevant therapeutic groups of medicines available on the European market according to the classification system developed in the project.
- To propose patient-oriented information on driving for each medicine and propose appropriate labeling systems regarding medicines and driving

The WP4 activities were planned to be implemented in close collaboration with the relevant EC Directorates and European agencies (like EMA). WP4 did benefit from previous experiences at national level (Belgium, France, The Netherlands, Slovenia, Spain) and from cooperation with international scientific panels (ICADTS, DG MOVE Working group on alcohol, drugs, medicines and driving, etc.).

WP4 outputs are aimed at physicians/pharmacists and other healthcare professionals, patients who drive taking medicines, regulatory agencies (European Medicines Agency (EMA) and national regulatory agencies) and healthcare provider services.

2.2.2. Methodology

To collect the necessary information on already existing classification systems, questionnaires were distributed to all institutions involved in DRUID and to some entities outside the DRUID consortium. Additionally internet searches were performed. To achieve comparability between the systems, the official ATC system maintained by the WHO Collaborating Centre for Drug Statistics Methodology was used as a base system.

For the development of input for a European categorisation system it has been decided to address the Pharmacovigilance Working Party of the Committee for Medicinal Products for Human Use (CHPM). Together with WP 4 partners three small-scale invitational workshops have been organised in 2008 in which representatives of regulatory agencies from nine Member States participated. Based on their discussions recommendations were derived to develop and implement a European categorisation system.

During the process of classifying medicines according to the categorization system developed within DRUID a methodology was used, which included several steps of evaluation taken into account the conditions of use of a medicine on the European Union market:

1. Pharmacodynamic and pharmacokinetic data
2. Pharmacovigilance data (including prevalence of unwanted effects reported in the SmPC)
3. Experimental and epidemiological data
4. Additional data derived from the Patient Information Leaflet (PIL) and existing categorization systems
5. Synthesis

Basically conditions of use of a medicine, pharmacodynamics, pharmacokinetic data, and pharmacovigilance data (including prevalence of unwanted effects) were derived from the SmPC, while section 3 was based on a scientific literature search. An additional step consisted of reviewing section 4.7 of the SmPC “Effects on ability to drive and use machines” and the PIL section on “driving and using machines” as well as reviewing the previous categorizations (if available) of a medicine in Belgium, France, Spain as well as to the ICADTS list. After evaluating all available data, a provisional category was assigned to each active substance. The provisional category was proposed and discussed at WP4 meetings where a final and definitive category was assigned and approved by all WP4 partners.

The existing methodology on DRUID categorization on medicines and driving, allows, if new evidences emerge, to re-categorise the medicine or confirm the previous categorisation following the same 5 step process.

2.2.3. Results

2.2.3.1. Review of existing classification efforts

In total, 16 systems were found (Table 17). Some of these systems are no true categorization systems: Germany directly reproduced ratings from Wolschrijn, and 5 systems have not defined categories (Greece, the Netherlands, Norway, Denmark and Finland). Only one true categorization system also included warning labels (France II).

Clear relations can be seen between different systems. All categorizations (except Portugal) are linked to Wolschrijn. With regard to systems structure, the largest differences concern the number and descriptions of categories. The list by Wolschrijn included 7 categories. At first, the categories were copied (Belgium), but later on the categories were summarized and only three categories remained (Spain I). The most recent and extensive lists (France II and ICADTS) have maintained these three categories, but have added practical guidelines for patient and physician. One list (ICADTS) introduced a calibration to BAC levels.

Although different categorisation systems are currently available across Europe, it is important to point out that none of these classifications have clearly described or published the criteria for the establishment of a categorisation system for potentially impairing medications nor were officially adopted at European level.

Table 17: Comparison of classification and labeling systems.

	Number of medicinal drugs	Classification	Number of categories	Warning label	Legal
Wolschrijn	572	X	7		
Germany	406		Scale values		
Belgium	182	X	7		
Spain I (DGT/UVa)	363	X	3		
Spain II (semFYC/UVa)	395	X	4		
Spain				X	
France I (CERMT)	508	X	4		
France II (official)	311	X	3	X	X
ICADTS	389	X	3		
Portugal	241	X	5		
Greece I (legal)	89	NA			X
Greece II (monographs)	92	NA			
The Netherlands	156	NA		X	
Norway	87	NA		X	
Denmark	83	NA		X	
Finland	68	NA		X	

2.2.3.2. The establishment of criteria for a European categorization system

After reviewing the most significant of existing categorisation systems in Europe, a critical discussion has been held to explain the need for such a categorisation system. It is clear that such system has to address the needs of health care professionals, drug regulatory agencies, drug manufacturers and patients. Patients need clear warnings and symbols to use their medicines in the best (and safest) way. Developments in France show clearly that a multi-level categorisation system is better in showing difference between the least and most impairing medicine within one therapeutic class and that warning labels are needed to guide patients in deciding about the use of the medicine.

Together with WP 4 Partners three small-scale invitational workshops have been organised in 2008 in which representatives of regulatory agencies from nine Member States participated. Based on their discussions a first step to harmonize categorisation systems could be achieved: the adoption of the Guidelines for the Summary of Product Characteristics in September 2009 (which is valid from 1st of May 2010), in which categories a) no or negligible influence, b) minor, c) moderate influence, and d) major influence on driving fitness are specified with some important guidance in special circumstances.

This adoption is in-line with the classification and labeling system developed by the DRUID WP4 expert group (Table 18).

Table 18: DRUID Categorization system for medicines and driving.

Information for physicians and pharmacists		Warning for patients (with warning symbols and standard descriptions per country)
Description of categories with levels of impairment	Information on how to advise their patients	
<p>Category 0</p> <p>Presumed to be safe or unlikely to produce an effect on fitness to drive.</p>	<p>Confirm that the medicine will be safe for driving, provided that combinations with alcohol and other psychotropic medicines are excluded.</p>	<p>[no warning needed]</p>
<p>Category 1</p> <p>Likely to produce minor adverse effects on fitness to drive.</p>	<p>Inform the patient that impairing side effects may occur especially during the first days and that have a negative influence on his/her driving ability. Give the patient the advice not to drive if these side effects occur.</p>	<p>Warning level 1</p> <p>Do not drive without having read the relevant section on driving impairment in the package insert.</p>
<p>Category 2</p> <p>Likely to produce moderate adverse effect on fitness to drive.</p>	<p>Inform the patient about the possible impairing side effects and the negative influence on his/her driving ability. Advise the patient not to drive during the first few days of the treatment. If possible prescribe a safer medicine, if acceptable by the patient.</p>	<p>Warning level 2</p> <p>Do not drive without advice of a health care professional. Read the relevant sections on driving impairment in the package insert before consulting the physician or pharmacist</p>
<p>Category 3</p> <p>Likely to produce severe effects on fitness to drive or presumed to be potentially dangerous.</p>	<p>Inform the patient about the possible impairing side effects and the negative influence on his/her driving ability. Urgently advise the patient not to drive. Consider prescribing a safer medicine, if acceptable by the patient.</p>	<p>Warning level 3</p> <p>Do not drive. Seek medical advice after a period of treatment about the conditions to restart driving again.</p>

* The assigned categories relate to the acute or first time use of the medicine (at the start of treatment)

The DRUID categorisation system should also be used as a tool to motivate health care professionals to provide patients with clear information, communicate to patients the risk associated with driving under the influence of medicines, and start HCP-patient discussion leading to both safer prescriptions and the patient's conscious decision whether to drive or not . From the patient point of view, this classification could play an

active role in helping them to be involved along the decision-making process, to understand the hazards of some medications to road safety, and to remind them to use caution while driving until their individual responses to the therapy have been well established.

In the last two years (2010 and 2011) the WP4 results were discussed with the Pharmacovigilance Working Party, resulting in consensus based on the following compromise. Currently national approaches differ substantially: from France at one end of the extreme (with three-level pictogram labeling) to Sweden at the other end where the pictogram was replaced with a generic warning in the patient leaflet. The consensus was reached that a basic two-level framework would be developed as the basis for warnings to patients in the Patient Information Leaflet. For medicines without a potential relevant influence on driving (no or negligible, or minor influence) and for medicines with a potential relevant influence on driving (moderate influence, or major influence) the wording has been proposed.

Emphasis is made on improving information related to effects on driving in the Patient Information Leaflet by simple and patient-centred directions. Therefore collaborative efforts of DRUID experts, members of the Pharmacovigilance Working Party and other relevant institutions are recommended, preferably with support of EC (DG SANCO, DG MOVE). The development of supplementary information for patients (e.g. warning levels and pictograms) and health care professionals (e.g. prescribing and dispensing guidelines) should be guided by using DRUID results (D4.2.1, D4.3.1, D7.3.2 and D7.4.2.) as well as experience in EU Member States.

It is clear that the criteria for a European categorisation system for medicines and driving should be established based on the consensus among all relevant stakeholders. It is suggested that European regulatory authorities will be informed about the DRUID-developed categorisation process, discuss and reach consensus on the criteria hereby proposed, and carry out special efforts to implement the system at both international and national level, taking into account country peculiarities. Since the categorisation needs a constant revision, it is recommended to establish an expert working group on drugs and driving in order to keep the system functional, up-to-date, and reliable.

2.2.3.3. Classification/categorization, labeling and patient oriented information for the relevant therapeutic groups of medicines available on the European Union market.

The categorisation was first performed according to the active substance (referring to the ATC classification). However, it is necessary to take into account other factors, e.g. the excipients (excipient with a notorious effect), the route of administration, the conditions of use and the general classification for supply (prescription only, OTC or self-medication).

After evaluating drug's pharmacodynamic, pharmacokinetic, preclinical and clinical pharmacological (clinical trials, pharmacovigilance) studies, epidemiological and additional data, the conclusion on the drug's effect is made integrating three parameters: likelihood, frequency and intensity.

Fact Sheets were produced for N01-N07 (nervous system) and R06 (respiratory system - antihistamines) ATC groups of medicines. Each Fact Sheet contains information on: source of information, presentations, indications, posology and method of administration, pharmacodynamic and pharmacokinetic properties, possible side-effects related to driving, Summary of Product Characteristics (SmPC) section 4.7, studies on psychomotor performance and risk studies, current categorization in some

EU countries, proposed DRUID categorization, information for the patient, and place and date of agreement by the DRUID WP4 members.

In total 3,054 medicines from the above ATC groups were considered by DRUID team (see Figure 8). Of these 3,054 medicines, 1,513 have not been categorized, because they are not available on the European Union market. The distribution of the remaining 1,541 categorized medicines was as follows: Category 0 – 50,3%, Category I – 26%, Category II – 11,2%, Category III – 5,8%, Multiple category – 4,4% and the Depending on the medicine in combination 2,3%.

The following ATC groups were not categorized: G (Genito urinary system and sex hormones), H (Systemic hormonal preparations, excluding sex hormones and insulins), J (Antiinfectives for systemic use), L (Antineoplastic and immunomodulating agents), P (Antiparasitic products, insecticides and repellents) and V (various).

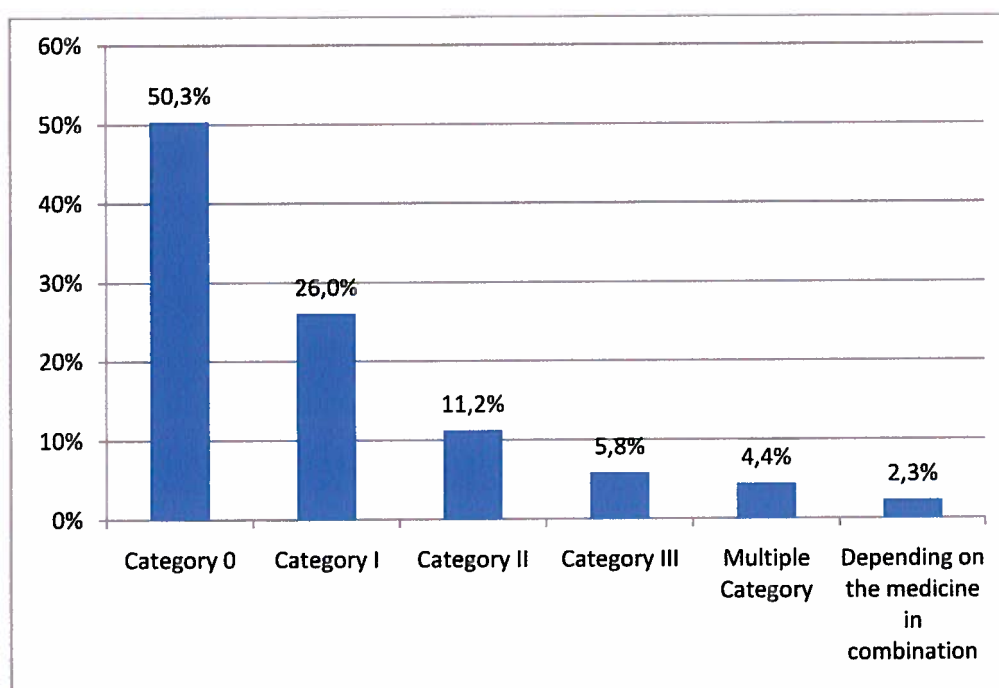


Figure 8: Percentage of medicines categorized within each DRUID category.

DRUID Categorisation: Four categories were proposed regarding the possible effect of the medicine on fitness to drive.

Category 0: Presumed to be safe on fitness to drive.

Category I: Likely to produce minor adverse effects on fitness to drive.

Category II: Likely to produce moderate adverse effect on fitness to drive.

Category III: Likely to produce severe effects on fitness to drive or presumed to be potentially dangerous.

