Project No. TREN-05-FP6TR-S07.61320-518404-DRUID

DRUID
Driving under the Influence of Drugs, Alcohol and Medicines

Integrated Project
1.6. Sustainable Development, Global Change and Ecosystem
1.6.2: Sustainable Surface Transport

6th Framework Programme
Deliverable (1.3.1)

Driving under the influence of alcohol, illicit drugs and medicines. Risk estimations from different methodological approaches.

Due date of deliverable: (14.07.2011)
Actual submission date: (28.11.2011)

Start date of project: 15.10.2006
Duration: 60 months
Organisation name of lead contractor for this deliverable: BASt / UWURZ
Revision 1.0

Project co-funded by the European Commission within the Sixth Framework Programme (2002-2006)		
Dissemination Level		
PU	Public	X
PP	Restricted to other programme participants (including the Commission Services)	
RE	Restricted to a group specified by the consortium (including the Commission Services)	
CO	Confidential, only for members of the consortium (including the Commission Services)	

Deliverable 1.3.1

Driving under the influence of alcohol, illicit drugs and medicines. Risk estimations from different methodological approaches.

Authors:
Volker Hargutt, Hans-Peter Krüger (IZVW, Center for Traffic Sciences, Department of Psychology, University of Würzburg, Germany)

Anja Knoche, Federal Highway Research Institute (BASt), Germany

Partners:

- Günter Berghaus, (IZVW, Center for Traffic Sciences, Department of Psychology, University of Würzburg, Germany)
- Inger Marie Bernhoft, Tove Hels, Kira Janstrup (DTU, Danish Transport Research Institute, Denmark)
- Jan Ramaekers (Department of Neuropsychology and Psychopharmacology, Maastricht University, the Netherlands)
- Sjoerd Houwing, René Mathijssen, Marjan Hagenzieker (SWOV, Institute for Road Safety Research, the Netherlands)
- Markus Schumacher, Kerstin Auerbach (BASt, Federal Highway Research Institute, Germany)

Task 1.3 Leader: Anja Knoche (BASt, Germany)

Work Package Leader: Anja Knoche (BASt)

Project Co-ordinator: Horst Schulze (BASt,)

Project Funded by the European Commission under the Transport RTD Programme of the 6th Framework Program

Acknowledgment

This deliverable came about through the cooperation of all DRUID partners. Therefore, we would like to thank the whole DRUID consortium to enable this report.

Special thanks for reviewing and contributing to this deliverable goes to:

Problem situation (WP1/2):

Anja Knoche, Kerstin Auerbach and Markus Schumacher (BASt)
Martina Walter, Eva Schnabel (UWURZ)
Jan Ramaekers (UMaas)
Inger Marie Bernhoft and Tove Hels (DTU)
Sjoerd Houwing (SWOV)
Kristin Thorsteinsdottir (LMU)
Alain Verstraete and Sara-Ann Legrand (UGent)

External peer review of the whole deliverable:

Mark Vollrath (Germany)

TABLE OF CONTENT

1 LIST OF ABBREVIATIONS

Abbreviation	Technical Term
BAC	Blood Alcohol Concentration
CF	Car Following Task
CF-RT	Car Following Reaction Time
conc.	concentration
D	Deliverable
DUI / DUID	Driving under the influence of alcohol / Driving under the influence of drugs and/or medicines
GAP	Gap Acceptance Task
GC-MS	Gas Chromatography - Mass Spectrometry
HPLC	High Performance Liquid Chromatography
MAIS	Maximum Abbreviated Injury Scale
NA	not available
not sign.	not significant
OR	odds ratio
RT	reaction time
SDLP	standard deviation of lane position
sign.	significant
THC	delta-9-tetrahydrocannabinol
THCCOOH	11-nor-9-carboxy-delta-9-tetrahydrocannabinol
UPLC-MS/MS	Ultra Performance liquid chromatography tandem mass spectrometry
z-drugs	in this document: zolpidem & zopiclone

Abbreviation	Country	Abbreviation	Country
GE	Germany	CZ	Czech Republic
DK	Denmark	SL	Slovakia
FI	Finland	IT	Italy
LT	Lithuania	PT	Portugal
SE	Sweden	ES	Spain
NO	Norway	BE	Belgium
PO	Poland	NL	The Netherlands
HU	Hungary		

Abbreviation	Institution	Country
BASt	Federal Highway Research Institute	Germany
CERTH-HIT	Centre for Research and Technology Hellas / Hellenic Institute of Transport	Greece
FHI	The Norwegian Institute of Public Health	Norway
DTU	Technical University of Denmark	Denmark
IFSTTAR	French institute of science and technology for transport, development and networks (=INRETS, old name)	France
LMU	Insitute of Forensic Medicine, University of Munich	Germany
RUGPha	University of Groningen, Department of Pharmacotherapy and Pharmaceutical Care	The Netherlands
RUGPsy	University of Groningen, Dept. of Psychology	The Netherlands
SIPSiVi	Italian Society of Road Safety Psychology	Italy
SWOV	Institute for Road Safety Research	The Netherlands
THL	National Institut for Health and Welfare Finland	Finland
TNO	Netherlands Organization for Applied Scientific Research TNO	The Netherlands
UTurku	University of Turku	Finland
UCAEN	University of Caen	France
UGent	Gent University	Belgium
UMaas	Faculty of Psychology, Maastricht University	The Netherlands
UWUERZ	University of Wuerzburg	Germany
VTI	Swedish National Road and Transport Research Institute,	Schweden

2 EXECUTIVE SUMMARY

The objective of this deliverable is to assess the risk of driving with alcohol, illicit drugs and medicines and to deliver substance concentration thresholds for per se legislation. Therefore the results of all epidemiological and experimental studies conducted in DRUID are integrated in this deliverable.

In case of combating driving under influence of alcohol, legislative regulations and enforcement practices are clearly defined. Regarding alcohol a clear correlation between consumption, blood concentrations and the score of driving impairment is proved for several years, whereas up to now defining limits for combating drugged driving comprises a lot of challenges. Thus per se limits for alcohol are based on scientific risk research which is a prerequisite to assure the compliance of the population with these regulations. Determining legislative regulations against drugged driving is more difficult, as a variety of aspects have to be taken into account. Especially defining risk thresholds for psychoactive substances is a challenging task.

The most relevant information in order to determine thresholds is the information about the accident risk in traffic dependent on different concentrations of single substances. Direct information about the accident risk in traffic can only be gained by conducting epidemiological studies. Thus the data regarding risk estimates of psychoactive substance use in traffic are taken from the DRUID deliverable 2.3.5

In cases where low prevalence epidemiological data do not allow risk calculation (odds ratios) of different concentration ranges from single psychoactive substances the results of experimental studies should be taken into account.

In order to integrate study results resulting from different methodologies, a reference curve is helpful. Here alcohol data delivered with these different study methodologies are used as the golden standard.

Further on a harmonization of the system for DUI of alcohol and non-alcohol drugs (DUID) leads to achieve the compliance of the population. Therefore impairment limits corresponding to the 0.5 g/L limit for alcohol were defined for the drugs where scientific evidence showed a dose-response relationship for impairment.

The main finding of this report is that the three substance categories, which are connected with extremly high risks (OR>10), are the two high alcohol concentrations (0.8 - 1.2 and > 1.2 g/L) and the combination of alcohol and drugs, all of them present with moderate prevalence rates of about 0.4%. In the risk range from a 5-to 10-fold injury alcohol including all concentrations is dominant with a prevalence rate of 3.5%. Moreover the epidemiological doubtful risk of amphetamines, medicinal opioids/opiates and drug-drug combinations are also in this range, but showing much lower prevalence rates (for amphetamines 0.08%) and therefore less demand for action. The group of illicit opiates, z-drugs and cocaine shows risks between 2-3 and prevalence rates lower than 0.5%. The risk associated with cannabis seems to be similar to the risk when driving with a low alcohol concentration (between 0.1 g/L and 0.5 g/L), which is slightly increased to about 1-3 times that of sober drivers. The proposed risk threshold for THC equivalent to 0.5 g/L alcohol is 3.8 ng/ml serum with an added value for measurement error and confidence interval.

Thus alcohol, especially in high concentrations must remain focus number one of traffic safety efforts and the combination of alcohol and drugs or medicines seems to

be a topic, which should be addressed more intensively because it leads to very high risks in traffic.

In determining substance concentration thresholds, 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 the accident risk is increased, but the data should be handled with care as the risk is calculated with only a few cases.

Regarding legally prescribed medicines use it is not reasonable to define cut-off values for patients especially if they are in long-term treatment. Other than with drug users, the responsibility and compliance of patients under long-term treatment is usually high. The disease itself may affect the driving behavior even more and the use of medication could decrease this effect. Dosage effects were only investigated and observed with single users or new users. Hence, an impairment check is an objective way to judge recreational use. Thus a balance between concerns about ensuring road safety and the therapeutic needs of individuals is guaranteed.

Additionally a separation of drinking, medicine consumption and driving is necessary and the respective information should be part of the physician’s consultation.

The epidemiological studies in DRUID have shown that drivers very often use more than one psychoactive substance including alcohol. The combination of alcohol and drugs or medicines, or the combination of more than one drug, increases the accident-risk exponentially. If risk thresholds respective lower effect limits will be implemented, they shouldn´t be simply combined in the case of combined consumption. Because of the highly increased accident risk of combined consumption stricter regulations should be elaborated for this case.

3 OPENING REMARKS

For a detailed understanding of D 1.3.1 one should be familiar with the content of Deliverable 1.1.1 “Theoretical Framework for Substance Effects on Safe Driving”, because in Deliverable 1.1.1 the basic methodologies are described. For reasons of clarity, some crucial points of evaluation will be mentioned in this document again. The same holds true for important steps of the study designs or evaluations. Relevant passages will partly be copied from the respective deliverables and are – in the case of long passages – either indicated by *italic text* or by the referencing the author in the according chapter headline.

Furthermore, it should be stressed that UWUERZ has the responsibility to provide a comprehensive overview of the data delivered from the relevant WPs (mainly WP 1 ”Research and Methodology” and WP 2 “Epidemiology”). So, UWUERZ is not responsible for the reliability of the data itself. The partners who conducted the different studies are responsible for all factors that are crucial to produce reliable scientific data themselves: study design, study implementation, subject instructions, study settings, etc. The calculation of important measures, like prevalence rates, ORs or mean values from the experiments, was also mainly done by the respective partners. Most of the study designs were determined beforehand in design protocols that had to be should be considered followed by every partner. As a consequence, all resulting data and results are accepted in this deliverable as reliable (even if the results do not seem to reflect reality reasonably seem contrary to expectations) if

- they were produced according to the respective scientific protocols, and
- no clear evidence can be found for biased data (e.g. by inspecting the study design or the data itself).

Moreover, all these data are evaluated and discussed in a detailed manner in the respective deliverables from the single partners. The different evaluations cannot be repeated or integrated in this deliverable. Instead a comprehensive comparison and overview of the main outcome measures is provided.

The integration of studies outside DRUID will only be possible for very specific and important issues (e.g. the risk of alcohol in traffic). So, this deliverable focuses mainly on the DRUID results without considering the huge amount of other research.

4 OBJECTIVES

The principle aim of DRUID is to achieve knowledge about the different factors that influence driving under the influence of psychoactive substances in order to combat DUI/DUID. Within this main objective several tasks are embedded in order to address different aspects of the problem such as

- collecting data about prevalence rates and accident risks of different substances in traffic (epidemiological approach)
- conducting reference studies in driving simulators in order to determine the impact of substances which are not sufficiently examined yet (experimental approach)
- testing and development of a “good practice” standard for detection and training measures for road traffic police (enforcement)
- development of an appropriate classification system for medicines affecting driving ability (classification)
- evaluating the efficiency of strategies of prevention, sanctioning and rehabilitation

A rather important aim within WP 1 (research and methodology) is task 1.3: “Recommendation of thresholds for psychoactive substances in traffic”. Within task 1.3 the results of WP1 and WP2 must be analyzed (based on the theoretical framework established in Task 1.1 subtask “Methodology”, D1.1.1) with respect to their impact on the definition of thresholds. The following data will be analyzed:

- prevalence rates of psychoactive substances among road users in the general traffic and in accident populations (Amoros, Gadegbeku, & Laumon, 2010; Houwing, Hagenzieker, Mathijssen, Bernhoft, Hels, & Kira, 2011; Isalberti et al., 2011; Walter, Hargutt, & Krueger, 2011b);
- consumption and driving patterns of psychoactive substance users (Walter et al., 2011b);
- estimations of impairing effects and definition of thresholds for psychoactive substances from experimental studies (Ramaekers, 2011; Ramaekers et al., 2010);
- estimations of impairing effects and definition of thresholds for psychoactive substances from meta-analysis (Berghaus et al., 2010; Morland & Strand, 2010; Schnabel, Hargutt, & Krueger, 2010);
- relative risk calculation from epidemiological studies (Gadegbeku, Amoros, & Laumon, 2010; Hels et al., 2011; Thorsteinsdóttir et al., 2011).

Due to a prolongation of the project, which was mainly caused by a delay of the epidemiological studies, D 1.4.1 “Evaluation of legal measures to combat DUI/DUID” was finalized without the synopsis of task 1.3. In D 1.4.1, the influence of legal measures was evaluated with their general impact on DUI/DUID without considering special thresholds. The aim was to describe the influence of different legal measures with respect to special substances and driver groups on a higher level. So, the results of task 1.3 can be related to D 1.4.1. Further on this deliverable provides the

scientific basis for recommending substance´ cut-offs for per se legislation discussed in D1.4.2.

5 SCOPE OF THE PROBLEM

Task 1.3 aims at the recommendation of concentration thresholds in blood for different substances with regard to their traffic safety impact. The most relevant information in order to determine thresholds is, besides political or ethical considerations, the accident risk dependent on different substance concentrations of single substances. Information about the accident risk in traffic is provided by epidemiological studies.

Representative studies on prevalence rates in accident-free populations and accident populations are difficult and expensive. Especially for substances with a low exposure rate in the population, a huge sample has to be examined in order to get reliable information. Thus, for most of the substances, either legal or illegal, the data necessary for calculating risk indices are missing or incomplete so far. This leads to substantial problems for the estimation of accident risks. The theoretical framework described in D 1.1.1 (Krüger, Hargutt, & Brookhuis, 2008) tries to establish a consistent method to make use of available substance data from all scientific sources in order to get estimates of concentration- or dose-based impairment levels that are closely related to accident risks.

Data which are useful for the estimation of substance related risk in traffic are epidemiological data and experimental data.

Within **epidemiological data** in DRUID different study types with different populations exist:

(1) roadside studies to estimate substance prevalence in accident-free traffic,

(2) hospital studies in which the cases of severely injured or killed people are matched with the controls of the roadside studies in order to estimate a risk of being injured or the risk of being killed under different substances, and

(3) culpability studies in which only accidents with fatally injured drivers are judged for culpability and, thus comparing drivers being responsible for causing the accident to those not culpable, results in a risk of being responsible for a fatal accident.

One major concern of this report is to provide an overview over the different risks based on different epidemiological approaches (for more detailed information see Del. 1.1.1, (Krüger et al., 2008).

The framework tries to transfer the results of the different approaches within DRUID in usable risk measures. As predicted in D 1.1.1 only very basic information is available for most of the interesting substances. The basic idea to fill the gap of information is to use available information about alcohol as reference for other substances:

- information about accident risks dependent on different blood alcohol concentrations (BAC) and
- a huge amount of experimental research.

If only one data source is available for a substance, traffic risk can be estimated from the relationship between experimental and epidemiological findings for alcohol (see Figure 1).

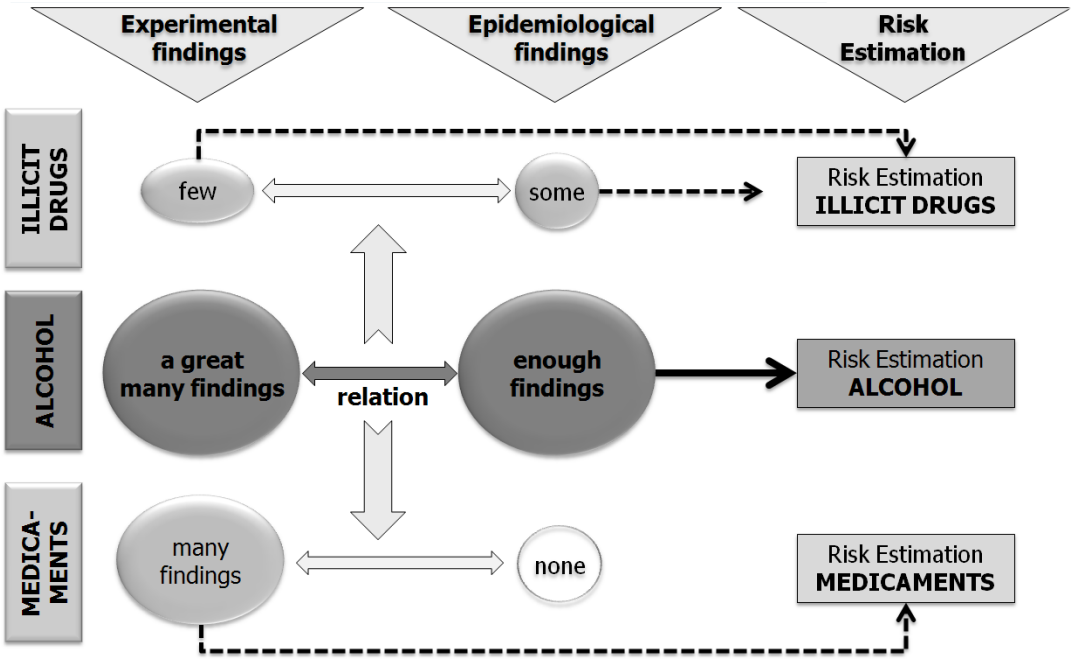


Figure 1: Rationale by using alcohol as reference for the estimation of traffic risk under different substances.

Therefore, an alcohol reference was established

(1) by inspecting all available epidemiological risk studies for alcohol in order to define a valid concentration risk function as reference (see chapter 8.2.7),

(2) by inspecting all available experimental studies for alcohol by means of meta-analysis in order to define a concentration risk function for different aspects of performance tests as reference (see chapter 8.2.5) and

(3) by introducing an alcohol calibration study at a BAC of 0.5 g/L in all used experimental settings.

6 OVERLAPPING METHODOLOGICAL ISSUES

6.1 The problem of three different research approaches

6.1.1 The independent variable

In the experimental studies (and therefore also in the meta-analytical approach) the independent variable is the substance dose. In epidemiological research the substance concentration in body fluids is used. Unfortunately, the relationship between substance dose and substance concentration in body fluids is highly dependent on a large number of factors:

- The kind of substance and it's dose itself,
- the body fluid itself,
- individual factors like weight, body water, gender, type of metabolizer,
- and mostly the time between administration and concentration measurement.