Multiple categories: This appeared when a medicine can be included in more than one category. There can be several reasons for this: In most cases, the different categorization depended on the route of administration (topical, oral, parenteral, etc). In the case of some medicines in special ophthalmological preparations (S01), the different categorization depended on the presentation form of the medication

(aqueous-vehicle, cream, drops or ointment, etc.), which is related with the duration of its influence. In one case, codeine, categorization was based on the dose of codeine base administered. For two hypnotics, zolpidem and zaleplon, categorization was based on the time after the medication was taken.

Depending on medicines in combination: This was stated when the categorization depended on another medicine combined with the one under evaluation.

Table 19 shows the DRUID categorisation of the medicines in the ATC groups A, B, C, D, M, N, R and S.

Table 19: Number of medicines categorized by ATC groups.

ATC GROUP	Not evaluated. Not available on EU market	DRUID Categorisation						TOTAL
		0	I	II	III	Multiple categories	Depending on the medicine in combination	
A - ALIMENTARY TRACT AND METABOLISM	243	234	69	8	1	4	4	563
B - BLOOD AND BLOOD FORMING ORGANS	86	135	1	1			2	225
C - CARDIOVASCULAR SYSTEM	246	90	200	11		1		548
D - DERMATOLOGICALS	156	192	1			4		353
M - MUSCULO- SKELETAL SYSTEM	88	22	44	28	15			197
N - NERVOUS SYSTEM	346	9	30	86	53	36		560
R - RESPIRATORY SYSTEM	195	62	24	32	10	5	14	342
S - SENSORY ORGANS	153	31	31	6	11	18	16	266
TOTAL	1513	775	400	172	90	68	36	3054

2.3. Rehabilitation

2.3.1. Objectives

DRUID WP 5 dealt with rehabilitation of substance impaired drivers. The overall aim of WP5 was to increase relevant knowledge and to elaborate common European standards for rehabilitation measures for drivers under the influence of alcohol (DUI) or illicit drugs (DUID).

The first task of DRUID WP 5 aimed at identifying different types of DUI/DUID offenders and options for DUI/DUID assessment including different available approaches. State of the art review of currently existing rehabilitation programmes in- and outside Europe was implemented. Rehabilitation programmes and measures were analysed concerning scientific evidences relevant for road safety.

In the second task of DRUID WP 5 the following main objectives were pursued:

1. In-depth analysis on reasons for recidivism of drivers under the influence of psychoactive substances who participated in driver rehabilitation programmes.
2. Analysis of existing quality management (QM) systems established along with driver rehabilitation schemes.
3. Development of an evaluation instrument for best practices.
4. Validation of existing driver rehabilitation schemes.

2.3.2. Methodology

Comprehensive reviews of the international literature were carried out concerning the following topics:

- Identification of different types of DUI/DUID offenders
- Existing DUI/DUID assessment procedures
- Existing DUI/DUID rehabilitation measures
- Addiction treatment and options for dependent DUI/DUID offenders

The investigation of driver rehabilitation measures implemented and applied in Europe at present was done by means of a questionnaire survey.

The in-depth analysis on reasons for recidivism was realized applying a case-control study design whereby recidivists (i.e. drivers with a BAC of 1.6g/L or more, who had participated in a driver rehabilitation course, yet must take part in another driver rehabilitation course due to a subsequent DUI offence within a trial period) were compared with a matched control group of non-recidivists (i.e. drivers with a BAC of 1.6g/L or more, who had participated in a driver rehabilitation course and made no offence during the following trial period) regarding their traffic psychological driver assessment data. This analysis was supplemented by an analysis of change processes and components in driver rehabilitation courses by means of a questionnaire survey addressed to driver rehabilitation courses participants.

The existing QM systems for rehabilitation measures were displayed using the information derived from country reports. These were developed in several steps and in collaboration with country experts. In a first step, literature and internet research served as the basis to define quality management criteria. In a second step, country experts

were asked to fill out a tailored questionnaire. After filing reports for each country, the experts reviewed the report for their country in order to validate the presented data. Thereby a decision-tree was developed (D5.2.3).

Aiming to introduce a common integrative evaluation methodology, WP5 partners developed the Driver Rehabilitation Evaluation Tool (DRET). Existing evaluation tools were reviewed and discussed within the team and with other experts from several disciplines relevant for or linked to driver rehabilitation.

The validation of existing driver rehabilitation measures was carried out by a compatibility assessment study. Applying DRET a standard of a good practice was developed, against which existing European driver rehabilitation programmes were compared. The assessments were carried out on a quantitative base by the WP5 research team.

2.3.3. Results

The literature review concerning different offender types revealed that the entire group of DUI/DUID offenders seems to be heterogeneous. Following characteristics of DUI/DUID offenders were identified:

- Socio-demographic variables: male gender; young age; lower educational or professional level; lower socio-economic status; single or separated marital status.
- Traffic related variables: prior traffic offence records.
- Consumption habits: heavy to problematic substance use (major risk factors); first offenders are often moderate drinkers; co-morbidity of substance use problems with other clinical disorders.
- Personality traits: e.g. sensation seeking or aggression; general risky life style; low self-control, poor coping styles.
- Decision making processes: deviant attitudes; poor knowledge; low risk perceptions; influence of the social surrounding, group norms and expectations.

Identified characteristics of the high risk group of DUI/DUID recidivists were:

- Socio-demographic variables: male gender; young age; lower educational level.
- Traffic related variables: the higher the amount of prior records, the higher the recidivism risk.

The review of assessment procedures shows that DUI/DUID assessments are carried out to evaluate fitness to drive and to assign offenders to rehabilitation programs. The context determines the selection of tools and the whole procedure. In contrast to the assessment for rehabilitation assignment, the legal context of a fitness to drive assessment requires particularly a high specificity and thus an integrated and comprehensive approach. Objective parameters like BAC or prior offences can serve as assignment criteria for deeper assessments or even directly for specific driver rehabilitation. In Europe DUI/DUID assessment is primarily carried out in the frame of the fitness to drive decision. It is mostly a multidisciplinary approach, covering medical, psychological and social aspects.

Driver rehabilitation programmes for DUI offenders are based on a rather long term tradition in development and practical application in Europe. They are also the basis for the later developed programmes for DUID offenders. WP5 found out that there is no uniformity in Europe regarding the implementation and application of DUI/DUID

rehabilitation. In the five selected European countries (Austria, Belgium, France, Germany and Hungary) national regulations on different aspects of DUI/DUID rehabilitation are established. Regarding the access to DUI/DUID rehabilitation programmes, the literature shows that European countries use very different approaches, ranging from voluntary, over recommended, up to obligatory participation.

The review of DUI/DUID driver rehabilitation effectiveness identifies 61 studies on the topic. European standard group intervention programmes for DUI offenders show an average recidivism reduction rate of 45.5% (36 studies and 2 reviews) although a large variation of recidivism reduction rates was observed (15% - 71%).

Based on the provider questionnaire survey, a comprehensive picture of the actual situation was drawn: At least 47 providers, mainly non-governmental, private organisations in 12 European countries (Austria, Belgium, France, Germany, Hungary, Italy, The Netherlands, Poland, Portugal, Sweden, Switzerland, and United Kingdom) carry out driver rehabilitation services on a regular basis. In total, 87 driver rehabilitation programmes are in use, thereby 53 for DUI offenders, 21 for DUID offenders and 13 for mixed groups (DUI/DUID/other traffic offenders). All above mentioned countries offer programmes for DUI offenders, in addition four Member States (Austria, Belgium, Germany, and Portugal) for DUID offenders. The vast majority of driver rehabilitation providers do not offer treatment programmes for substance dependent offenders.

The main results of the literature review of addiction treatment and options for dependent DUI/DUID offenders can be summarized as follows:

- Psychosocial treatments of alcohol and drug dependent patients are well established interventions to support the maintenance of abstinence and to decrease the scope and frequency of alcohol and drug consumption.
- No superior general strategy could be identified.
- It is important to consider characteristics of the patient, predominant symptoms of the dependence, and also motivation aspects while matching patients and treatment approaches. A combination of different treatment strategies provides the advantage of simultaneously addressing different factors and levels of influence.
- The addiction-specific approach is a fundamental element within the rehabilitation of dependent DUI/DUID offenders.

For the in-depth analysis on recidivism reasons a sample of n=303 recidivists and a matched control-group of n=303 non-recidivists were analysed. Group comparisons on univariate level reveal 20 significant differences between study and control group. On multivariate level, six of them show predictive value in a regression analysis additionally.

Based on the entire results, the following risk profile of DUI offenders who might not profit from a driver rehabilitation course can be deduced:

- Having high BAC levels at the current offence or refusing the breath test
- Having additional prior drink-driving or already several DUI offences (i.e. not the first one) and consequently having longer suspension periods of driving licence
- Having a habitual drinking pattern in the past and in spite of past or current abstinence periods having an increased alcohol tolerance, thus having also felt less impaired at the actual DUI offence
- Denying or not having any alcohol related health problems, being a smoker and being less aware of own health status

- Showing an unrealistic self-perception and less self-reflection whereby alcohol related risks in traffic are underestimated
- Not living in a partnership
- Being assessed as having an enhanced re-offence risk by a qualified expert (traffic psychologist).

The results of the participant questionnaire survey indicate that driver rehabilitation participants feel that such programmes provide strong support for their cognitive and behavioural change processes. The findings suggest that participants feel encouraged to establish new behavioural goals and the commitment to stick to them. At the same time, the participants' ratings emphasise the important role of the course leader in encouraging such changes. About 95% of all European DUI offenders who participated in this study assess the driver rehabilitation course as good or very good. Only about 2% rate the course as bad or very bad (about 3% gave no answer).

The analysis of the existing QM systems revealed that QM systems in driver rehabilitation schemes are expedient to create transparency by setting rules and instructions (standards). The compliance with the standards is a necessary precondition for winning a trust of all stakeholders: legislators, authorities, individuals and the public. The decision-tree developed in DRUID may serve as a tool to evaluate the established QM system on a national, provider and programme level. It could also be used by international and national legislators and providers while implementing a QM system in the domain of driver rehabilitation.

The Driver Rehabilitation Evaluation Tool (DRET), developed in WP5, covers the main technical issues of driver rehabilitation measures. 28 items have to be evaluated in total whereby 11 items focus on (national) driver rehabilitation system issues and 17 items on single programme level. Evaluation of driver rehabilitation system and single programme is separated, DRET-L refers to the first and DRET-P to the second one. In order to assess single DRET items against the DRUID WP5 standards, additional studies were implemented. The evaluation was carried out by means of a categorical answering mode with four alternatives (yes, partly yes, no, don't know) supported by a colour system. In principle, answering could be done either in an electronic or paper-pencil mode.

In total, 90 driver rehabilitation programmes from 12 countries (Austria, Belgium, France, Germany, Hungary, Italy, Netherlands, Poland, Portugal, Sweden, United Kingdom and Switzerland) were included in the validation study, thereby n=55 for DUI offenders, n=21 for DUID offenders and n=14 for mixed offender groups (alcohol and drug offenders or both mixed with general traffic offenders). This set of driver rehabilitation programmes for substance impaired drivers provides a comprehensive picture on actually existing driver rehabilitation programmes in Europe, although it does not claim to be fully representative. Out of the assessed 23 driver rehabilitation items crucial for successful driver rehabilitation interventions, 9 were completely fulfilled and further 9 at least partly by the assessed European driver rehabilitation programmes. Only 5 driver rehabilitation relevant topics showed a low compliance with the compared DRUID WP5 standard, namely existence of a national QM body, definition of operative tasks of QM body, multidisciplinary approach in case of prior driver assessment, objective, valid, reliable tools in driver assessment and evaluation of driver rehabilitation programmes. An additional comparison of driver rehabilitation programmes for DUI and DUID offenders revealed some differences in the fulfilment of the legal frame conditions as well as in driver rehabilitation content related requirements. Thereby, except of the evaluation requirement, DUID programmes comply better with the WP5 standard than the programmes for the DUI offenders.

2.4. Withdrawal

2.4.1. Objectives

The DRUID Work Package 6 dealt with driving licence withdrawal and re-granting legislation and practices. The aims of DRUID WP 6 were threefold:

1. To review the state-of-the-art on withdrawal of driving licences by collecting and evaluating information on existing legislations and practices in various European countries.
2. To assess effectiveness of these strategies, particularly with a focus on conditional driving licence withdrawal.
3. To develop corresponding recommendations for road safety policy makers at the national and EU level.

2.4.2. Methodology

In order to gain information about existing legal regulations and sanctioning practices, a special DRUID questionnaire was designed. The questionnaire consisted of four parts, each referring to psychoactive substances and driving. The first part dealt with legislation in the different countries. The focus of the second part was on detection and police enforcement. The third part concerned toxicology. The fourth part referred to the sanctioning practice of administrative bodies and/or public prosecutors/courts.

The questionnaires were sent out to country experts. All 27 Member States and 3 non-EU countries responded to the questionnaire. The responses were subsequently entered into a database and finally resulted in a report for each participating country. To ensure the quality of data, all country reports, except for Bulgaria, were once again reviewed and approved by the country experts.

The analysis of the survey data revealed further research demands, e.g. due to the various interpretations of the terms "driving ban" and "licence withdrawal" and a lack of information on some specific issues, e.g. conditional licensing. Therefore, a second survey among the European countries was carried out in order to get complete, reliable and differentiated information about the use of the instrument "withdrawal" in case of driving under impairment of psychoactive substances. Additional data on specific withdrawal procedures in the European countries were collected.

The questionnaire for the second survey was developed by the Task 6.2 research team. In order to provide a high standardization of the survey procedure, to ease and to fasten answering of the questionnaire, a closed answering format was chosen whenever possible. Nevertheless, an open answering format was included as well to include answers other than the predefined ones or to give space for exact and further detailed information or explanations about the national realities. The survey had an electronic answering format and was sent out by e-mail to experts. Additionally, a responsible research team member contacted experts via telephone to assist them by answering the questionnaire.

In addition, findings from empirical primary studies on the general and special deterrent/preventive impact of withdrawal were analysed. Results from non-empirical literature were also considered. The search for criminological empirical primary studies was carried out in journals and databases in order to find research work which deals with the sanctioning of impaired driving (especially licence measures). Finally, the

reference lists of the examined empirical primary studies were checked for further appropriate empirical research findings.

In a next step, results from other WPs regarding legal issues were summarised. To supplement all findings, expert workshops were held in order to discuss and cross-check the research results. Experts provided input on specific problem groups and withdrawal concerning topics for which empirical results were insufficient. Two kinds of expert workshops were conducted:

- Country expert workshops

These workshops aimed at getting feedback and additional input from national experts regarding withdrawal and accompanying issues. Research outcomes of Task 6.2 were presented and discussed considered from two sides: the legal realities in the European countries and the scientific findings on the effectiveness of withdrawal and accompanying measures. In order to make outputs comparable, national workshops were conducted in each country according to the standard scheme, prepared and agreed upon within the Task 6.2 research team. The target groups of national experts to be involved were specified: Ministry of justice; courts, administrative authorities; Ministry of health; rehabilitation system; police, Ministry of interior; Ministry of transport.

- International expert workshops

These workshops, conducted in close cooperation with the WP1, focussed on withdrawal related solutions for specific problem groups, namely drivers in substitution treatment and drivers in long-term medication treatment. The workshops aimed at developing recommendations based on expert knowledge.

2.4.3. Results

The WP6 created a comprehensive database of the legal systems as well as practices in European countries with respect to withdrawal of driving licenses as a consequence of driving under influence of alcohol, illicit drugs or medicines. Besides, procedures and practices of re-granting driving licences to drivers, from whom a licence has been withdrawn due to impaired driving, were analysed.

The focus has been put on the following issues:

- Licensing system in general (withdrawal – renewal, special provisions for novice / young / professional drivers)
- Alcohol / illicit drugs / medicines and driving legislation (zero tolerance or impaired approach, specified levels, special laws for novice / young / professional drivers)
- Legal regulations for detection (testing at random or on the basis of suspicion; regulations regarding testing of alcohol / illicit drugs / medicines)
- Different kinds of sanctions for impaired driving (e.g. criminal or administrative penalty, fine, withdrawal, imprisonment)

The collected database provides reliable data for administrators, politicians and researchers.

In most EU countries (24/30 countries or 80 %) driving under the influence of alcohol leads to withdrawal of the driving licence. Thirteen out of 20 countries state a BAC threshold of 0.5g/L or above. A considerable number of EU countries have a withdrawal sanction for driving under the influence of both alcohol and drugs (19/30). About half of the EU countries (12/30 countries) have withdrawal sanctions for all three groups of psychoactive substances, i.e., alcohol, drugs and medicines. A typical approach (2/3 of all countries) is a temporary withdrawal of a licence.

In 21 of the European countries, conditional withdrawal is not possible, but at least 10 countries provide this possibility. The conditions are mostly time related (e.g. withdrawal is only effective during weekends). In a few cases, the conditions are related to geographical area (distance between home and working place/school/doctor's practice) or vehicle technology (alcohol interlocks). Other conditions, such as driver's profession, driving licence categories or health reasons were indicated as well. In 4 of the 10 countries which have implemented conditional withdrawal some additional diagnostic information is required for the decision on conditional withdrawal. This information can be obtained through medical or psychological assessment.

Regarding conditional re-granting, the conditions are mostly time related, i.e. the licence is re-granted only for a certain period of time or is limited to special situations, e.g. time for driving to work, for driving kids to school or for medical consultations. Conditions can also be related to the geographical area (e.g. distance between home and working place/school/doctor's practice) and to vehicle technology (e.g. alcohol interlocks). Apart from these, other conditions can be imposed like addiction treatment, regular screening of substances, driver rehabilitation. Some other conditions are: type of driver (professional or non-professional), restriction to a certain speed limit, medical assessment, proven abstinence for at least one year, stable change of the consumption behaviour, attendance in a course for drink and drive offenders. In 11 of the 13 countries which have implemented conditional re-granting, additional diagnostic information is required for the decision if the driving licence can be re-granted conditionally. The additional information is acquired by means of medical and/or psychological assessment. In some countries, it depends on screening results (blood, urine, hair) or a driving test carried out by the traffic authority's physician.

Further on, it was inquired if there are any options to reduce the withdrawal period after the driving licence has been withdrawn. 22 of the countries do not have any options to reduce the withdrawal period after the driving licence has been withdrawn, while 9 countries have this possibility. Thereby, in some countries the withdrawal period can be reduced after participation in a treatment, rehabilitation or ignition interlock program. The withdrawal period can also be reduced for some other reasons, such as personal, professional or social circumstances, the character of the applying offender, his conduct after conviction or the nature of the offence.

Altogether, 19 countries have more severe sanctions for recidivists driving under the influence of illicit drugs, while 11 countries do not differentiate between first time and persistent offenders. More severe sanctions for recidivists comprise imprisonment, fine, driver rehabilitation and licence withdrawal.

Generally, there are 9 different conditions for re-granting a driving licence in Europe after it has been withdrawn for driving under the influence of alcohol, illicit drugs and medicines:

- a. Medical assessment
- b. Psychological assessment
- c. Screening for substance markers in blood/urine/hair
- d. Driver rehabilitation
- e. Treatment programme
- f. Theoretical driving lessons
- g. Practical driving lessons
- h. Theoretical driving test
- i. Practical driving test

Almost all European countries have police control strategies concerning driving under the influence of psychoactive substances (26/30), while only 4 (Czech Republic, Denmark, United Kingdom and Ireland) do not have systematic police controls. All 27 Member States use a systematic approach in relation to specific locations or specific events, weekdays or daytime.

The outcomes of the second survey showed that 22 out of 31 European countries distinguish between licence withdrawal and driving ban, while 9 do not.

Regarding withdrawal periods, sizable differences between the European countries can be observed in case of alcohol. The withdrawal periods in most countries depend on certain BAC limits which differ considerably between the countries. Accidents under the influence of alcohol as well as recidivism, i.e. another DUI offence within a certain time period, entail in some countries an extension of withdrawal period.

Only 22 out of 31 countries informed DRUID researchers on withdrawal periods regarding DUID. Thereby, 8 countries indicated periods up to six months. Withdrawal periods between six and twelve months exist in 4 European countries. Longer periods, namely between twelve and 24 months and above 24 months were quoted in 5 countries.

13 out of 31 European countries indicated requirements for patients in substitution maintenance treatment who would like to own or regain a driving licence. Thereby, the requirements are often connected with a fitness to drive examination. In some countries regular medical checks are necessary. 18 of the countries either do not have any criteria or do not allow patients in substitution therapy to drive at all. One country does not apply licence withdrawal or driving ban in this case.

The existence of regulations for patients under long term treatment was confirmed by 6 out of 31 European countries, 25 of the responding countries indicated to have no special regulations for this group. In all of the countries with regulations, a fitness to drive examination (medical or medical and psychological) is required.

The analysis of the empirical literature revealed that the general deterrent approach includes three main factors which often overlap:

- punishment certainty (including risk of detection and probability of sanctioning in the narrow sense),
- punishment severity (including the legal threat of sanctions and the judicial/administrative practice of imposition),
- punishment celerity.

The perceived risk of detection (not the real risk) is the main general deterrent factor. In most cases, the first one is higher than the second one, which is mainly influenced by the intensity of the media coverage. Laws without discretion for the authorities are major factors to increase the probability of sanctioning in the narrow sense. But this element must be accompanied by a high level of detection risk to achieve significant levels of general deterrence. Empirical primary findings support the statement that an increase of the sanctioning certainty is much more effective than an enhancement of the sanctioning severity. The punishment celerity is - besides the punishment certainty - a further important deterrent factor.

The results of driving licences measures can be summarised as follows (Table 20 and Table 21):

Table 20: Results on general deterrence.

Topics	Results on general deterrence
General mode of functioning	<p>Driving licence measures show measurable closer correlations between their imposition and the increase of the general deterrent level than other sanctions (e. g.: imprisonment or fines)</p> <p>Three main factors (in accordance to their importance for the achievement of law-abiding behaviour): sanction certainty (perceived risk most important), sanction celerity and severity</p>
Administrative vs. criminal procedure	<p>Advantages of administrative procedure due to sanction celerity and sanction certainty (especially in case of per se legislation)</p> <p>Disadvantages of criminal procedure due to huge differences in the severity of the imposed sanctions</p>
Duration of driving licence measures	<p>No significant impact of short-term driving ban (12 – 24 hours)</p> <p>Significant deterrent impact of driving licence measures with a duration between three and six months</p>

Table 21: Results on special deterrence.

Topics	Results on special deterrence
General mode of functioning	<p>Driving licence measures show measurable closer correlations between their imposition and the increase of the general deterrent level than other sanctions (e. g.: imprisonment or fines)</p> <p>Three main factors (in accordance to their importance for the achievement of law-abiding behaviour): sanction certainty (perceived risk most important), sanction celerity and severity</p>
Administrative vs. criminal procedure	<p>In many cases: Significant reduction of recidivism rates after implementation of administrative driving ban laws for both first-offenders and recidivists</p> <p>In many cases: Significant impact of withdrawal imposition in an administrative procedure combined with per se laws</p>
Re-granting	<p>Deterrent effect of withdrawal might be highly determined by the re-granting procedure (promising results can be achieved if a medical-psychological examination is included)</p> <p>Some empirical hints for a lack of increased recidivism rates in case of reduced withdrawal periods after medical-psychological assessment followed by an educative/rehabilitative measure</p>
Duration of driving license measures	<p>Mostly: Significant reductions of recidivism rates in case of driving licence measures with a duration between three and twelve months. From twelve months upward, an increase of the recidivism rates can be observed in a lot of cases.</p> <p>Significant increase of offences (driving while suspended) in case of long duration of withdrawal, worst effect from three years upwards. Higher compliance rates in case of shorter durations.</p>

<p>Conditions, reductions, restrictions</p>	<p>Better special deterrent outcome of restricted licence (e. g.: permission to drive to work and treatment related activities) combined with treatment/rehabilitation compared to the sole imposition of driving licence measures</p> <p>Some empirical studies show the worst effects in case of the sole imposition of restricted licence, valid for both first- and especially multiple-offenders</p> <p>Close monitoring of offenders is important</p>
<p>Rehabilitation</p>	<p>In case of addiction or misuse, punitive sanctions alone are generally not effectively deterrent</p> <p>Best effects can be achieved by a combination of driving licence measures with treatment/rehabilitation</p> <p>Treatment/rehabilitation has to complement, but not to substitute licence measures</p> <p>In case of combination of treatment/rehabilitation and licence measures, withdrawal periods can be shortened or replaced by licence restrictions</p>

Within the international expert workshop on driving licence and substitution maintenance treatment consensus was achieved regarding the following statements:

- It is not adequate to generate over-regulation for a small group which is of minor importance for road safety.
- There should be no basic difference made between patients in substitution treatment and patients in other medicinal treatments.
- In comparison to other patients, patients in substitution treatment show a high compliance.
- An early integration and the option of conditional licence are important and support the rehabilitation progress.
- A model of conditional licence with regular follow-up-controls is recommendable.
- The development of a rigid assessment and evaluation model is inadequate. It should be individually adaptable.
- Abstinence of relevant parallel consumption of other drugs (besides alcohol) is important. Alcohol-driving-abstinence (separation of drinking and driving) is necessarily required as well as the ability to separate parallel consumption of other drugs and driving.
- Alcohol addiction or other substance addictions are exclusion criteria.
- Regular checks for other drugs are indispensable. Hair analysis should be carried out every six months or urine screenings more frequently. Immunological tests are sufficient. Confirmation analyses are necessary if patients deny positive results.
- "Psycho-social integration" is not a reasonable criterion, psychiatric diagnostic preferred instead. Hence, a successfully completed therapy is not a reason for considering the social integration as restored.
- Substitution substance (Methadone vs. Buprenorphine vs. Morphine) and the height of the daily dosage in milligrams aren't criteria to judge on fitness to drive. The substance and dosage being adequate for each client are crucial issues.

- A follow-up-period after tapering the dose (treatment end) should be defined individually.
- For older long-term patients, specific regulations should be implemented as they often consume prescribed medicines in parallel.
- In cases of the intake of other disease-related prescribed medicine, tests of the cognitive performance are recommended to assess the fitness to drive.
- Patients treated with diamorphine (pharmacological heroin) are not fit to drive due to massive secondary impairing disorders as a result of long-term heroin use and heavy addiction (which are necessary requirements for being treated with diamorphine). Additionally, patients in diamorphine treatment need to inject the substance twice a day. As a consequence, they are left in a slight flush until first signs of withdrawal symptoms appear.

No consensus was found regarding the statement that patients in substitution treatment are basically not fit to drive Group 2 vehicles (C1, CE, C1E, D, D1, DE, D1E and passenger transport).

The experts of the international workshop on driving licensing issues and long-term medication found consensus on the following statements:

- No approach solely based on substance classes is needed.
- Impairment is the key for sanctioning. Patients should be adequately informed on possible impairing effects and how to recognize them (leaflets, consultation by physician or pharmacist).
- A model of conditional licensing is only recommendable after an incident which was sanctioned by full withdrawal.
- A primary preventive approach with a reporting obligation of physicians is disproportionate.
- Primary preventive licensing measures to be introduced only due to a prescription of psychoactive medicine are not necessary.
- A medical expertise / assessment should be ordered case-by-case. In this frame, an individual solution, e.g. regarding certain conditions, can be developed. The expertise should include the medication at hand and also personal issues.