That means, that in case of meta-analysis the results cannot be simply summarized by the administered dose because the time between substance administration and performance test varies considerably in all these different studies. As a consequence, substance concentrations were estimated based on time-dependent concentration gradients for drugs drawn from an evaluation on pharmacokinetic data (Berghaus et al., 2010). The concentration gradients were standardized for a defined dose (standard dose) and a defined weight of the user of 70 kg (standard gradient). Nonetheless, in reality in most cases there is a low correlation both between dose and actual concentration[1] and between concentration and performance (behaviour).

In epidemiological research, however, only the substance concentration is available without knowledge about the dose and the moment of intake.

Detailed knowledge about substance effects and the relation between substance concentration and substance dose could be used for different aims. Information about **substance concentration** is crucial for the establishment of substance thresholds in legislation to define DUI/DUID and to enable prosecution. Information about impairing **substances and corresponding substance doses** is more relevant for medical doctors and patients.

6.1.2 The dependent variable

As pointed out in chapter 5, three main research approaches are used in DRUID in order to use all available information for threshold estimation:

(1) meta-analytic approach,
(2) experimental approach, and
(3) epidemiological approach.

Within the **meta-analysis** a huge number of already conducted experimental studies is evaluated with respect to substance effects on many different aspects of performance. The evaluation is based on published papers. So, the available infor-

[1] even by considering the time between application and concentration measurement.

mation is mostly limited to (1) the administered substance dose, (2) the experimental task in which the substance effect was tested and (3) the outcome of the experiment, i.e. if the difference between substance and placebo was significant or not. So, the main outcome of the meta-analytic approach is the percentage of significant experimental results (i.e. proven impaired performance) for different dosages – and after transformation (see chapter 7.4.2.2) also for substance blood concentrations. The percentages of significantly impaired findings per substance dosage/ concentration are calculated and illustrated. This empirical function is interpreted as an "impairment function" (Berghaus, Schulz, & Szegedi, 1998). In order to get an estimation of risk, the percentages of significant results for different substances will be compared to the percentage of significant results for the reference alcohol level of BAC 0.5 g/L, for which a traffic risk is established (see Berghaus et al., 1998; Schnabel et al., 2010, chapter 3.1.2).

Within **experimental research** in DRUID different driving experiments were carried out that should look at substance effects of substances which are important from a traffic safety perspective but not well studied up until now (for details see Ramaekers et al., 2010).

Concerning the dependent variable in the experiments *"all partners adhered to a standard set of driving parameters to increase comparability between studies. 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*

All partners agreed on a minimum of 3 driving scenarios to be included in each and every study. These scenarios represent the behavioural levels above, and constituted the primary driving measures over all studies.

- *Road tracking scenario (automated behaviours)*
- *Car-Following scenario (controlled behaviours)*
- *Risk taking scenario (strategic behaviours)*

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 driving parameters." (Ramaekers et al., 2010)

The dependent variables that are a priori chosen for comparison or further calculations in this deliverable are only the three main performance measures, which were agreed upon within task 1.2:

- standard deviation of lane position [SDLP] (tracking as automated behaviour),
- reaction time in a car-follow scenario [CF-RT] (controlled behaviour), and
- gap acceptance in a gap acceptance task [GAP] as a measure for risky behaviour in driving experiments with stimulant substances (risk taking as strategic behaviour).

Within **epidemiological research** the dependent variable is the OR, which represents the change of accident risk under a certain substance concentration in body fluids (blood or saliva) compared to a reference group. For DRUID two different reference groups exist:

- The “sober” group without any substance and
- the alcohol reference group with a alcohol level of 0.5 g/L (i.e. 0.4 - 0.6 g/L). This OR will represent the risk (for being injured, having a fatality, etc.) with a certain substance or a specific substance concentration compared to the according risk with an alcohol level of 0.5 g/L.

As a consequence, the dependent variables of the meta-analytic and the experimental approach must be transformed by certain pragmatic procedures in order to be comparable with the golden standard for risk estimation, the OR.

6.1.3 The problem of sample-size

In general the reliability of all results depends on the sample-size. Depending on the methodological approach, different strategies are tracked in order to deal with a low sample-size.

In **meta-analysis** the number of published evaluable publications depends on the substance and the amount of scientific interest. In order to give reliable information about the dose- or concentration-related impairment, the number of publications or effects per substance concentration category should be reasonably high. Due to the fact that on the one hand these numbers differ considerable from substance to substance and on the other hand the author was trying to include information whenever possible, there was no hard criterion regarding the minimum number of effects, which was used for the different evaluations. Among all reported results, the minimum number of effects on which parameter estimation was based upon, is 86 from 8 studies (N05AL01, Sulpiride), the maximum number of effects was 2104 from 103 studies (N05BA01, Diazepam). For details see Berghaus et al., 2010).

Especially in the meta-analytical part which examines the

- effect of single dose administration of opioids, narcoanalgesics and hallucinogens to drug naïve subjects and the
- effect of morphine or methadone / buprenorphine in patients treated chronically

not enough studies/effects were available in order to compile an meta-analytic analysis (Morland & Strand, 2010). In all of these cases the results were summarized in the form of a systematic review.

All **experiments** were planned with a sufficient number of subjects (Krüger et al., 2008). Nonetheless, technical problems or drop-outs of subjects sometimes lead to a lower number of subjects than intended. The actually achieved subject numbers in the DRUID experiments of task 1.2 (including the alcohol calibration studies) range between 12 and 20, which is sufficient to calculate ORs with the chosen approach (see chapter 7.3, Table 17). For reasons of the sample size, only the study of VTI must be dropped because they used an old alcohol study for calibration that comprises only 8 subjects, so an OR calculation is not possible (see also chapter

7.3.1.3). The study with Benzodiazepines & Insomniacs was delayed, so the results could not be included in this report.

In **epidemiological studies** hard criteria regarding the necessary number of cases and controls for the calculation of an OR is also missing. In many cases there will be not enough cases or controls in order to do a reliable OR calculation. So, in case of very small samples even if the estimated risk for the specific substance or concentration is high, there are hardly any traffic participants who are introducing this risk in traffic. The real risk for the whole traffic is always the result of many aspects, the two most important being basically the risk itself and the according prevalence rate.

Nonetheless, in a first step, all possible ORs (from a statistical view) were calculated by DTU (Hels et al., 2011). ORs that are based on very low cell numbers can be easily identified by huge confidence intervals. In a second step, the cases and controls are merged over countries (following certain criteria) in order to increase sample sizes and to get a risk estimation for Europe. So, merging risk estimations from different countries can make the interpretation of the results somewhat difficult. If there are still not enough cases/controls for a reliable OR calculation, no information will be available.

6.1.4 Summary of methodological differences

Table 1 shows the major differences between the three methodological approaches.

Table 1: Major differences between the three methodological approaches.

	Independent Variable	Dependent variable in single studies	Dependent variable for comparison	sample size
meta-analysis	dose and/or concentration	performance measures (significant impairment vs. non significant impairment)	ratio significant / non significant	low: review high: meta-analysis
experi-ments	dose	distribution of performance measures[2] (plabebo/substance)	kind of odds ratio: number of bad performers in the experimental vs. control group	low: no eval. possible high: odds ratio, relative risk
epidemi-ology	concentration	prevalence cases / controls	prevalence, odds ratio (OR)	low: no eval. possible high: odds ratio

6.2 The Problem of body fluids (Alain Verstraete)

Both due to different legal preconditions in the different countries and due to different study designs, blood as standard analyte could not be taken in all countries. Moreover the body fluid is dependent on the research approach, because it easier to justify a blood sample in case of a fatality as in case of roadside surveys, where drivers are stopped in suspicious free traffic. So the Situation in DRUID presents as follows:

- In **roadside surveys**, whole blood was taken in Belgium, Italy, Lithuania and the Netherlands. Saliva was taken in all countries (Belgium, Czech Republic,

[2] In the single experimental studies the main dependent variable is the significance of a group difference between substance and placebo. But for risk calculation this information is not sufficient, so the distribution of the performance in both groups is evaluated (see Krüger et al., 2008).

Denmark, Finland, Hungary, Italy, The Netherlands, Norway, Poland, Portugal, Spain and Sweden) except Lithuania.

- In the **hospital studies**, all samples were whole blood samples, so the results are comparable among the different countries.
- In the **killed driver studies**, whole blood was taken.

For most substances the correlation of concentrations determined from blood and saliva are very weak so that one concentration (i.e. in blood) cannot be simply estimated by knowing the other (e.g. from saliva). Many efforts were made to describe the relationship between oral blood and saliva drug concentrations (D1.4.2: (Verstraete et al., 2011), and (Gjerde & Verstraete, 2010; Wille et al., 2009). But for most drugs, a wide scatter remains when whole blood and saliva concentrations were plotted. In the end, equivalent drug cut-offs were proposed and used (see Table 2).

Table 2: Recommended equivalent cut-offs for DRUID core substances.