2.5. Dissemination

2.5.1. Objectives

The main goals of WP7 were the development of guidelines for healthcare professionals and on risk communication aimed at different target groups based on DRUID outcomes.

The following objectives were pursued in DRUID WP7:

- State-of-the-art review of existing campaigns concerning psychoactive substances;
- Reflections on improvements of procedures for assessing fitness to drive;
- Development of prescribing and dispensing guidelines for physicians and pharmacists to select the least impairing medicine within a therapeutic class and to inform a patient meeting his/her needs;

Conditions, reductions, restrictions	<p>Better special deterrent outcome of restricted licence (e. g.: permission to drive to work and treatment related activities) combined with treatment/rehabilitation compared to the sole imposition of driving licence measures</p> <p>Some empirical studies show the worst effects in case of the sole imposition of restricted licence, valid for both first- and especially multiple-offenders</p> <p>Close monitoring of offenders is important</p>
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- Development of prescribing and dispensing guidelines for physicians and pharmacists to select the least impairing medicine within a therapeutic class and to inform a patient meeting his/her needs;

- Evaluation of practice guidelines and protocols in every day medical and pharmaceutical practice by focussing on different practice models, with and without the application of Information and Communication Technologies (ICT), as well as the evaluation of risk communication to patients;
- Development of information aimed at various target groups (general public, drivers as patients, younger people, health care professionals and policy makers);
- Development of a strategy for risk communication to young drivers.

2.5.2. Methodology

Due to a variety of tasks performed in WP7, different methodological approaches were required.

Overview over existing campaigns and their impact on road safety

A review was conducted on the state-of-the-art of existing information campaigns regarding psychoactive substances, as well as the documented effectiveness of those campaigns (D7.1.1). A questionnaire was sent out to all 37 DRUID partners to collect information on public campaigns regarding driving under the influence of psychoactive substances. The effects that were considered when collecting information on the impact of the campaigns went from effects on the awareness of the campaign (minimum effect) to effects on attitude and behaviour (maximum effect). Information was also collected by using Internet (websites of relevant organisations, Google and YouTube).

Guidelines and Professional Standards

A questionnaire survey among driving licensing authorities and experts was conducted in 29 European countries (all EU member states, Switzerland, Norway) in order to obtain better insights into the current situation in Europe concerning guidelines for physicians on prescribing medicines with impact on driving performance and on assessing fitness to drive (D7.2.1). In addition, existing guidelines for pharmacists on advising patients while dispensing those medicines were considered (D7.2.2).

Evaluation and implementation of new technologies

The effectiveness of the implementation of developed protocols and guidelines on the attitude, knowledge and reported behaviour of healthcare professionals' (physicians, pharmacists, nurses) in clinical practice were evaluated via two different approaches: i) by using an integrated (ICT) tool (additional software integrated into the ICT software used by professionals in daily practice; country specific development) and ii) by using a non-integrated tool for presenting the protocols and guidelines (ICT tool developed within the framework of the project).

The target populations were health care professionals in the primary care setting: i) physicians (Belgium, Spain), ii) pharmacists (Belgium, the Netherlands, Spain) and iii) Nurses (Spain). In addition, a "pure" control group was added to evaluate the effectiveness of current practices with no DRUID-relevant information.

Participants were introduced to the tools/software(s) through a training scheme. Some of the participants did not receive training (e.g. the integrated group of physicians (SoSoeMe)). In addition, participants were informed about the DRUID guidelines

regarding driving and medicines intake. The time sequence involved a standard procedure of recruitment, briefing, and consent. Participants filled in the pre-questionnaire at the start of their training and a post-questionnaire after six months of using the DRUID guidelines in their practice). They used the software during their daily practice for either prescribing or dispensing medicines depending on the professional groups they belonged to. After the testing period ended they filled in a post-questionnaire in order to evaluate the effectiveness of the tool and the applied guidelines (D7.4.1 und D7.4.2).

Main DRUID results to be communicated to different target groups and prototype documents

The Deliverable D7.3.2 contains a summary of the main DRUID results. The authors of D7.3.2 provided a describing text and a summarizing overview table per WP. These texts and summaries were discussed in two rounds, first with the DRUID coordinator and WP7 partners at various work sessions and secondly with WP leaders and authors of main deliverables.

An on-line survey on the criteria for the design of prototype documents for information regarding psychoactive substances and driving was conducted to assess the opinions of experts in various fields (policy makers, physicians, pharmacists, researchers, professionals working in the field of illicit drugs, etc.). The documents were developed for various previously defined target populations (D7.3.1).

Effectiveness of pictograms in communicating risk to patients who drive under the influence of medicines

Two studies using a 2x3 design were conducted to compare the effectiveness of two pictograms (rating model and triangle model pictograms) in communicating risk associated with driving impairing medicines to patients and to assess patients' level of understanding and intention to change driving behaviour when looking at various pictograms. In the first study, the respondents (patients with a driving license visiting a community pharmacy) were exposed to a pictogram (rating model or homologue triangle model pictogram) and a category (category 1, 2 or 3). In this study, both pictograms were accompanied by the same side-text (experiment 1). In the second study the added value of the side-text was examined. Here, the respondents were exposed to the rating model pictogram with or without side-text and again one of the three risk categories (D7.3.2).

DRUID outcomes and risk communication to young drivers

In order to develop recommendations for appropriate media-based concepts for risk communication on the base of the DRUID outcomes a workshop with media experts, psychologists, social workers, police bodies and representatives from road safety agencies and governmental institutions was organized. The recommendations of the experts served as input for the subsequent formative evaluation. A representative sample of 15 to 24-years olds in Germany was interviewed about (A) their personal experiences and attitudes concerning driving under the influence of drugs, alcohol and/or medicines, (B) the knowledge and motivational base for processing thematic risk communication messages, and (C) specific issues in media use and preferences for risk message contents and channels (D7.4.3).

2.5.3. Results

Overview over existing campaigns and their impact on road safety

A total of 75 campaigns were found, from 13 different countries. The majority of the retrieved campaigns concerned driving under the influence of drugs and was aimed at young people. Other possible target populations include the general public, physicians, pharmacists, teachers, patients, drug users or other types of populations. Most of the retrieved information campaigns were conducted through the mass media. Brochures are the type of medium that is used most frequently, followed by posters, paper press, websites, booklets, TV commercials, radio spots, leaflets, tutorials or another type of medium. Most campaigns are organized by governmental organisations and road safety organisations.

Information on the impact of the campaign was found for only 7 campaigns. All these evaluations documented a positive outcome of a campaign. As only a few evaluations were found, and these campaigns and their evaluations were performed in different ways, it is not possible to draw conclusions concerning the association between the design of the campaigns and their effectiveness. It can be concluded that more evaluations should be performed on future campaigns concerning driving under the influence of drugs and/or medicines, and that these evaluations should be made in a uniform way and design in order to determine guidelines for developing future campaigns (D7.1.1).

Guidelines and professional standards

Based on the feedback on the questionnaire, an overview of the current European regulations and guidelines is presented. Concerning prescribing and dispensing of psychotropic medicines, which might have an impact on the driving performance, it was concluded that strict and binding regulations are the exception rather than the rule. The compiled guidelines are typically recommendations, not regulations. The role, responsibilities and tasks of physicians and pharmacists are not defined uniformly. Despite the great diversification of recommendations in the different countries one can deduct a common denominator. Physicians and pharmacists usually should give their patients the most comprehensive and adequate advice on medicines and their effect on driving performance. This includes a recommendation of not leaving the patient alone with the decision whether to drive or not while using medicines.

In most cases physicians and pharmacists will not be made legally responsible in case an accident happens to one of their patients under a certain medication. But they are advised to keep a proper record of the consultation, as they might be sued in civil court cases (by insurance companies).

The regulations in the different countries dealing with the procedures of assessing fitness to drive are mainly in line with the Council Directive. Practical implementations and the assignment of responsibilities differ from country to country. It is very difficult to derive a "best practice" from the present results.

Several opportunities to improve guidelines and procedures for assessing fitness to drive are presented based on the progress made within DRUID Work Packages 4 and 7. Several reflections on the existing guidelines and regulations, in particular on the text of Art 15 of Council Directive 91-439-EEC, resulted in 8 recommendations.

Some of the recommendations point at the vague terms that are used in Article 15 (such as "substance abuse", "regular use", both for medicines and illicit drugs, etc.), whereas more internationally accepted terms exist. It is also recommended to include

the underlying cause or reason for taking medicines, as well as all co-morbidity factors, while assessing fitness to drive. Another recommendation points at the term "combinations of medicines with central nervous system activity". It is emphasized that combinations of psychotropic medicines with other medication that can alter the metabolism of the psychotropic medicine (with a possible consequence of increased blood levels of the latter) will always call for an individual judgement by prescribing physicians and dispensing pharmacists. This is especially of interest for drivers with co-morbidities and in case of polypharmacy.

It is also recommended to apply the DRUID categorization system for medicines affecting driving performance in developing national requirements on fitness to drive.

Finally it is recommended that in situations where physicians will advise a patient to start driving again after a period in which the advice was given not to drive while using the medicine, specific procedures are needed to structure and document a consultation and to manage the risk of litigation in case an accident could occur.

It will take special efforts to derive a consensus at a European level for the use of terms and procedures that allow improvements for assessing fitness to drive. Therefore it is recommended that working groups and expert rounds should discuss the DRUID recommendations involving physicians, pharmacists, driving licensing authorities and policy makers (D 7.2.1 and D 7.2.2).

Evaluation and implementation of new technologies

The country studies showed that almost 74% of participants received no education regarding medicines and driving during their academic studies and their professional participation in post-graduate education. The information received during the training did change their knowledge about the potentially detrimental effects of medicines on driving fitness for more than half the participants (55%). After the implementation of DRUID guidelines, a 10% increase in the positive change of reported behaviour was observed in the overall physicians' samples across the country studies. Patients visiting pharmacists in the intervention group (Dutch study) were significantly better informed about driving impairing effects of their medication, but did not change their driving behaviour. The majority of patients (83.4%) visiting a health service or pharmacy (Spanish study) would reduce frequency of driving, if a prescribed medicine has the warning pictogram on the package.

The application of DRUID guidelines was successful and pinpoints the readiness of health care professionals to adopt them. The findings support the statement that guidelines are important and can improve the quality of health care. Physicians and pharmacists have shown a change in behaviour after the implementation of DRUID guidelines, therefore these guidelines could be successfully incorporated in existing decision support systems. These guidelines fill in an important "gap" linking prescribing and dispensing of medicine with both patient and road safety. Physicians are affected by the DRUID training. However, this training should not be a short-term endeavour, but flexible, adaptable, and personalized to local settings.

Based on the comments made by the health professionals within the country reports, the implementation of computerized guidelines and DRUID categorization was highly accepted as practical information by both physicians and pharmacists and participants were willing to continue using the DRUID information if integrated in their prescribing and dispensing computer systems for easier incorporation in their daily practices. Participants offered ideas for future developments such as inclusion of other medicines in the categorization scheme and the adaptation of information to the native language. Future recommendations should also include specialized and elderly directed advices

incorporated in the system and adaptation to other target groups and not only drivers (e.g. heavy machinery usage and seniors information).

A long term goal would be to evaluate the impact of guidelines on the health care system, various stakeholder groups and to compare it with other studies' findings. In addition, further research could facilitate adaptation and customization of guidelines for different groups of health care professionals and national settings. A set of DRUID recommendations has been derived from the main conclusions of both composite cross comparisons and country studies. The key message is clear about the necessity of diffusion of DRUID information to physicians, pharmacists, and nurses in all clinical settings (D7.4.1 und D7.4.2).

Main DRUID results to be communicated to different target groups and prototype documents

A presentation of DRUID results was made taking into account various target groups in terms of problem definition (alcohol, illicit drugs and medicines) and countermeasures (legal regulation, enforcement, classification of medicines, rehabilitation, withdrawal, guidelines for health care professionals, risk communication).

Eight overview boxes were produced to summarize the most relevant information per topic:

- Alcohol,
- Illicit drugs,
- Psychoactive medicines,
- Enforcement,
- Classification,
- Rehabilitation,
- Withdrawal (of driving license),
- Guidelines/risk communication.

The most relevant issues were extracted for each of the following target groups: (1) general public, (2) drivers as patients, (3) young drivers, (4) physicians and pharmacists and (5) policy makers on EU and national level (D7.3.2).

In a broader perspective the theoretic frame of risk communication was described (definitions and communication theory, risk communication and sources for patients, managing risk communication related to driving with impairing substances, risk management framework and risk acceptability).

A risk management framework was developed for effective risk communication in DRUID by defining all steps that need to be addressed in building good risk communication. The framework consists of 7 steps: identifying and consulting stakeholders (initiation), risk identification, risk estimation, risk evaluation, risk control, implementation and monitoring (D7.3.2).

Effectiveness of pictograms in communicating risk to patients who drive under the influence of medicines

In two separate studies in Spain and the Netherlands the effects of pictograms for communicating risk to patients were investigated, comparing the triangle model (e.g. French model) with rating model developed by DRUID WP 7 Partners (Figure 9).

Risk communication based on a developed DRUID rating model pictogram compared to an existing triangle model shows that a vast majority of patients (70-80%) consider these pictograms clear and self-explanatory, with a preference for selecting the DRUID model. 78.5% of the patients declared to change driving behaviour if confronted with the pictogram on the medicine box (D7.3.2).

The results of these studies show that both pictograms were effective in communicating risk. Those who participated in the studies were able to recognize and understand the risk of driving under the influence of medicines and have shown their intention to change their driving behaviour by driving less frequently. In both studies, the rating pictogram was preferred over the triangle pictogram.

In the Dutch study, for the rating model pictogram, a clear and direct correlation between the likelihood of changing driving behaviour and the level of impairment of a medicine has been observed: the higher the category, the more likely a change of behaviour by decreasing driving frequency.