Substance	initial cut-off in whole blood (ng/mL)	initial cut-off in oral fluid (ng/mL)	Recommended equivalent cut-off in oral fluid (ng/mL)	Recommended equivalent cut-off in whole blood (ng/mL)
6-acetylmorphine	10	5	**16**[1]	10
Alprazolam	10	1	**3.5**	10
Amphetamine	20	25	**360**	20
Benzoylecgonine	50	10	**95**	50
Clonazepam	10	1	**1.7**	10
Cocaine	10	10	**170**	10
Codeine	10	20	**94**	10
Diazepam	20	5	5.0[2]	**140**
Flunitrazepam	2	1	1.0[2]	**5.3**[1]
Lorazepam	10	1	**1.1**	10
MDA	20	25	**220**[1]	20
MDEA	20	25	**270**[3]	20
MDMA	20	25	**270**[1]	20
Methadone	10	20	**22**	10
Methamphetamine	20	25	**410**	20
Morphine	10	20	**95**	10
Nordiazepam	20	1	**1.1**	20
Oxazepam	50	5	**13**	50
THC	1	1	**27**	1.0
Zolpidem	20	10	10[2]	**37**
Zopiclone	10	10	**25**[1]	10
Tramadol	50	50	**480**	50
7-amino-clonazepam	10	1	**3.1**[1]	10
7-amino-flunitrazepam	2	1	1.0[2]	**8.5**[1]

[1] data based on less than 10 individual cases
[2] recommended cut-off for OF lower than the original DRUID cut-off in oral fluid, therefore the cut-off of blood has been raised
[3] no positive cases; cut-off of MDMA used for MDEA

A comparison between the prevalence rate based on whole blood results and saliva results and the equivalent cut-offs in 2750 subjects (for which both samples were available) in Belgium, showed that for most drugs the prevalence rate was very similar (Houwing, Hagenzieker, Mathijssen, Bernhoft, Hels, Janstrup et al., 2011; Country report Belgium, table 26), except for THC, where 30 subjects were above the cut-off based on their saliva drug concentrations and only 13 based on the blood concentrations ($p = 0.002$).

For DRUID that means, that with the use of the equivalent cut-offs a similar prevalence rate was found based on the analysis of blood or oral fluid, with the exception of cannabis.

6.3 Pharmacological issues

6.3.1 Pharmacokinetic issues (Alain Verstraete)

Another problem is the dependency of substance concentration on the pharmacokinetics of the specific drugs, which again is highly time-dependent – besides many other factors. So if concentrations are measured not at the same time as the accident or police stop, different biases might occur. In DRUID these time lags between e.g. the accident and blood sampling differs inherently with the research approach:

- In **roadside studies** of course the sampling is exactly at the time of the traffic participation, so no time lag exists.
- In the **hospital studies**, the maximum delay between the accident and blood sampling was three hours; the median time was 1.17 hours.
- In the **killed driver studies**, the maximum interval was 24 hours.

One can expect that in most cases drug concentrations will decrease between the time of the accident and the blood sampling. Therefore, in most cases the measured concentrations will be lower than the concentrations that were present at the time of the accident or at the stop.

For THC, the half-life of the distribution phase is less than 1.4 h ± 0.1 h (Kauert, Ramaekers, Schneider, Moeller, & Toennes, 2007) and plasma THC concentrations greater than 10 ng/ml are uncommon after 1 h even after moderate to high doses of cannabis. Since the blood to plasma distribution is about 0.5, this represents about 5 ng/ml in blood (Drummer, 2004).

Because of the very large interindividual variation in drug metabolism, no attempt was made to back calculate the concentration of the drug for the time of the accident. In killed drivers, at the time of death, metabolism slows down or stops. But post-mortem redistribution can occur. This means that the drug can diffuse from places with a high concentration like the stomach or the liver to places with lower concentrations, like the blood. This phenomenon depends on the physicochemical characteristics of the drug, and is most pronounced for drugs with high lipid solubility or high tissue concentrations, e.g. designer amphetamines, methadone and other potent opioids (Drummer, 2004). Surprisingly, post-mortem distribution has not been described for THC (Drummer, 2004). However, Drummer considers the likely extent of post-mortem redistribution as low for amphetamine, methamphetamine, cocaine, benzodiazepines and zolpidem, low to moderate for heroin, morphine, codeine, buprenorphine, tramadol and THC and moderate for MDMA and methadone. So in post-mortem cases, it is also possible that the drug concentration in blood taken at autopsy is higher than the drug concentration at the time of death. In order to minimise the risk of post-mortem redistribution, blood is taken from peripheral sites like the femoral vein. This was done as much as possible by all the centres that participated in the killed driver study.

Another issue is the instability of some drugs like nitro-benzodiazepines (nitrazepam, flunitrazepam and clonazepam), 6-acetylmorphine and cocaine. The addition of fluoride to the tubes slowed down the degradation. Due to post-mortem bacterial and fungal activity, alcohol may be both produced and consumed in a body.

For the interpretation of the DRUID results there is a major implication of these facts: Especially for hospital studies (injured drivers) the measured substance concentrations will be lower than the substance concentrations at the moment of the critical event (accident, fatality, etc.), the risk is attributed at. For the killed driver studies, the reverse is likely. Consequently the calculated OR, which are based on the measured concentrations some hours later will be related to a risk. Actually the accident related concentrations are much higher so that for low substance concentrations an overestimation of the risk must be expected.

For DRUID that means that the concentrations (associated with an increased risk of being involved in an accident) might be underestimated when calculated from the hospital studies and overestimated in the killed driver studies.

6.3.2 THC illustration of OR with decreasing concentrations

In order to illustrate the fictive change of OR depending on the time delay between accident and blood sample, a fictive data set of 1000 cases and 1000 controls was prepared. THC is taken as example because the period of absorption is very short (see Figure 2), so, a decrease of the substance concentration in time can be assumed shortly after intake.

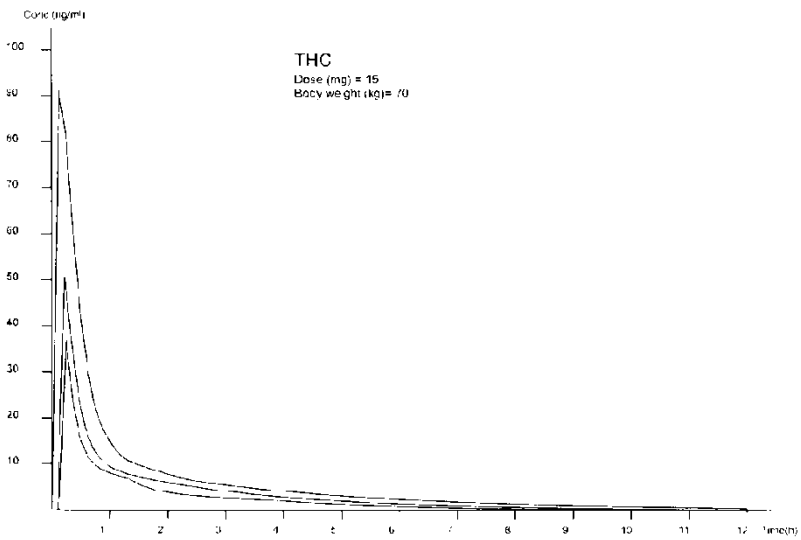


Figure 2: Plasma concentration-time curve of Δ^9-tetrahydrocannabinol (THC) after smoking of 15 mg THC.

THC concentrations for controls were drawn from the data from the Netherlands (intern communication) that show a prevalence rate of THC alone of 1.67% and a median THC blood concentration of 5.35 ng/ml. The distribution of the respective THC concentrations of the cases is not valid for this simulation, because they are already biased regarding the time delay. So the simple assumption was made that

both the number of cases and the THC concentrations at the time of the accident is simply 2-fold compared to the controls.

In a next step the THC values of the single cases[3] were decreased following the elimination function of THC[4] (see Figure 2). Due to the fact that

- the exact empirical elimination function follows not a mathematical function depending on time, and that
- assessing a THC value in traffic allows no assumptions about the time of intake,

an elimination function has to be found that is only based on a starting value and leads to comparable concentrations as the elimination function. While this was not possible in a satisfactory manner for the whole function, a very good approximation can be found for the part of the elimination function for t >= 1 hour. In consequence, an additional assumption must be made for this simulation, namely that all cases drive at the earliest one hour after the intake of THC[5].

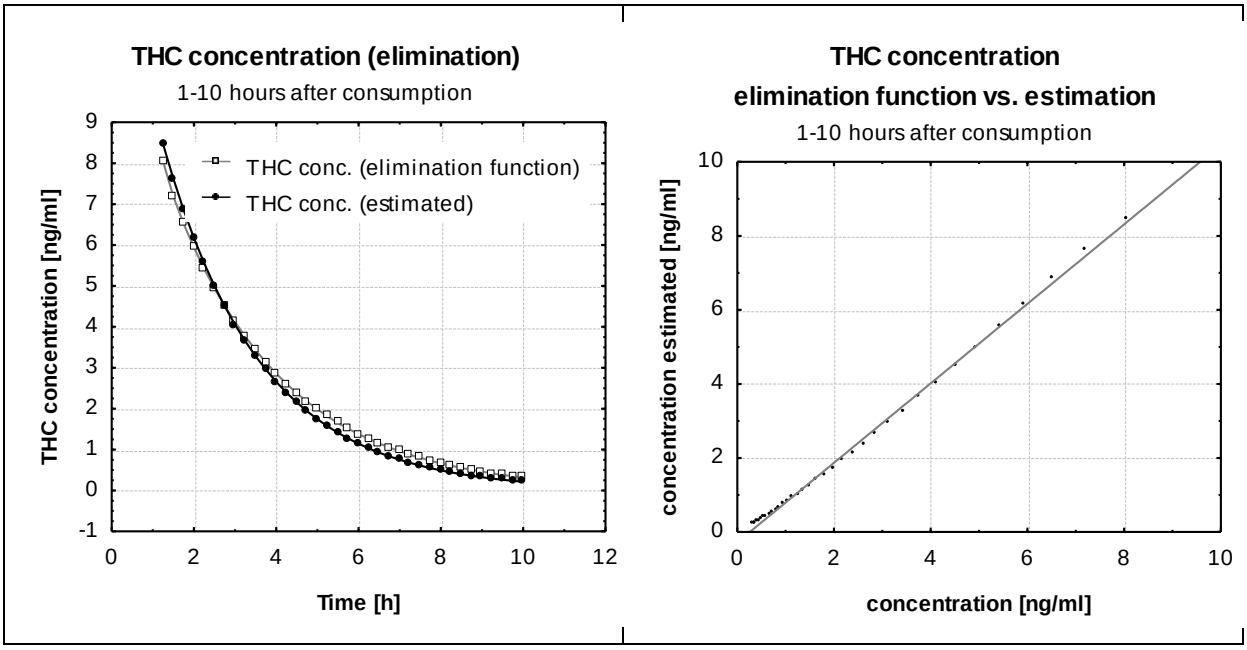


Figure 3: Relation between the elimination function by Sticht (Berghaus et al., 2010) and the approximated elimination with a factor 0.6561 per hour (valid for time periods greater than 1 hour after intake).