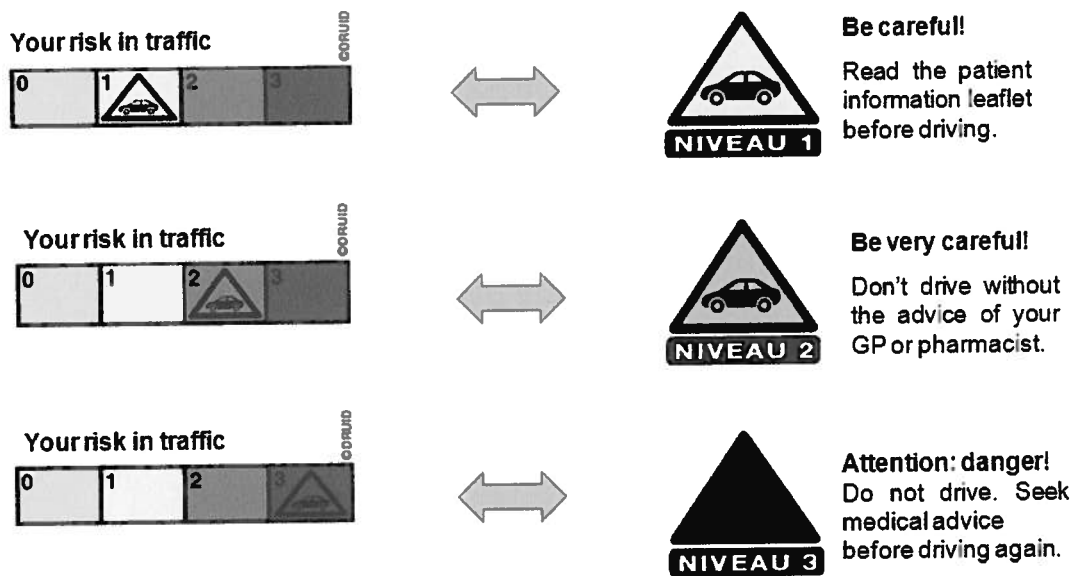


Figure 9: Pictograms – Rating Model (DRUID) vs. Triangle Model (France).

DRUID outcomes and risk communication to young drivers

In risk communication to young people, relevant content, necessary preconditions and promising strategies have been derived from a German approach in social marketing research.

Findings of the survey indicate that susceptibility to drink-driving and drug-driving applies to about 25% of young people. Permissive attitudes are more common among males and among formally low-educated individuals. Prospective drivers (mostly aged 15 to 17) display a slightly more positive attitude towards drink-driving and drug-driving than active, young drivers. This fact should be considered, when defining the target group for communication. With regard to talking and learning about DUI topics, strong preferences for peer communication were observed. In terms of important media channels, social network sites turned out as a promising pathway to reach out to young people. Overall, these and further results provide important foundations for adjusting DUI-related risk communication to low- and high-risk groups among prospective and active young drivers (D7.4.3).

2.6. Legal perspectives

It was the aim of DRUID to generate a solid knowledge basis for harmonized, EU-wide regulations on driving under the influence of alcohol, drugs and medicines that would embrace empirical, scientifically proven evidences.

The information presented in this section at a glance can be found in detail in D1.4.1 and D1.4.2.

2.6.1. Objectives

A basic prerequisite for developing recommendations concerning legal measures to combat DUI/DUID is an evaluation of relevant legal measures which are already installed. This evaluation has to be done from a legal perspective, i.e. to address the question, how driving under the influence of psychoactive substances can be effectively combated by means of legal interventions.

In the attempt to establish cut-off limits for drugs, close interdisciplinary collaboration between researchers involved in empirical research and in toxicology was necessary. To give recommendations for cut-off limits the experts had to cope with the following issues:

- Selection of scientific data necessary to estimate substance related accident risk
- Pros and cons of different research methods
- List of criteria for definition of a cut-off
- Selection of the psychoactive substances for which cut-offs should be determined
- Determination of substances that should be included, based on their prevalence
- How to deal with metabolites
- How to deal with combined consumption
- How to deal with legally prescribed medicine use
- Determination of analytical procedures and definition of the analytical substrate(s)
- Quality assurance of laboratory analysis and determination of measurement errors
- Pros and cons of whole blood and plasma as analytes
- Saliva (oral fluid), blood spots and the conversion factors between the different body fluids

2.6.2. Methodology

For the evaluation of legal measures to combat driving under influence of psychoactive substances an extensive literature study was done focusing among others on theories of sanctioning and empirical research results on DUI/DUID sanctioning (e.g. general deterrence of DUI policies and law changes, deterrence of jail sanctions and fines).

DRUID experts in the fields of experimental studies, epidemiology and toxicology collaborated closely to give recommendations on how to determine *per se* cut-off limits. A questionnaire concerning legal regulations regarding drugged driving and legally imposed cut-offs for illegal psychoactive substances was distributed in the European member states, Norway, Switzerland and Croatia. The reply was complemented with the official data of the EMCDDA.

Recently, three EU countries determined cut-offs for *per se* legislation. Information about the procedures and criteria used was collected by directly contacting national

experts involved in that topic. Concentration ratios between oral fluid and blood were established by collecting paired samples of oral fluid and whole blood from drivers in the RSS and in some of experimental studies. To evaluate the method of dried blood spots (DBS), samples of whole blood have been taken and concentrations of active agents have been measured in whole blood and in the blood spots.

2.6.3. Results

2.6.3.1. Evaluation of legal measures to combat DUI/DUID

Driving under influence of alcohol

There are several ways to diminish the risk of alcohol impaired driving. The most general of those, and also a suitable one for special risk groups, is the enactment and implementation of legal BAC thresholds. In this respect, the per se laws must be considered as the most effective approach to combat DUI. The standard per se value should not be higher than 0.5 g/L as recommended by EU to all member states (Commission Recommendation 2001/115/EC of 17 January 2001). The effectiveness of per se BAC values below 0.5 g/L is very much dependent on the prevailing societal, legal, political environment and the enforcement activity of the police in the respective member state, but also on habituation.

Results of studies show that informal non-legal consequences (e. g.: social disapproval, especially by peers and friends) can be very important to bring people to law-abiding behaviour. Especially on adolescent offenders, they seem to have much higher impact than formal legal consequences.

Evaluation studies are demonstrating that jail sanctions and prison sentences are not effective to combat DUI. Therefore they should be avoided as far as possible, in particular for first-offenders, at least in cases without aggravating circumstances. In contrast, probation periods are very suitable for first-offenders as well as for repeat-offenders. Fines are much more effective among adolescent offenders than among adults.

The implementation of a zero-tolerance approach seems to be very promising for young and novice drivers. Lowering the legal threshold for a certain period of time for convicted DUI offenders is an effective countermeasure to enhance road safety, but the practical implementation has to be assured. For other risk groups (e. g.: professional drivers, drivers of large vehicles or drivers of vehicles carrying dangerous goods), the enactment of lower legal per se BAC levels should be discussed with respect to the specialties of these driver groups. The implementation of BAC thresholds of at maximum 0.2 g/L was recommended by the European Commission (Commission Recommendation 2001/115/EC of 17 January 2001).

The risk of detection is crucial because only apprehended drivers are subjected to punitive or rehabilitative measures. The implementation of random breath testing laws is inevitable for securing a vigorous enforcement of zero-tolerance laws in general, but also for higher risk thresholds. As low amounts of alcohol regularly do not cause any visible signs of impairment, the otherwise effective suspicion based strategy is not promising here. In consequence, the implementation of analytical procedures that can be used as evidences is necessary.

Driving under influence of illicit drugs

In the near future for most of the drugs, only zero-tolerance and the impairment approach are available alternatives in combating DUID. As far as the first approach is favoured, it must be considered, that limits of detection and limits of quantification (LOQ) are based on technical limits.

In case an offender is above this limit, this doesn't necessarily indicate recent consumption of the psychoactive substance or being under influence. Thus, it is better to implement lower effect limits. Those limits can prove that a negative impact on driving existed.

Zero-tolerance is more promising particularly with regard to enforcement procedure. Especially the implementation of random drug tests is necessary to increase the currently very low risk of detection. As far as the development of valid screening devices is possible, the enactment of legally imposed analytical procedures is recommendable.

Until now the effectiveness of enforced impairment laws was relatively low. For the effective enforcement of impairment laws, it is necessary that policemen are able to detect all signs of impairment to register them in official protocols. Later on these records are the basis for a court conviction. Therefore policemen need regular special training that would enable them to detect all signs of impairment while implementing roadside checks.

The enforcement strategies must be targeted at special driver groups. On a general level, it must be distinguished between the detection-based and the deterrence-based strategy. The detection-based strategy is more effective for high-BAC drivers and regular consumers of drugs, because they can hardly be deterred by other strategies. In contrast, the deterrence-based strategy is more effective for the majority of social drinkers, young drink drivers and occasional drug users. To achieve this objective, highly visible testing sessions at places and during times with high traffic density, low density of offenders (e. g. in the early morning hours) must be conducted. For the detection strategy, places with inverse characteristics must be chosen and controls must be conducted unobtrusively. For both strategies it is important to conduct tests regularly.

Overall young drivers are rarely aware of legal interventions and enforcement strategies. Therefore information campaigns as well as education campaigns are highly recommended.

Driving under influence of medicines

Zero-tolerance is not appropriate for psychoactive medicines. Normally medicines are prescribed to treat diseases and complaints, some of which can impair driving by themselves. Therefore impairment law is more suitable.

Mixed intoxication through alcohol and other psychoactive substances (including medicines) is a much greater threat to road safety than the sole consumption of these substances. Consequently, the per se BAC limit in those cases must be lower than for the single substance consumption.

2.6.3.2. Determination of per se cut-off levels

Current state of legislation concerning drug driving

Most European countries adhere to one of two possible approaches or definitions of the act of drug driving: 11 countries use the impairment approach, 8 countries use zero-tolerance or *per se* limits and 9 countries combine these two approaches into a two-tier system.

Until now, all countries that have *per se* legislation use analytical cut-offs, i.e. the concentrations, lower than that can be reliably determined by forensic laboratories. In some countries, these are the lowest limits of quantification of the forensic laboratories, in other countries they have been established by experts. In some countries, even if they are called analytical cut-offs, some consideration was given to a relationship with effects, e.g. by measuring only the active cannabis component THC, instead of the inactive metabolite, and using a cut-off that corresponds to a concentration after a single dose, when the drug still has effects.

Substance thresholds

There are three classes of substance thresholds. "Risk thresholds": concentrations in blood that indicate a certain accident risk or impaired driving. "Lower effect limits": the lowest concentration where an effect on driving is observed. "Limit of detection" and "Limit of quantification": based on technical limitations in order to guarantee a valid and reliable analytical result and avoid false positive results.

In establishing thresholds, one must realize that the relationship between the concentration and the effect is not linear for most drugs, and that a given concentration could correspond to low effects (e.g. in a tolerant individual) or high effects (e.g. in a drug-naive subject).

The list of drugs to be included in *per se* legislation will depend on the situation in each country, e.g. the drugs that are most often found in the driving population or in drivers involved in an accident. Most countries have a very limited list of 10 substances or less. There is a consensus on not including medicinal drugs in the list. It is not reasonable to define cut-off values for patients in long-term treatment. Even high doses may lead to fewer effects because of tolerance.

Norway and the Netherlands recently tried to determine safe driving limits and they arrived to very similar values, e.g. 3ng/mL THC or 48 and 50ng/mL for MDMA in whole blood. Both countries defined a risk threshold for THC, where the impairment is equivalent to 0.5 g/L BAC.

In determining "lower effect limits", stimulant drugs like amphetamines and cocaine pose a particular challenge. The correlation between drug concentration and risk of traffic accidents/impairment is variable or insufficiently documented. In experimental studies, at the (rather low) doses that were given, driving performance increases rather than decreases.

However, in epidemiological studies indications of increased accident risk could be found. To define cut-offs the results of experimental studies and of epidemiological studies should be taken into account. In case there is not enough data available, another approach has to be chosen: The pharmacokinetics of these substances could be used together with data on consumption patterns to determine cut-offs. The cut-off can be set at a certain time after use, e.g. the duration of the effects.

Usually, inactive metabolites are not included in the legislation, except when the parent drug is unstable and is metabolized very rapidly. Some drugs like THC have a very rapid metabolism, and if the delay between the stop or accident and the blood sampling is long, the concentration could decrease remarkably (based on a half-life of 1.4 hours, 3ng/mL of THC decrease to 0.68ng/mL after 3 hours). The "lower effect limits" should be established taking this into account. Another possibility, but less easy to implement, is that the lowest concentration that can be accurately measured (LOQ, limit of quantisation) is used instead of the lower effect limit when the sampling delay is longer than 2 or 3 hours.

The epidemiological studies in DRUID have shown that people very often use more than one drug. The question has been raised if the *per se* lower effect limits or the LOQ should be used when more than one drug (or alcohol) is detected. Some have recommended using the LOQs. One of the problems of using lower effect or safe driving limits is a definition of the dose that can be taken still remaining under the limit. One should realize that establishment of lower effect limits does not mean that one excuses drug use. In many countries (e.g. Sweden and Finland), people who are sanctioned for driving under the influence of narcotics will also be sanctioned for drug use, or sanctioned for drug use even if inactive metabolites are detected. But to achieve the compliance of the population, a clear legislation should be implemented, which differentiates drug and traffic policy.

It is not a problem to limit the list of drugs in *per se* legislation to a few substances, if the *per se* law is combined with an impairment law, where all other impairing substances are covered. In this scenario, a quick and easy to enforce procedure exists for the most common drugs, and a more elaborated procedure exists for the less frequent cases, including medicinal drugs and combination of drugs. It is not realistic to develop cut-offs for all existing medicinal and recreational drugs. Moreover, for new drugs it might take some time before cut-offs have been established.