Then the time-course of the THC concentration can be approximated by decreasing a starting THC concentration by 10% for each 15 minutes or by $1-0.9^4 = 0.35 = 35\%$ for 1 hour (see Figure 3).

[3] For the controls, whose THC is measured at the relevant point in time the THC is not decreased.
[4] reported by Sticht in Günter Berghaus, et al. (2010).
[5] This assumption would also allow to transfer this simulation to alcohol, because in most cases the elimination phase of alcohol starts 60 min after the end of intake, but 120 min at the latest (Madea & Dettmeyer, 2007, p. 193).

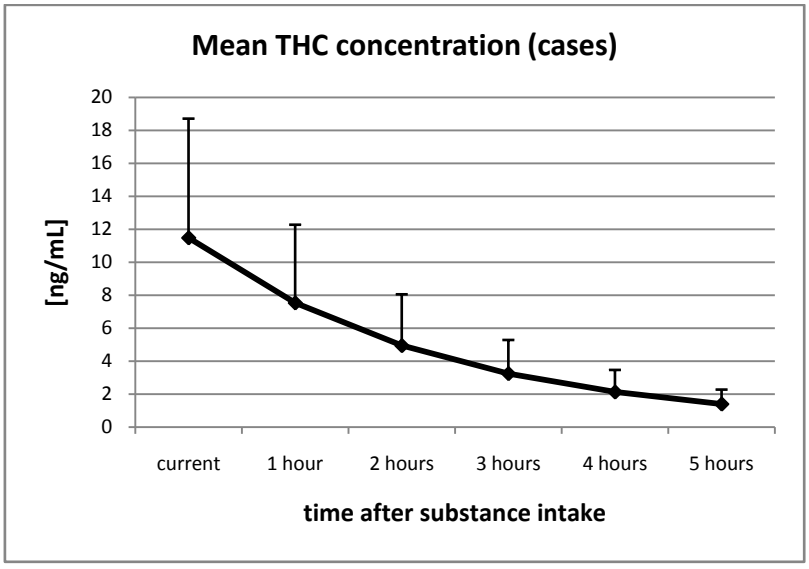


Figure 4: Change of mean THC concentrations (and standard deviations) within a period of 5 hours after substance intake (for cases).

When using this approximated elimination function certain changes occur with time regarding the resulting OR. With an increasing delay between accident and blood sample and in consequence with a decreasing mean THC concentration (see Figure 4)

- the cell counts change from higher THC classes stepwise to lower categories (see Table 3) which should result in a
- decrease of the risk of higher THC classes and an increase of risk for the lower THC classes.

Table 3: Change of cell counts of the different THC classes for cases and controls with time. A green colour illustrates a low number of cases at that time (columns) with the according substance concentration (rows), yellow a medium and red a high number of cases.

THC conc. [ng/ml]	control	cases 0h	cases 1h	cases 2h	cases 3h	cases 4h	cases 5h
0	983	967	967	968	973	975	980
0..3	3	3	7	10	9	14	19
3..5	6	5	6	6	8	11	1
5..8	6	5	5	8	10	0	0
>8	2	20	15	8	0	0	0
	1000	1000	1000	1000	1000	1000	1000

When the time delay is long enough, the THC concentrations even become lower than the detection threshold, which means that cases with initially moderate THC concentrations - which had actually increased the risk in this example - are now considered as non-intoxicated. This leads to decrease the risks for all other THC classes.

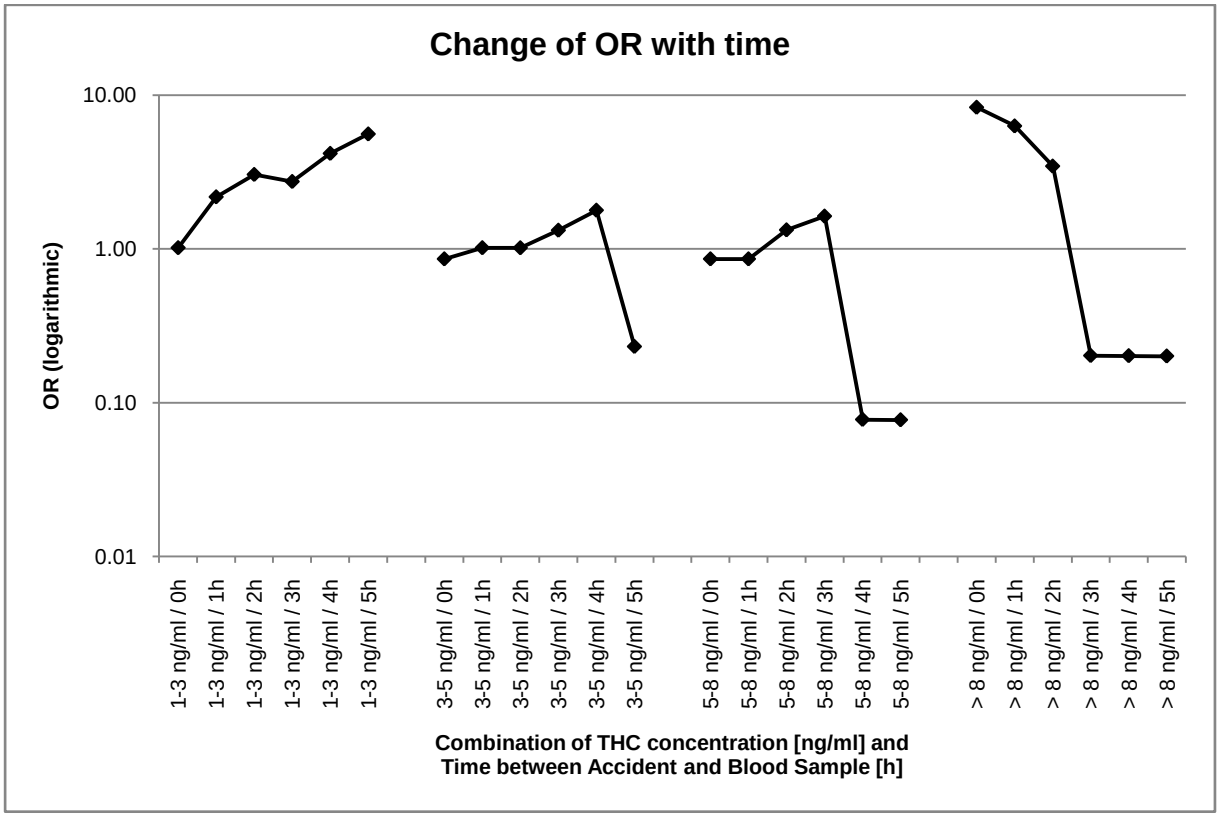


Figure 5: Change of the odds ratio for different THC concentration classes (vs. THC < 1 ng/ml) and different time delays (1-5 hours) between accident and blood sample.

For this example the change of the OR is illustrated in Figure 5. Obviously the OR of the highest THC class (> 8 ng/ml, right block) is decreasing consistently with time. Due to the elimination of THC after 3 hours there are no cases left in the high THC category. From there on the OR hardly changes and is mainly determined by the ratio of cases and controls in the reference category (< 1 ng/ml). In contrast, the OR for the lowest THC category is increasing consistently with time, because the cases from the high concentration classes “migrate” into the lower concentration classes with time. So after some hours the risk of an actual high substance concentration is attributed to lower concentrations.

This simulation was done in order to illustrate the effect of a delayed blood sample with respect to the calculated risk by tendency. Of course, both the half life of particular substance and the kind of absorption and elimination play a major role in how far the simulation is applicable. But nonetheless, the trend of an increasing risk for lower substance concentrations is obvious with an increasing time delay between the time of interest (e.g. accident) and blood sample. So, for all substances that show a short absorption phase, the risk of low substance concentrations might be overestimated in all epidemiological studies in which the blood is taken hours after the accident.

7 DRUID DATA-POOLS AND DATA-PROCESSING

7.1 Overview

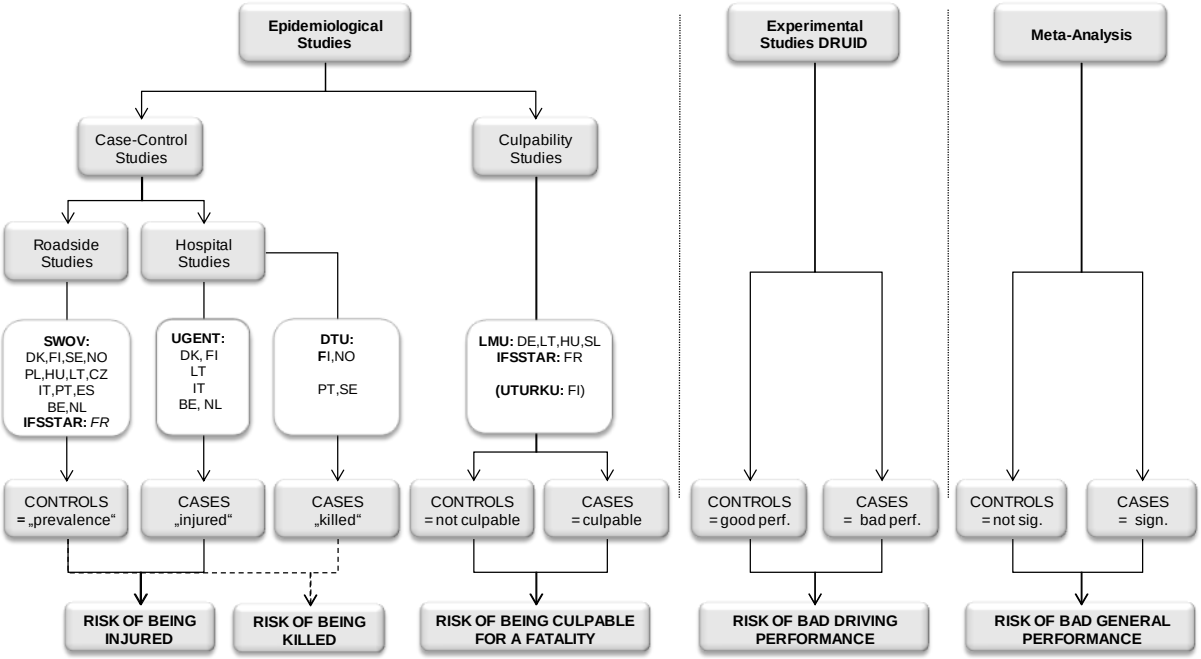


Figure 6: Overview of all DRUID data-pools concerning risk-calculations.

In DRUID three different pools of data are available: Epidemiological data, experimental data, and a meta-analysis. The basic differences of these three approaches are explained in chapter 6.1. Figure 6 gives a graphical overview of the different approaches, the related data-pools and the different interpretations of the three approaches. The table on the next page shows for each of the three approaches for which substances a calculation of risk is possible. It becomes obvious that:

- Within epidemiology no concentration based risk is available for any substance besides alcohol because of the low prevalence rates of all drugs and medicines. Therefore alcohol will be the only substance for which risk values might be compared on a concentration base between the three data-pools. Concentration based risk estimations will be done for THC in hospital studies (injured) and in the culpability study of IFSTTAR.[6]
- Illicit drugs (THC and stimulants) are examined in different concentrations in the experimental studies and in the meta-analysis. So, a further concentration (or dose) based comparison is possible.
- Epidemiology provides no concentration based information for medicinal drugs. In the experiments only alprazolam and zopiclone are examined[7] and can be compared with results from the meta-analysis.
- For all other medicinal drugs only the meta-analysis provides information for a concentration based risk.

[6] For other THC risk studies, which were not part of DRUID see the review of (Biecheler, Gadegbeku, & Amoros, 2007).
[7] The study of codein must be excluded due to methodological reasons (see chapter 7.3.1.1)

CLASSIFICATION		META-ANALYSIS			EXPERIMENT	EPIDEMIOLOGY		
subst. group	**analytical finding**	**dosages or concentrations**	**application**	**eval.**	**dosages (partners)**	**Prevalence**	**Risk Injury/ Killed**	**Risk Culpable**
ALCOHOL								
alcohol	ethanol	0.1 - 1.1 mg/ml	SD in social user	MA	0.3 mg/ml *(IFSTTAR, RugPsy)* 0.5 mg/ml *(TNO, IFSTTAR, RugPsy, Umaas, CERTH, SIPSiVi, BASt, VTI Missing)* 0.8 mg/ml *(IFSTTAR & RugPsy & TNO)*	2) 3) 0.1-0.5 0.5-0.8 0.8-1.2 > 1.2 …mg/ml	BE,DK, LT,NL[1)] 0.1-0.5 0.5-0.8 0.8-1.2 > 1.2 …mg/ml	GE,HU, LT,SL[1)] 0.1-0.5 0.5-0.8 0.8-1.2 > 1.2 …mg/ml
ILLICIT DRUGS								
cannabis	THC (or THC and THC-COOH)	~8 / 13 / 24 mg (oral) ~5 / 13 / 35 mg (smok.)	SD in HV	MA MA	10 / 20 mg (Dronabinol in light & heavy users, *UMAAS*)	2) 3) Yes/No	BE,IT, (LT, NL)[1)] 1-3, 3-5, >5ng/ml	FR 1-3, 3-5, >5 ng/ml
stimu-lants	amph., MDA, MDEA, methamph.	~ 4 / 24 mg	SD in HV	MA	10 mg (& alc. 0.8 mg/ml; *TNO*) 10 / 40 mg (dexamph.; *VTI*)	2) 3) Yes/No	not available	FR: Yes/No
	MDMA				25 / 50 / 100 mg (& sleep dep.; *UMAAS*) 75 / 100 mg (& alc. 0.5 mg/ml; *UMAAS*) 100 mg (& alc. 0.5 mg/ml; *RUGPSY*)			
	cocaine or cocaine and benzoylecgonine		SD in HV	R		2) 3) Yes/No	not available	FR: Yes/No
illicit opiates	6-acetylmorphine, morphine, codein	see below (morphine/codein)				2) Yes/No	not available	FR: Yes/No
MEDICINAL DRUGS								
opiates & opioids	morphine	VD	SD in HV/CU	R		2) Yes/No	BE,DK,FI, IT,NL[1)] Yes/No	not available
	narcoanalgesics atypical opioids	VS	SD in HV	R				
	codein	VD	SD in HV		20 / 40 / 60 mg (paracetamol & codein, *IFSTTAR*)			
	Methadone (& buprenorphine)	VD VD bupren. vs. meth.	SD in HV/P P P	R R R				
benzo & z-drugs	diazepam	5 / 10 / 15 / 20 mg	SD in HV	MA		2) Yes/No	BE,DK,FI, NL,LT[1)] Yes/No	GE,HU, LT,SL[1)] Yes/No
	alprazolam	1 mg	SD in HV	MA	0.5 mg (in treated and untr. P.; *CERTH*)			
	oxazepam	15 / 30 mg	SD in HV	MA				
	lorazepam	1 / 2 / 2.5 mg	SD in HV	MA				
	bromazepam	6 / 12 mg	SD in HV	MA				
	clobazam	10 / 20 mg	SD in HV	MA				
	buspirone	10 / 20 mg	SD in HV	MA				
	meprobamate	400 / 800 / 2400 mg	SD in HV	MA				
	flunitrazepam	1 / 2 mg	SD in HV	MA				
	zolpidem	5 / 10 / 20 mg	SD in HV	MA		2) Yes/No		
	zopiclone	7.5 mg	SD in HV	MA	7.5 mg: IS vs. GS (UMAAS)			
antide-pressants	amitriptyline	25 / 50 mg	SD in HV	MA		not available	not available	not available
	imipramine	75 mg	SD in HV	MA				
	mianserin	10 mg	SD in HV	MA				
	trazodone	100 mg	SD in HV	MA				
	fluoxetine	60 mg	SD in HV	MA				
	paroxetine	30 mg	SD in HV	MA				
antihis-tamines	diphenhydramine	25 / 50 mg	SD in HV	MA		not available	not available	not available
	loratadine	10 mg	SD in HV	MA				
	terfenadine	60 mg	SD in HV	MA				
	triprolidine	10 mg	SD in HV	MA				
antipsy-chotics	haloperidol	3 mg	SD in HV	MA		not available	not available	not available
	sulpiride	400 mg	SD in HV	MA				
	promethazine	27 mg	SD in HV	MA				
OTHER								
	sleep apnea				noCPAP vs. CPAP *(CERTH)*			
	risperidone				different dosages *(SIPSIVI)*			
	opiods	VS	SD in HV	R	VS / VD (BAST)			
	hypnotics				VS / VD: IS vs. GS(*UMAAS*)			
COMBINATIONS								
drug-alcohol		alcohol & THC		R	alcohol & metamphetamine alcohol and MDMA	2) Yes/No	BE, DK,(NL)	not available
drug-drug						2) Yes/No	DK, FI (BE,IT)	not available

MA / R — *meta-analysis / review*
SD / CU — *Single Dose / Chronic Use(r)*
HV / P — *Healthy Volunteers / Patients*
VS / VD — *Various Substances / Various Dosages*
IS / GS — *Insomniacs / Good Sleepers*

1) *risk merged for this following countries*
2) *DK, FI, LT, SE, NO, PO, HU, CZ, IT, PT, ES, BE, NL (for each country)*
3) *also concentration based prevalence rates from the German Smartphone Survey of UWURZ*

7.2 Epidemiological studies

All epidemiological studies were conducted following the working paper "Uniform design and protocols for carrying out case-control studies" (Bernhoft et al., 2007):

- in all studies the population were car-drivers (no motorbikes, vans or pedestrians), aged > 18 years; single and multiple vehicle accidents were included
- all hospital studies regarding **injury** refer to injuries judged as MAIS ≥ 2 (but alive) and all ORs were adjusted for age and gender
- all hospital studies regarding **killed drivers** refer to killed drivers and ORs were adjusted for age and gender,
- all culpability studies with killed drivers who were judged for **culpability** refer to fatalities where drivers were judged afterwards if they were culpable or not.