Usability of conversion factors between analytes

In DRUID many experimental results were collected and a literature review was performed on conversion factors between plasma and whole blood and between whole blood (B) and oral fluid (OF). The drug concentration ratios between oral fluid and blood (sometimes called oral fluid to blood conversion factors) were studied by collecting paired samples of oral fluid and whole blood from drivers. Oral fluid to blood (OF/B) concentration ratios were calculated but large variations were found between individuals; typically the coefficient of variation (relative standard deviation) was 50 to 100%. Therefore, conversion factors cannot be used to accurately estimate drug concentrations in blood based on drug concentrations in oral fluid. The estimated equivalent cut-off concentrations for oral fluid and blood were used for the calculations of drug prevalence (D2.2.3) and for the odds ratio calculations (D2.3.5).

Drug analysis in samples of oral fluid can be used to estimate the drug prevalence in blood if using equivalent cut-off concentrations. Three formulas were used for estimating equivalent cut-off concentrations using the average OF/B ratio, median OF/B ratio or percentile regression. To determine which formula fits best the original paired data, the prevalence of samples above selected cut-off concentrations in blood was estimated using the formula and compared with the actual prevalence in blood. The accuracies of the three procedures were calculated for the chosen cut-off concentrations in blood and for concentrations corresponding to 2.5 times and 5 times the analytical cut-off. The procedure with the least average percent deviation (in absolute value) from the actual number of subjects with drug concentrations above the cut-offs in blood was identified as the best one for each substance separately. Based on this equivalent cut-offs were established for oral fluid.

Dried blood spots as alternative method for collecting blood samples

The use of dried blood spots (DBS) has potential as a precise and inexpensive option for the determination of several analytes in small blood samples. But the small sample volume requires very sensitive techniques. By using LC-MS/MS, all investigated analytes could be determined with sufficient lower limits of quantisation (LLOQs). Evaluation data showed no significant differences in precision as well as lower limits of detection (LLODs) and LLOQs. Analysis of DBS is feasible with the advent of increasingly sensitive MS technologies such as LC-MS/MS. The DBS/B ratios were very close to 1.00, and the relative standard deviations 8.56%. Thus, the use of DBS in routine analysis will result in simplifying blood sampling, transport and storage as well as sample processing in the laboratory. DBS drug analysis can be regarded as a valuable and inexpensive alternative to determination of substances from whole blood. It should be noted that no evaluations for THC have been performed yet. Therefore these results should be taken with some care.

Section 3 – Conclusions

The following section summarizes main results of the integrated project DRUID and aims at drawing conclusions relevant for policy makers on EU and Member States level. 50 deliverables, in which the outcomes obtained in the seven work packages of the project are described in detail, can be found on the DRUID website (www.druid-project.eu). Deliverable D7.3.2 “Main DRUID results to be communicated to different target groups” gives an overview of the project achievements across all work packages. In the deliverable D1.3.1 “Driving under the influence of alcohol, illicit drugs and medicines: Risk estimations from different methodological approaches” the results obtained in epidemiological and experimental studies conducted in DRUID are integrated. Deliverable D1.4.2 “Per se limits - Methods of defining cut-off values for zero tolerance” aims at giving pertinent considerations when a nation wants to determine per se cut-off levels.

As DRUID focuses on the effects of driving under the influence of (1) alcohol, (2) illicit drugs, and (3) psychoactive medicines, the following conclusions are divided into three corresponding chapters.

1. Alcohol

The roadside surveys (RSS) that were conducted in DRUID to obtain **prevalence rates** of driving under influence of psychoactive substances indicate that alcohol is the most frequently detected psychoactive substance in the general driving population as well as in the seriously injured and killed drivers in Europe (hospital studies, HS). On average in all European countries in which RSS were conducted⁷ (later on referred to as EU mean) 3.5% of drivers were driving under influence of alcohol ($\geq 0.1\text{g/L}$). There were rather big national differences (0.15-8.59%). Nevertheless alcohol was the most common toxicological finding in most countries. Referring to blood alcohol concentrations of 0.5g/L or above the EU mean prevalence in the general driving population reduces to 1.5% (range: 0.07-5.23%) and to 0.4% (range: 0.01-1.47%) for heavy alcohol consumers ($\geq 1.2\text{g/L}$).

The prevalence rates of alcohol impaired drivers being involved in an accident are even much higher in the participating countries⁸. In seriously injured ($\geq 0.1\text{g/L}$: 17.7-42.5%; $\geq 0.5\text{g/L}$: 16.1-38.2%) and killed drivers ($\geq 0.1\text{g/L}$: 19.0-44.9%; $\geq 0.5\text{g/L}$: 16.3-35.1%) alcohol was the most frequently detected substance. This means that drivers involved in an accident have more often higher alcohol concentrations in blood than drivers in the general driving population.

Referring to the results of these case-control studies the **risk of serious injury or fatality** for alcohol ($\geq 0.5\text{g/L}$) is significantly increased compared to sober drivers (i.e. drivers who are below the DRUID cut-offs for any substance). When the whole group of alcohol impaired drivers is divided in different alcohol categories the risk of injury and fatality continuously increases: 0.1-0.5g/L: 1-3 times higher risk; 0.5-0.8g/L: 2-10 times higher risk; 0.8-1.2g/L: 5-30 times higher risk; $\geq 1.2\text{g/L}$: 20-200 times higher risk (D 2.3.5). Taking into account the responsibility for the accident the DRUID results reveal that the risk of being responsible for a fatal accident is 5-8 times higher for an alcohol impaired driver ($\geq 0.1\text{g/L}$) than for a sober driver. Severely intoxicated drivers

⁷ RSS were conducted in Belgium, Czech Republic, Denmark, Finland, Hungary, Italy, Lithuania, Netherlands, Norway, Poland, Portugal, Spain and Sweden.

⁸ HS on injured/killed drivers were conducted in Belgium, Denmark, Finland, Italy, Lithuania, Netherlands, Norway, Portugal and Sweden.

($\geq 1.2\text{g/L}$) have a 15-21 times higher risk of being responsible for a fatal accident (D2.3.2). The risk of alcohol impaired driving is clearly confirmed in the experimental studies: Alcohol has a negative impact on driving performance and on skills related to driving (D1.1.2B, D1.2.1, D1.2.2).

Thus, alcohol is still a most dangerous psychoactive substance in traffic. This holds true for all EU Member States in which studies were implemented. Regarding this problem the following conclusions can be drawn:

- The first priority of countermeasures should always be on alcohol; other psychoactive substances are of second priority. This implies that any activities, regarding e.g. policy issues, enforcement, education or campaigns, should never be carried out at the cost of alcohol countermeasures.
- The concurrent implementation of diverse countermeasure, like drivers' education, enforcement, rehabilitation, etc. is necessary to combat driving under the influence of alcohol.
- The scientific assessment of the "alcohol problem" in the driving population should be carried out on a regular basis. DRUID established standards how to conduct national roadside surveys to gain comparable and valid data in Europe. A continuation of this work offers the possibility to assess the problem in the long run and to study the development of prevalence rates of alcohol cases. This could also be a valuable method for the evaluation of national campaigns against drunk driving. However, the conduction of roadside surveys is cost and time expensive. Further on the problem of national and/or European representativity is very complex and hard to solve. As participation in a roadside survey is voluntary, there is always a risk of bias through non-participation of impaired drivers. Therefore other ways of monitoring the prevalence of alcohol (and illicit drugs and psychoactive medicines) should be sought for as well.

In addition to determining the significance of the alcohol problem in the general driving population and in the population of seriously injured/killed drivers, DRUID tried to characterize **problem groups**. In the driving population alcohol was mainly detected among older male drivers: In most countries the share of alcohol positive male drivers was the highest for the two oldest age groups (35-49 and 50+).

Within accident involved drivers (i.e. seriously injured or killed drivers) alcohol was mainly detected among younger (25-35 years) male drivers with high BAC levels. High BAC level, young age and speed are associated with an increased risk. Further on the risk of having an accident multiplies with combined use. DRUID results demonstrate that the combined use of alcohol and drugs is very common and in terms of risk a serious problem (D2.2.3, D2.2.5, D2.3.5).

- Therefore countermeasures to combat driving under influence of alcohol should take into account driver characteristics. This means that enforcement strategies, educational activities or legislative measures should address special target groups and not the driving population as a whole.
- Countermeasures especially for young male drivers should be promoted. In Germany in 2007 zero tolerance for young (< 21 years) and novice drivers was implemented ("Null Promille für Fahranfänger"). The rate of alcohol related accidents within the target group could be lowered about 15% in the first year.

Appropriate countermeasures to combat alcohol impaired driving are **rehabilitation programs** (D5.1.1, D5.2.4). An average recidivism reduction rate of 46% (range: 15-71%) was found in standard group intervention programs for DUI offenders. The implementation and the quality of such programs in Europe vary from country to country. DRUID established the most comprehensive database on European rehabilitation schemes and measures as well as on quality assurance measures for rehabilitation programs, compiled up-to-date statistics of recidivism, analyzed recidivism reasons and suggested best practices in the field of rehabilitation.

Referring to alcohol rehabilitation programs the following conclusion can be drawn:

- Driving rehabilitation should be harmonized within Europe, e.g. by using common European standards and recommendations on rehabilitation good practices developed within DRUID.
- Driver assessment and rehabilitation should be legally regulated and based on defined criteria.
- Alcohol offenders should be treated in separate groups, not together with drug offenders.
- Non-addicts and addicts should be distinguished as they require different interventions or treatments.
- Multiple offenders and offenders with a BAC $\geq 1.6\text{g/L}$ should undergo an examination aiming to enable a provider to detect/exclude driver's addiction.
- An alcohol ignition interlock can be used during the rehabilitation phase, yet it should be combined with rehabilitation/treatment and close monitoring.

Further on DRUID analyzed practices of **driving license withdrawal** in European countries. The study revealed that national strategies are very heterogeneous. It can be stated that withdrawal is an effective general and special deterrent factor, if sanction certainty and celerity are assured. Sanction severity is less important. This means that an immediate withdrawal/suspension of driving license and a high level of perceived detection risk are decisive. Sanction certainty can be increased by strict enforcement (e.g. implementation of random alcohol and drug controls).

Additionally it can be stated that the combination of license withdrawal and treatment/rehabilitation is more effective in terms of deterrence than license withdrawal alone. This holds true especially for addicted drivers and in cases of medicines misuse. **Conditional withdrawal** is a measure to support the reintegration process of drivers. Conditional withdrawal seems to be effective when it is combined with rehabilitative measures and close monitoring (D6.2).

DRUID conclusions concerning withdrawal:

- Practices of driving license withdrawal should be harmonized across Europe.
- The withdrawal duration should be between 3 and 12 months.
- Driver rehabilitation should be an integrated part of driving license withdrawal.
- Conditional withdrawal should always be combined with rehabilitative measures and close monitoring.
- Zero alcohol limits for novice drivers are very effective.

2. Illicit drugs

The **prevalence of illicit drugs** in the general driver population (based on RSS) is much lower than the prevalence of alcohol. The estimated EU mean for all investigated illicit drugs is 1.9% (individual countries' range 0.2 to 8.2%), but there is a high national variability. Cannabis (THC) (EU mean prevalence: 1.32%; range: 0.0-5.99%) and cocaine (EU mean prevalence: 0.42%; range: 0.0-1.45%) are the most frequently detected illicit substances in most countries (D2.2.3).

Within the accident involved drivers the prevalence of the different substances shows great national variability as well, so no clear picture of the distributions can be identified. THC seems to be one of the most prevalent illicit drugs, followed by cocaine and amphetamines. The majority of illicit drugs is used in combination with other psychoactive substances, mainly with alcohol. Among seriously injured and killed drivers, those having consumed alcohol together with drugs, are the second most common group in all countries (except for LT). The group of drug-drug combined users represents either the third (BE, DK, FI, I) or fourth (LT, NL) most common group (D2.2.3, D 2.2.5, D2.3.4)⁹.

The DRUID results based on case-control studies show that the **injury risk** is extremely increased with combined use of drugs and alcohol comparable to the risk of alcohol consumption alone $\geq 1.2\text{g/L}$. Drug-drug combinations causes the second highest risk of injury, showing a highly increased risk comparable to the risk of alcohol consumption alone 0.8-1.2g/L.

The high risk of combined drug-alcohol or drug-drug consumption is confirmed by the experimental studies. With regard to MDMA it was found that drug use alone does not impair, but MDMA in combination with alcohol (or sleep deprivation) impairs driving performance dramatically. These results are validated by on road and simulator experiments (D1.2.1).

For the different investigated illicit drugs ORs between 2 and 7 were found. This increase of risk corresponds to the risk caused by BAC of 0.5-0.8g/L, which has an OR of about 4. Due to the low prevalence of illicit drugs in the RSS and HS it was not possible to differ between concentrations. Therefore drivers with (very) low and (very) high substance concentrations of the investigated agent were pooled. Furthermore due to the low numbers of positive cases and controls the confidence intervals are very wide. This indicates low accuracy of the ORs. In addition the ORs differ between the countries involved in DRUID (D2.3.5).

The sole use of illicit drugs is not frequently detected in Europe. There are great national differences in prevalence. The main problem has to be seen in combined consumption, i.e. when illicit drugs are consumed in combination with other psychoactive substances, especially with alcohol. Though the prevalence rates of combined consumption are not high either, the injury risk is clearly increased in these cases. The following conclusions can be drawn:

- Due to the great national variability regarding prevalence rates of illicit drug use countermeasures should be adapted to national requirements.
- Increase of drug enforcement is a countermeasure, which is potentially cost-beneficial for countries that currently have a low enforcement level. It is not beneficial when the increase is financed at the costs of drink-driving enforcement.
- Enforcement activities should take into account that especially combined consumption (drug-alcohol or drug-drug) is most dangerous.