Table 4: Major differences between the epidemiological approaches.

	country	cases	controls	specimen cases	specimen controls	time
"hospital" injury	BE	348	2949	whole blood	saliva / blood	<3h
	DK	839	3002	whole blood	saliva	<3h
	FI	54	3841	saliva / blood	saliva	<3h
	IT	676	1310	saliva / blood	saliva / blood	<3h
	LT	420	1267	whole blood	whole blood	<3h
	NL	190	4822	whole blood	saliva / blood	<3h
"hospital" killed	FI	478	3841	whole blood	saliva	-/-
	NO	193	9236	whole blood	saliva	-/-
	PT	285	3965	whole blood	saliva	-/-
	SE	156	6199	whole blood	saliva	-/-
killed/ culpable (LMU)	DE	32	200	whole blood	whole blood	<3h[1)]
	LT	3	38	whole blood	whole blood	<3h[1)]
	HU	8	85	whole blood	whole blood	<3h[1)]
	SL	21	128	whole blood	whole blood	<3h[1)]
fatality/culpable[2)] (IFSTTAR)	FR	1986	4946	whole blood	whole blood	60%<3h[3)]

1) "Cases were excluded if more than 10 hours had elapsed until death. In the majority of cases death occurred immediately after the accident or within the first three hours after accident (94.8% of all subjects). (Thorsteinsdóttir et al., 2011)

2) In the French study the study population were drivers involved in a fatal crash, that means that also people, who survived the crash, are part of the study population. In the LMU study only killed drivers were included.

3) "For drivers where it is reported, the elapsed time is less than 10% within 1 hour, and about: one quarter between 1 and 2 hours, one quarter between 2 and 3 hours, 20% between 3 and 4 hours, and 20% after 4 hours. Consequently, doses and prevalence rate are probably somewhat under-estimated (Gadegbeku et al., 2010).

7.2.1 Case-control studies

7.2.1.1 Controls: Roadside studies (Houwing, Hagenzieker, Mathijssen, Bernhoft, Hels, & Kira, 2011)

7.2.1.1.1 Europe

For assessing the prevalence rates (controls) in Europe 48545 drivers of passenger cars and vans were randomly stopped in 13 countries using a stratified multistage sampling design (for methodological details see Houwing, Hagenzieker, Mathijssen, Bernhoft, Hels, & Kira, 2011).

The main problem in interpreting prevalence rates is the non-response bias. Several study design factors affect the size and nature of the non-response bias (e.g. choice of body fluids, mandatory testing, etc.). Table 5 gives an overview of the non-response bias in the 13 countries and the different study design factors. In all countries where the police performed a mandatory drug test or where drug testing by researchers preceded the mandatory breath test for alcohol, non-response was very low (Italy, Poland, Portugal: 0-5%). In Lithuania the non-response is 24%, although the researchers preceded the mandatory breath test because blood was taken as body fluid. So, a lot of study design factors may lead to very different non-response rates.

Table 5: Non-Responder rates and related factors for the countries in the prevalence studies (Houwing, Hagenzieker, Mathijssen, Bernhoft, Hels, & Kira, 2011).

Country	Body fluid controls	Precedence	Mandatory	Informed consent	Non-response
Belgium	saliva/blood	Police first	No	Yes	52%
Czech Republic	saliva	Police first	No	No	23%
Denmark	saliva	Police first	No	No	5%
Spain	saliva	Police first	No	Yes	2%
Finland	saliva	Police first	No	Yes	48%
Hungary	saliva	Police first	No	Yes	10%
Italy	saliva/blood	Police first	Yes	not avail.	0%
Lithuania	blood	Researcher first	No	No	24%
Netherlands	saliva/blood	Researcher first	No	No	5%
Norway	saliva	Police first	No	Yes	6%
Poland	saliva	Researcher first	No	Yes	1%
Portugal	saliva	Researcher first	No	No	3%
Sweden	saliva	Police first	No	No	38%

Additionally, several external factors, which are hardly quantifiable (drivers' time-pressure in the morning, reputation of the study in the respective country, weather conditions), do also have an impact on the response rate.

The most endangering factor for the reliability of the prevalence rates is a selectivity of the non-response group. 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 of psychoactive substances among the general driving population is especially problematic if the roadside survey sample is used as a control sample in a case-control study. Underestimation of the prevalence rate among controls will then result in overestimation of the risk associated with psychoactive substance use. The only way to exclude a selective non-response bias is to compare the response and the non-response group for other variables in order to show their comparability. This was done by (Houwing, Hagenzieker, Mathijssen, Bernhoft, Hels, & Kira, 2011) for all countries where the non-response bias exceeds the prevalence rate of the investigated substances (see Table 6).

Table 6: Overview of prevalence rates and non-response rates of the "suspicious" countries.

Country	Prevalence [%]	non-response [%]	Comment
Belgium	10.65	52	no indication for a selective non-response bias from comparison of age, gender, transport mode and alcohol use
Czech Republic	2.8	23	comparable in gender, no other information
Finland	2.9	48	no information
Hungary	2.3	12	small overrepresentation in non-response group of female drivers and driver aged 35-40 ⇨ probably no large bias
Lithuania	5.5	24	large overrepresentation in non-response group of female drivers aged <35 years. Most of them with lack of time and no signs of impairment. ⇨ probably no large bias
Sweden	1.3	38	no information

So, the non-response rates in Belgium, Hungary, and Lithuania do not seem to be selective. Therefore, prevalence rates and ORs may be interpreted. Prevalence rates and ORs from the Czech Republic, Finland, and Sweden should be interpreted with caution. Table 7 shows the absolute numbers. All numbers and prevalence rates attributed to single substances reflect the situation of single use, which means "THC" = only THC with no other substance. All combinations, irrespective of illicit drug or medicine are subsumed under "alcohol in combi" or "drugs-drugs combi".

Table 7: Absolute number of negative and positive controls for different substances and countries.

	NOTHERN				EASTERN				SOUTHERN			WESTERN	
Substance	**DK**	**FI**	**SE**	**NO**	**PL**	**HU**	**LT**	**CZ**	**IT**	**PT**	**ES**	**BE**	**NL**
positive	*144*	*111*	*89*	*275*	*102*	*65*	*76*	*61*	*196*	*408*	*631*	*352*	*396*
negative	2858	3730	6110	8961	3903	2673	1191	1976	1114	3557	2543	2597	4426
alcohol	81	26	NA	33	49	4	67	22	123	207	224	220	190
alcohol in combi	5	3	NA	7	0	0	1	1	23	20	84	12	22
stimulants[8]	1	1	3	7	6	0	2	6	0	0	7	0	13
cocaine	0	1	0	6	0	2	0	0	14	2	56	6	20
THC	7	2	3	46	33	4	0	11	13	59	191	15	104
illicit opiates	0	0	0	0	2	0	0	0	4	6	2	3	1
benzodiazepines	14	31	13	73	8	43	6	13	5	100	35	56	13
z-drugs	8	15	15	60	0	1	0	0	0	0	0	6	2
opiates and opioids	26	22	50	15	2	6	0	3	2	4	6	23	7
drugs-drugs combi	2	10	5	28	2	5	0	5	12	10	26	11	24
SUM	**3002**	**3841**	**6199**	**9236**	**4005**	**2738**	**1267**	**2037**	**1310**	**3965**	**3174**	**2949**	**4822**

One should keep in mind that low cell numbers (1-3 cases) make the estimation of weighted [9] prevalence rates necessary (Table 8). The estimation for the European regions and whole Europe is based on the number of inhabitants in the respective countries.

[8] The term stimulants is in the following used for Metamphetamine, Amphetamine, MDMA, MDEA and MDA. In the prevalence Deliverable (Houwing, Hagenzieker, Mathijssen, Bernhoft, Hels, & Kira, 2011) this category is denoted with "amphetamines". (e.g. in Table 8).

[9] Weighting needed to be done in order to correct for the difference between the distribution of the roadside samples and the distribution of traffic over the eight different time periods (for further details see Houwing, Hagenzieker, Mathijssen, Bernhoft, Hels, & Kira, 2011).