⁹ In these Deliverables „drugs“ means both illicit drugs and medicines.

- Referring to combined drug-alcohol consumption it is supposed that even an alcohol level of 0.1 or 0.2g/L is enough to increase accident risk. This has to be taken into account when enforcement or legislative measures are adopted.
- The scientific monitoring of the "illicit drug problem" in the driving population should be carried out on a regular basis. However, RSS are very expensive and time consuming and their efficiency is doubtful. Time and amounts to be invested in RSS will have to be even increased in the future. Otherwise, taking into account low prevalence rates, it will be impossible to detect enough positive drivers in order to come to comparable and valid European data. The risk of bias in prevalence rates due to voluntary participation in roadside surveys aggravates this problem. In order to prevent drivers positive for illicit drugs from refusing to give a sample of any body fluid, the legal regulations would have to be changed in a way that would make mandatory collection of random samples possible. Therefore (even to a greater degree than for alcohol) other ways of monitoring the prevalence and risk of illicit drugs (and psychoactive medicines) should be investigated.

To make countermeasures more effective **characteristics of drivers tested positive for illicit drugs** were studied. DRUID shows that in the general driving population illicit drugs are mainly detected among young (< 35 years) male drivers, during all times of the day but mainly at the weekend. Combined use of alcohol and drugs is more prevalent among young (< 35 years) male drivers during night time hours. Combined drug-drug use is in general most common in middle aged male drivers. Referring to injured and killed drivers the use of illicit drugs is most prevalent in young and middle aged male drivers as well. Consequently countermeasures should be targeted to this driver group:

- Countermeasures against drug driving should take into account driver characteristics and should be target-group-specific.
- Enforcement strategies, educational activities or legislative measures should be addressed especially to young drivers.

Drug detection, especially in the context of roadside surveys and/or everyday drug-driving police enforcement, is a great challenge. In contrast to alcohol that can be easily and reliably detected by breathalyzers, illicit drugs have to be detected by **on-site drug screenings**. Police officers tested, within DRUID, the practicability of available oral fluid drug screening devices. Besides, scientific requirements on these devices were formulated and devices were evaluated correspondingly. The results show that most of the investigated systems are not effective enough concerning specificity and sensitivity. Thus, the roadside assessment of illicit drug consumption might be deficient, depending on the used device. Further on it has to be taken into account that large-scale random drug testing (which has the largest general deterrence effect) is not feasible, because the devices are too expensive and it takes too much time to collect and analyze samples.

Checklists (Clinical Signs Inventory, CSI) used by the police to preselect suspected drivers would be a good method to support on-site drug screenings. But DRUID results were not very encouraging in this regard. More experience and better training of police officers may improve the results.

Oral drug screenings and checklists have the advantage of being non-invasive methods, but are lacking high standards of reliability and validity. Blood analyses to the contrary allow precise detection of drug amounts, but are invasive and therefore not feasible for on-site screenings. The use of **dried blood spot testing (DBS)** might open new perspectives, since it is a minor invasive method and it has potential to be a precise and inexpensive option for the determination of several analytes in small blood

samples (D1.2.1, D1.2.2., D1.4.2). Analyses of DBS are feasible with the advent of increasingly sensitive technologies such as LC-MS/MS. The DBS-blood ratios are very close to 1.00, and the relative standard deviations $\leq 9\%$. The use of DBS will result in simplified handling during blood sampling, transport and storage as well as sample processing in the laboratory. Thus the DRUID results regarding dried blood spot analyses are very promising, though the practicability in the daily work of police has not been studied yet.

Conclusions with regard to illicit drug detection can be formulated as follows:

- Drug screening devices should be optimized regarding scientific requirements and practical use. National and regional circumstances should be considered when selecting screening devices.
- Checklists to preselect suspected drivers should only be used by sufficiently trained police officers.
- Dried blood spot testing is a very promising method and should be further developed and tested, especially for practicability regarding enforcement measures by the police.

Referring to blood analyses to detect illicit drug use DRUID established **common analytical cut-offs** and standardized analyzing procedures. These measures are crucial for comparing study results of different countries. The DRUID-standards already gained acceptance worldwide.

- An agreement should be established across Europe on the kind of body fluid to be used for drug analyses. Particularly important is to make a choice between whole blood and plasma.
- European harmonization of drug analyses should be carried on, i.e. common analytical cut-offs and standardized analyzing procedures should be introduced.

The development of **conversion factors** between plasma and whole blood and between whole blood and saliva became a major objective in the course of DRUID. Oral fluid to blood conversion factors were calculated by analyzing paired samples of oral fluid and whole blood from drivers in BE, FI, I, and NO. Large variations were found between individuals (coefficient of variation: 50-100%). Therefore, conversion factors cannot be used to accurately estimate drug concentrations in blood based on drug concentrations in oral fluid for most psychoactive substance. However, drug analysis in samples of oral fluid can be used to estimate the drug prevalence in blood if using equivalent cut-off concentrations. Therefore a method developed in DRUID can be used (D 1.4.2).

Valid detection of impaired drivers and appropriate analyses of body fluid samples are just one side of the coin. The other side is the establishment of effective **sanctions for offenders**. Almost all of the research findings refer to DUI, but of course general deterrent principles are valid for DUID offenders, too (see section "Alcohol").

A major problem is – in contrast to alcohol – that no legally defined risk thresholds are available. The implementation of thresholds (per se laws) increases sanction certainty and thus general and special deterrence. Clear information about thresholds and the compulsory consequences of driving under the influence need to be communicated by public campaigns. Especially young people should be better informed about the risks.

Taking these results into account we conclude that:

- Driver assessment (e.g. driving tests, medicinal or psychological examinations) should always be carried out for the decision on fitness to drive and further intervention (rehabilitation/treatment).
- Measures to improve sanction certainty and sanction celerity should be undertaken.

As already stated for alcohol, **driver rehabilitation** helps to prevent people from impaired driving. It can be concluded:

- Driver rehabilitation should be an integrated part of a comprehensive countermeasure system. Legal regulation of participating in rehabilitation measures should be established in order to assure interventions by offenders.
- Driving rehabilitation should be harmonized within Europe, e.g. by using common European standards and recommendations on rehabilitation good practices developed within DRUID.
- Different types of DUI/DUID offenders should be treated separately according to their special needs.
- Non-addicts and addicts should be distinguished as they require different interventions or treatments.

One major objective of DRUID is to make recommendations on establishing **cut-off levels for drugs in per se legislation** with regard to driving under the influence. Three classes of cut-offs can be used (D1.4.2):

- (1) "Risk thresholds": Concentrations in blood that indicate a certain accident risk or impaired driving.
- (2) "Lower effect limits": The lowest concentration where an effect on driving is observed.
- (3) "Limit of detection" and "Limit of quantification" (analytical cut-offs): Based on technical limitations in order to guarantee a valid and reliable analytical result.

Currently all countries that have per se legislation use analytical cut-offs for illicit drugs. In some countries these are the lowest limits of quantisation of the forensic laboratories, in other countries they have been established by experts. In some countries, although if they are called analytical cut-offs, the relations to effects have been considered, e.g. by measuring only the active cannabis component THC, instead of the inactive metabolite.

To determine risk thresholds for illicit drugs DRUID partners intended to find, for each substance, a concentration in blood at which the accident risk is equivalent to the risk associated with 0.5g/L BAC. This approach starts from the premise that alcohol impaired driving is tolerated up to a BAC of 0.5g/L in most European countries. This means that a certain risk is accepted and that this approach should be applied, also quantitatively, to the use of illicit drugs as well. The list of drugs to be included in per se legislation could embrace the drugs most frequently found in the driving population and/or in drivers involved in an accident. To calculate risk equivalents it is necessary to include impaired drivers with different substance concentrations (in blood).

However, in the epidemiological studies the number of drug impaired drivers was too small to determine different concentration classes. In addition from the RSS mostly only saliva samples were available. DRUID affirmed that it is not possible to convert the saliva concentration of a certain agent into blood concentration (D1.4.2). Therefore it was not possible to calculate risk thresholds for all substances.

Risk thresholds could be formulated only for **THC** which was the most prevalent illicit drug in the general driving population and in injured/killed drivers. The prevalence of THC across all countries that participated in DRUID is 1.37%. This is about one third of the alcohol prevalence. The epidemiological, the experimental and the meta-analytical approaches result in rather low risk estimations. Epidemiological case-control studies assess at maximum a 2.4-fold risk for injury, experimental studies and meta-analysis rank the risk between 0.5 and 2 times than that of sober driving. So THC seems to be much less impairing and risky than most of the other examined substances. Although a relationship between THC concentration and accident risk was found in the epidemiological studies, it was only possible to set an exact THC cut-off by a meta-analysis of experimental studies. Thereby it was found that the serum concentration of 3.8ng/mL THC (\approx 2ng/mL in whole blood) causes the same amount of impairment as 0.5g/L alcohol. This value could be an empirical basis for a threshold discussion. The meta-analysis could also be used to define limits comparable to lower BAC levels.

Any **threshold discussion** should address the question if the DRUID approach to determine risk threshold as equivalents to 0.5g/L alcohol is feasible. From a scientific point of view it can only be justified to accept the same risk for all psychoactive substances (including alcohol). From a political point of view the determination of risk thresholds as equivalents to 0.5g/L alcohol might be questionable, because a BAC of 0.5g/L is not a legal limit in all European countries. Some Member States have lower alcohol limits and therefore risk threshold calculations for THC would have to be adapted accordingly. Besides, in European countries in which presently a certain risk is accepted, a discussion continues concerning alcohol zero tolerance approach.

It has to be taken into account that the results of DRUID epidemiological studies have to be interpreted cautiously for most substances due to low numbers of drivers tested positive on illicit drugs in the RSS as well as in the HS. The confidence intervals, which are indicating the reliability of the calculated risks, are rather wide. This indicates that that the risk measures are not very precise.

In general the following top-down procedure for cut-off determination is recommended:

- use the epidemiological data on the accident risk of different single substance concentrations. If this data is not sufficient,
- use the experimental data. If this data is not sufficient,
- let national expert rounds determine cut-offs by using additional information (e.g. pharmacokinetic drug profiles, consumption behavior). If this information is not sufficient,
- use the limit of quantification (here the advantage is that new drugs may easily be implemented into the list of impairing substances).

The (empirical) determination of risk thresholds is much more complex and costly, especially when they should be based on case-control-studies. The list of drugs in per se legislation can even be limited to a few substances, if the per se law is combined with an impairment law, where all other impairing substances are covered. Moreover, with regard to new drugs it might take some time before the different cut-offs have been established.

In the course of DRUID two EU countries changed their legislation regarding drug risk thresholds. In The Netherlands and in Norway efforts were made to define cut-off levels for drugs in per se legislation. Both countries tried to determine lower effect limits and risk thresholds. The cut-off levels are based on the expertise of scientists of different subjects and politicians. Norway and The Netherlands introduced a THC risk threshold of 3ng/mL in whole blood (D1.4.2).

The following conclusions can be drawn:

- It is advised to establish legal risk thresholds for illicit drugs on the basis of solid empirical data, i.e. experimental and epidemiological results. If the empirical basis is too weak, pharmacokinetic substance characteristics could help to define a lower effect limit.
- The risk thresholds for drugs should reflect the impairment equal to that of 0.5g/L BAC or to any other legally relevant BAC.
- The risk threshold for THC should be set adequate to 0.5 BAC at 3.8 ng/mL serum plus an added value for measurement error and confidence interval.
- For all other illicit drugs a zero-tolerance should be implemented, as the empirical database does not allow a definition of risk thresholds yet. In order to determine the limit of effect, all information regarding the drug effects and its pharmacokinetics should be considered by national expert teams. Those teams could use the comprehensive data provided by DRUID. Thereby it could be avoided that further development of the analyzing methods leads to a constant decline of the limits of quantification.

3. Psychoactive Medicines

DRUID **prevalence studies** indicate that medicines (benzodiazepines, medicinal opiates and opioids, and Z-drugs) are less prevalent in the driving population (EU mean, all psychoactive medicines: 1.4%; range across countries: 0.17-2.99%) than alcohol and illicit drugs. The same holds true for the prevalence among accident involved drivers (D2.2.3, D2.2.5). Due to low prevalence rates risks can be estimated only for broad substance categories, i.e. benzodiazepines, medicinal opioids, and Z-drugs. Further on the national results show large variations.

In the DRUID prevalence studies an EU mean of 0.9% (range: 0.14-2.73%) is assessed for **benzodiazepines**, which is rank four in the prevalence ranking of all investigated substances. Among the injured drivers benzodiazepines (0.0-10.2%) were the third most frequent finding after alcohol and THC. Among the killed drivers the benzodiazepines (range: 1.8-13.3%) was the second most frequent toxicological finding after alcohol, followed by amphetamines. The risk of benzodiazepines was also a subject of the responsibility studies. About 6% of all tested drivers were under the influence of psychoactive substances, mainly benzodiazepines. **Medicinal opioids** are less common in the general driving population. For the prevalence of these substances an EU mean of 0.35% (range: 0.00-0.79%) is estimated. Medicinal opioids are relatively often used in combination with other psychoactive substances. The same holds true for Z-drugs. The estimated EU mean for **Z-drugs** is 0.09% (range: 0.00-0.69%).

DRUID results show that psychoactive medicines can be a problem for road safety. Although medicines are normally prescribed to treat diseases and complaints, some of these by themselves will impair driving fitness of patients. Patients fitness to drive will only be improved by medicines under specific conditions: a) use of medication by the patient according to the prescription, b) patient refrains from alcohol and other medicines besides those prescribed by the attending physician, c) patients restrain from driving at the beginning of a treatment or when medication or dose is changed.

The **risk** estimated by the DRUID case-control studies for benzodiazepines and Z-drugs is 2-3 for a serious injury and 5-7 for fatality. For medicinal opiates and opioids the European risk estimation is 5-8 for a serious injury and around 5 for fatality.

Experimental driving tests conducted in DRUID show a comparable or even impairment level for patients taking different hypnotics or opioids than drivers impaired by 0.5g/L alcohol. Zopiclone was less impairing than the alcohol reference as well. Only alprazolam proved to be highly impairing showing a 5-fold risk by already medicated anxiety patients and a 16-fold risk by healthy volunteers, both compared to 0.5g/L alcohol. This result indicates that the development of tolerance and habituation plays a major role for resulting impairment.

A meta-analysis conducted in DRUID reveals that impairment strongly depends on the kind of substance and dosage (concentration). The relevant studies have been conducted with healthy volunteers with single application. The results deliver important information regarding driver fitness after single intake and/or the beginning of a persisting medical treatment. But these results cannot be transferred to the situation of patients under long-term treatment because habituation leads to decrease of impairing side effects. In addition the medicinal treatment by itself could result in improving driving fitness.

In the epidemiologic studies (general driving population) psychoactive medicines were mainly detected among older (> 35 years) female drivers during daytime hours. The same holds true for accident involved drivers impaired by psychoactive medicines. These driver characteristics already imply that the associated target group that should be focused by countermeasures differs from alcohol and drug offenders (who are mostly young and male).

Medicines are usually prescribed to people suffering from a disease or complaint in order to treat or stabilise their condition. In case of impairment of psychomotor functioning by their disease condition, medicines could reduce impairment caused by the illness or complaint. Although the treatment effects of medicines are different comparing patients and health subjects, both groups can suffer from impairing side effects on driving fitness. There are evidences that, while being under long-term medical treatment, depressed patients and patients using analgetics perform better than patients without treatment or in comparison to healthy controls. A **DRUID expert workshop** was conducted on this topic, resulting in three main statements:

- (1) A proper prescription of a medicine includes correct information given to a patient by a practitioner. Patients under long-term treatment with psychoactive medicines should not be stigmatized by obligation to carry a special "medication passport". Other than by drug users, the responsibility and willingness to follow instructions regarding medicines use and driving under long-term treatment is usually observed in patients with insight in their condition and circumstances of impaired fitness to drive..
- (2) It is not reasonable to define cut-off values for patients in long-term treatment. Even high doses may lead to fewer effects. The correlation between dosage and impairment is only intra-individual. There is no clear inter-individual correlation. Dosage effects are mostly investigated and observed with single users or new users.
- (3) Alcohol increases impairment and interacts with many medicines in an unfavorable way. Hence, a separation of drinking, medicine consumption and driving is necessary and the respective information should be part of the physician's consultation.

The above statements together with the empirical DRUID results implicate:

- In general the preservation or recovery of a patient's mobility should be the ultimate ambition. Therefore patients taking psychoactive medicines are different compared to alcohol/drug offenders, i.e. the use of legally prescribed medicines should not be controlled by the same legal countermeasures as

provided for alcohol/drug offenders. Risk thresholds for psychoactive medicines should not be established. Moreover it is nearly impossible to define those thresholds because the impairment and accordingly the risk are depending on the type of substance, the dosage and the duration of the treatment as well as the interaction between disease and medication.

- The adequate countermeasure to combat impaired driving is information. A comprehensive information system for medical doctors, pharmacists and patients in order to inform them about the potential risk of the different psychoactive substances, the maximum impairment, and the duration of intake after which habituation has taken place, etc. should be implemented.
- Drinking, medicine consumption and driving should be separated. The respective information should be part of the physicians and pharmacists consultations.

DRUID suggests the implementation of a four level **classification and labeling system** (D4.2.1, D7.3.2) regarding the influence of medicines on driving performance. Over 3000 medicines were reviewed and over 1500 of them were categorized (D4.3.1, D4.4.1). It is suggested to integrate the classification and labeling system in existing computerized prescribing and dispensing systems for physicians and pharmacists (D7.4.1, D7.4.2). The system was developed in close cooperation with EMA and is in line with the recently approved SmPC guidelines. DRUID results are compatible with any existing national classification system and can be integrated in them. Thus the way for implementing the DRUID system is paved.

- DRUID proposes a four level classification and labeling system regarding the influence of medicines on driving performance. The European (or even worldwide) implementation of this system should be supported.
- The categorization of medicines should be continued. This implicates that the scientific examination of the effects of medicines on driving has to be encouraged. The same is true for medication only available on prescription as well as over-the-counter medication.

A **special problem** arises when medicines are misused by patients or by healthy drivers. In these cases the medicines tend to lose their desired effects and might reduce fitness to drive. Therefore the corresponding legal procedures and consequences should be in line with combating DUID policies. The same holds true for the combined consumption of medicines and alcohol.

- Legal procedures and consequences of misuse of medicines should be in line with DUID.
- Legal measures should only be taken after an incident in traffic, whereby impairment is the key for sanctioning.

Another special case is patients in **substitution treatment**. There should be no basic difference made between patients in substitution treatment and patients in other medicinal treatments. However, it has to be considered that consumption of or even addiction to other psychoactive substances (alcohol, medicines and/or illicit drugs) is often a problem (D1.1.2c). Addiction to other substances is clearly an exclusion criterion for driving. In other cases a conditional licensing based on the results of a fitness to drive examination might be promising.

Each patient in substitution treatment should be assessed individually regarding fitness to drive, taking into account addictions to and abuse of other substances as well as kind of substance used for treatment (e.g. patients treated with diamorphine are not fit to drive).

Section 4 – Recommendations

In the following section we formulate recommendations for policy makers on the EU and Member States levels based on the empirical research evidences that were generated in DRUID. The recommendations are conceived as a scientific support to developing countermeasures to combat impaired driving. Recommendations are divided into three groups referring to three classes of investigated psychoactive substance - "alcohol", "illicit drugs" and "medicines".

1. Countermeasures to combat alcohol impaired driving

Alcohol is still a most prevalent psychoactive substance in traffic, a problem common for all EU Member States. The number of drivers in the general driving population with BAC > 0.5g/L is rather low. Accident involved drivers (injured or killed) often show higher BAC. Further on the combined use of alcohol and illicit drugs or medicines is a rather seldom but dangerous problem.

Target groups	<ul style="list-style-type: none"> • Young male drivers with high BAC • Male drivers above 50 years of age • Drivers addicted to alcohol and alcohol misuse • Drivers with combined consumption of alcohol and illicit drugs
Legal regulations	<ul style="list-style-type: none"> • The legal limit of BAC 0.5g/L that is established in most European countries is reasonable as the injury risk of drivers being impaired by 0.1-0.5g/L is rather low. There are no scientific reasons to alter this risk threshold. • Countries that have established lower legal limits than BAC 0.5g/L, have in general lower prevalence rates of alcohol impaired drivers in the general driving population. Nevertheless injured drivers with high alcohol concentration in blood are still a problem. • The establishment of lower legal limit for specific target groups is promising (e.g. BAC 0.0g/L for novice and inexperienced drivers as proposed in the Commission Recommendation of 17 January 2001 on the maximum permitted blood alcohol content (BAC) for drivers of motorized vehicles (notified under document number C(2000) 4397)). • For combined consumption lower legal limits should be imposed (e.g. BAC 0.0g/L). • Mandatory alcohol testing for drivers involved in accidents with injuries should be introduced.
Enforcement strategies	<ul style="list-style-type: none"> • Drink-driving enforcement is cost-beneficial. Previous efforts should be continued and if necessary (countries with high prevalence rates for alcohol) extended. • The first priority of countermeasures should always be the alcohol; other psychoactive substances are second priority. • To enhance general deterrence effects random police checks are appropriate.

<p>Rehabilitation measures</p>	<ul style="list-style-type: none"> • Driver rehabilitation should be harmonized, e.g. by applying common European standards and using recommendations on good practices for rehabilitation measures developed within DRUID. • Driver assessment and rehabilitation should be legally regulated and based on defined criteria. • Alcohol offenders should be treated in separate groups, not together with drug offenders. • Non-addicts and addicts should be treated in separate programs as they require different interventions or treatments. • Multiple offenders and offenders with a BAC \geq 1.6g/L should undergo an examination to preclude addiction. • An alcohol ignition interlock can be installed during the rehabilitation phase, yet should be combined with rehabilitation/treatment and close monitoring.
<p>Withdrawal measures</p>	<ul style="list-style-type: none"> • Practices of driving license withdrawal should be harmonized across Europe. • Withdrawal is an effective general and special deterrent factor. Immediate withdrawal/suspension of driving license and a high level of perceived risk of detection are decisive. Sanction certainty can be increased by strict enforcement (e.g. implementation of random alcohol and drug controls). • The withdrawal duration should be between 3 and 12 months. • Driver rehabilitation should be an integrated part of driving license withdrawal. • Conditional withdrawal should always be combined with rehabilitative measures and close monitoring.
<p>Future needs of scientific investigations</p>	<ul style="list-style-type: none"> • The collection of epidemiological data on a regular basis is useful having implemented new legal alcohol limits or sanctions. • As the case-control studies are very time-consuming, expensive and encounter legal and ethical restrictions, it is advised to find alternative study methods of collecting reliable data.

2. Countermeasures to combat illicit drug impaired driving

The prevalence of illicit drugs in the general driver population is much lower than the prevalence of alcohol. The estimated EU mean for all investigated illicit drugs is 1.9%. Compared to alcohol (3.5%) the prevalence of single illicit drugs is very low. THC and cocaine are the most frequently detected illicit substances in most countries. There are high national variations in prevalence.

<p>Target groups</p>	<ul style="list-style-type: none"> • Young male drivers • Drivers with combined consumption of illicit drugs and alcohol; several illicit drugs • Drug consumers (stimulants, e.g. MDMA) with sleep deprivation
<p>Legal regulations</p>	<ul style="list-style-type: none"> • European agreement regarding the body fluid (especially whole blood versus plasma) to be used for drug detection • Regulations should be based on scientific findings; if epidemiological and experimental data are not sufficient, an expert team should determine cut-offs taking into account other findings (e.g. pharmacokinetic profiles). • European harmonization of drug analyses (e.g. cut-offs; standardized analyzing procedures). • Based on scientific results a risk threshold for THC equivalent to 0.5 BAC at 3.8 ng/mL serum plus an added value for measurement error and confidence interval could be defined. • Regarding legal regulations a two-tier system is recommended. The combination of per se limits with an impairment approach allows graded sanctions: a less severe sanction when drugs are present above the per se limit and a more severe sanction when the driver was impaired in addition.
<p>Enforcement strategies</p>	<ul style="list-style-type: none"> • Increase of drug enforcement is potentially cost-beneficial, especially for countries that currently have a low enforcement level. It is not beneficial from the road safety point of view (in terms of fatalities) if it happens at costs of drink-driving enforcement. • The use of only those screening devices which fulfill practical and scientific requirements is advised. • Training of police officers (drug recognition expert programs) to improve drug detection. • Drug detection roadside actions should be conceived taking into account pre-selection by time, place and target group (e.g. alcohol impaired drivers) and national prevalence data.

Rehabilitation measures	<ul style="list-style-type: none"> • Harmonization of driver rehabilitation (see section on alcohol) • Driver assessment and rehabilitation should be legally regulated and based on defined criteria. • Drug offenders should be treated in separate groups, not together with alcohol offenders. • Non-addicts and addicts should be distinguished as they require different interventions or treatments
Withdrawal measures	<ul style="list-style-type: none"> • Withdrawal in case of regular consumption of drugs should be combined with adequate rehabilitation programs
Future needs of scientific investigations	<ul style="list-style-type: none"> • Improvement of drug recognition expert programs and impairment checklists • Improvement of on-site screening devices which fulfill practical as well as scientific requirements • Further development of dried blood spot method • The collection of epidemiological data on a regular basis is useful having implemented new legal limits or sanctions.

3. Countermeasures to combat driving impaired by medicines

On a European level medicines are taken by 1.4% of drivers, as was estimated based on the results of 13 countries. The use of medicines varies very much per country. The risk assessment reveals medium increased accident risk when driving under influence of psychoactive medicines.

Target groups	<ul style="list-style-type: none"> • Health care providers and patients • Female drivers above 50 years; especially drivers using benzodiazepines and medicinal opiates
Legal regulations	<ul style="list-style-type: none"> • No thresholds should be defined for medicines. • The adequate countermeasure to combat impaired driving is information about the possible side effects and how to act and decide on using medicines in a safe manner while driving. Therefore a comprehensive information system for physicians, pharmacists and patients should be implemented. • Implementation of the four level classification and labeling system developed in DRUID
Enforcement strategies	<ul style="list-style-type: none"> • Only appropriate if medicines are misused by patients or by healthy drivers. Legal procedures and consequences of misuse of medicines should be in line with combating DUID policies. • Should focus on combined consumption of medicines and alcohol
Rehabilitation measures	<ul style="list-style-type: none"> • In case of misuse comparable to recommendations on combating illicit drugs
Withdrawal measure	<ul style="list-style-type: none"> • In case of misuse and combined consumption with alcohol comparable to recommendations on combating illicit drugs (see section on illicit drugs)
Future needs of scientific investigations	<ul style="list-style-type: none"> • Expansion of research on impact of medicines on driving fitness • Expansion of research to examine the association between the use of commonly prescribed psychoactive medicines and road traffic accidents. • Expansion of research to determine effective risk communication strategies to inform the general public, health care providers and patients on medicines and traffic safety. • Development of procedures for the assessment of fitness to drive

Section 5 – Dissemination and use

All deliverables submitted and approved by the European Commission. See the complete list of outputs and dissemination activities in Annex I.

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