		Inhabitants (million)	negative	amphetamines	cocaine	THC	illicit opiates	benzodiazepines	Z-drugs	medicinal opiates and opioids	alcohol	alcohol-drugs	drugs-drugs
Northern Europe	DK	5.4	95.52 *94.72 - 96.2*	0.02 *0 - 0.16*	- -	0.2 *0.09 - 0.43*	- -	0.47 *0.28 - 0.79*	0.32 *0.17 - 0.59*	0.79 *0.53 - 1.18*	2.53 *2.02 - 3.15*	0.1 *0.03 - 0.3*	0.06 *0.02 - 0.24*
	FI	5.3	97.15 *96.58 - 97.63*	0.05 *0.02 - 0.19*	0.03 *0.01 - 0.16*	0.04 *0.01 - 0.17*	- -	0.79 *0.56 - 1.13*	0.36 *0.21 - 0.6*	0.56 *0.37 - 0.85*	0.64 *0.43 - 0.94*	0.08 *0.03 - 0.23*	0.29 *0.16 - 0.52*
	NO	4.7	97.03 *96.67 - 97.36*	0.06 *0.02 - 0.13*	0.06 *0.03 - 0.14*	0.48 *0.36 - 0.64*	- -	0.84 *0.67 - 1.05*	0.69 *0.54 - 0.88*	0.16 *0.1 - 0.27*	0.32 *0.23 - 0.46*	0.07 *0.03 - 0.15*	0.28 *0.19 - 0.42*
	SE	9.1	98.66 *98.34 - 98.92*	0.07 *0.03 - 0.17*	- -	0.03 *0.01 - 0.12*	- -	0.19 *0.11 - 0.33*	0.31 *0.2 - 0.48*	0.63 *0.46 - 0.86*	NA	NA	0.12 *0.06 - 0.25*
	Total N-EU	*93.3*	*97.32*	*0.05*	*0.02*	*0.16*	*0.00*	*0.51*	*0.40*	*0.56*	*1.20*	*0.05*	*0.17*
Eastern Europe	CZ	10.3	97.2 *96.39 - 97.83*	0.36 *0.17 - 0.72*	- -	0.46 *0.25 - 0.86*	- -	0.62 *0.36 - 1.07*	- -	0.21 *0.08 - 0.52*	0.99 *0.65 - 1.53*	0.05 *0.01 - 0.28*	0.11 *0.03 - 0.38*
	HU	10.1	97.68 *97.04 - 98.18*	- -	0.04 *0.01 - 0.21*	0.19 *0.08 - 0.44*	- -	1.5 *1.11 - 2.03*	0.07 *0.02 - 0.26*	0.11 *0.04 - 0.32*	0.15 *0.06 - 0.38*	- -	0.27 *0.13 - 0.54*
	LT	3.4	94.49 93.09 - 95.61	0.22 0.07 - 0.66	- -	- -	- -	1.41 0.9 - 2.23	- -	- -	3.86 2.93 - 5.06	0.03 0 - 0.36	- -
	PL	38.2	97.63 *97.11 - 98.05*	0.05 *0.01 - 0.18*	- -	0.57 *0.38 - 0.85*	0.09 *0.04 - 0.25*	0.14 *0.06 - 0.31*	- -	0.03 *0.01 - 0.15*	1.47 *1.14 - 1.9*	- -	0.02 *0 - 0.14*
	Total E-EU	*96.7*	*97.57*	*0.09*	*0.01*	*0.47*	*0.06*	*0.52*	*0.02*	*0.08*	*1.10*	*0.01*	*0.07*
Southern Europe	ES	44.5	85.15 *83.87 - 86.34*	0.11 *0.04 - 0.3*	1.49 *1.12 - 1.97*	5.99 *5.22 - 6.87*	0.05 *0.01 - 0.2*	1.4 *1.05 - 1.87*	- -	0.19 *0.09 - 0.41*	3.92 *3.3 - 4.66*	1.14 *0.83 - 1.58*	0.57 *0.36 - 0.89*
	IT	59.1	84.99 *82.95 - 86.82*	- -	1.25 *0.78 - 2.01*	1.15 *0.7 - 1.89*	0.3 *0.12 - 0.78*	0.97 *0.57 - 1.67*	- -	0.53 *0.25 - 1.09*	8.59 *7.19 - 10.23*	1.01 *0.59 - 1.71*	1.22 *0.75 - 1.97*
	PT	10.6	90.01 *89.04 - 90.91*	- -	0.03 *0.01 - 0.16*	1.38 *1.07 - 1.8*	0.15 *0.07 - 0.33*	2.73 *2.27 - 3.29*	- -	0.11 *0.04 - 0.27*	4.93 *4.29 - 5.64*	0.42 *0.26 - 0.67*	0.23 *0.12 - 0.44*
	Total S-EU	*128.6*	*85.52*	*0.04*	*1.23*	*3.06*	*0.19*	*1.30*	*0.00*	*0.36*	*6.43*	*1.01*	*0.87*
Western Europe	BE	10.6	89.35 *88.18 - 90.41*	- -	0.2 *0.09 - 0.43*	0.35 *0.19 - 0.64*	0.09 *0.03 - 0.28*	2.01 *1.57 - 2.59*	0.22 *0.1 - 0.47*	0.75 *0.5 - 1.13*	6.42 *5.59 - 7.36*	0.31 *0.16 - 0.58*	0.3 *0.16 - 0.58*
	NL	16.4	94.49 *93.81 - 95.1*	0.19 *0.1 - 0.36*	0.3 *0.18 - 0.5*	1.67 *1.34 - 2.07*	0.01 *0 - 0.09*	0.4 *0.25 - 0.62*	0.04 *0.01 - 0.15*	0.16 *0.08 - 0.32*	2.15 *1.78 - 2.6*	0.24 *0.13 - 0.42*	0.35 *0.22 - 0.56*
	Total W-EU	*181.4*	*92.46*	*0.12*	*0.26*	*1.15*	*0.04*	*1.03*	*0.11*	*0.39*	*3.83*	*0.27*	*0.33*
Weighted European mean		***500.0***	***92.57***	***0.08***	***0.42***	***1.32***	***0.07***	***0.90***	***0.12***	***0.35***	***3.48***	***0.37***	***0.39***

Table 8: Overview of the estimated European prevalence rates for driving under the influence of psychoactive substances; prevalence rates in percentage; 95% confidence intervals in italics (from Houwing, Hagenzieker, Mathijssen, Bernhoft, Hels, & Kira, 2011).

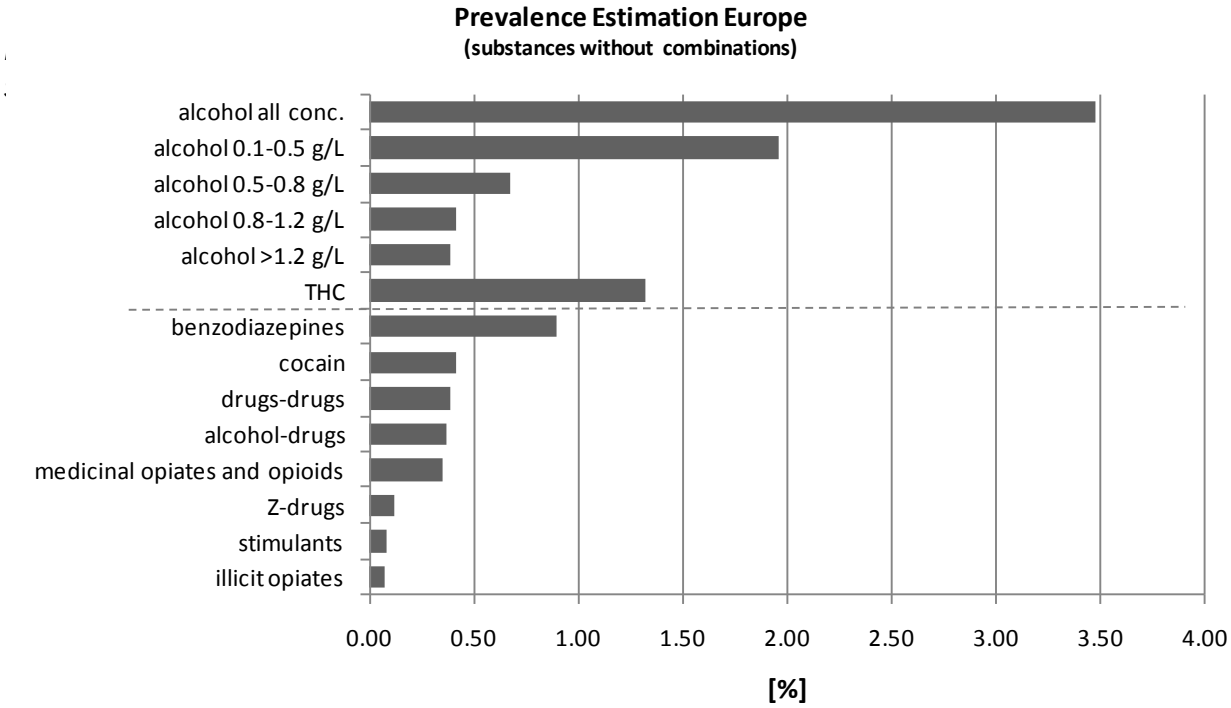


Figure 8: Estimated European prevalence rates (sorted).

Based on these prevalence rates (Houwing, Hagenzieker, Mathijssen, Bernhoft, Hels, & Kira, 2011) conclude the following main results:

- *Alcohol is still by far the number one psychoactive substance on European roads, followed by illicit drugs and medicinal drugs (Figure 11).*
- *On a European level alcohol is estimated to be used by 3.48% of the drivers, illicit drugs by 1.90% of the drivers, medicinal drugs by 1.36% of the drivers, drug-drug combinations by 0.39% of the drivers and alcohol-drug combinations by 0.37% of the drivers.*
- *For illicit drugs THC is 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 in 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 present.*
- *The use of substances among drivers in the general driving population in Europe (prevalence) varies very much per country, but general patterns can be distinguished on the level of European regions:*
    - *The medicinal drugs Z-drugs, medicinal opiates and opioids were in general relatively frequently detected in Northern European countries.*

- *Illicit drugs, alcohol, and benzodiazepines are relatively frequently detected in Southern European countries.*
- *In Eastern Europe the prevalence rate of alcohol and drugs was relatively low compared to the other European regions.*
- *In Western Europe, drug use is more or less on the European average*.

7.2.1.1.2 France

The prevalence rates in France were estimated by the prevalence rates in the control group (car drivers involved in a fatal crash, not culpable) of the culpability study, which examines the culpability of drivers involved in fatal crashes. *"The representativity of this control group towards the driving population has been positively assessed"* (Amoros et al., 2010).

Both the prevalence rates for alcohol (6.8%) and cannabis (3.3%) are higher than the European mean (consider the methodological differences according to Houwing, Hagenzieker, Mathijssen, Bernhoft, Hels, & Kira, 2011). The same accounts for amphetamines[10], but the interpretation is difficult because lower detection thresholds were applied for amphetamines, cocaine and opiates (see 7.2.2).

Table 9: Prevalence rate of psychoactive substances in the driving population (all drivers and car drivers), over 18 years old, using DRUID thresholds, n=1986 (combined use included!).

Psychoactive Substance	Control group of ALL drivers	Control group of CAR drivers
Alcohol (≥ 0.1 g/l)	5.0%	6.8%
Cannabis (THC ≥ 1 ng/ml)	2.8%	3.3%
Amphetamines (≥ 20 ng/ml)	0.3%	0.4%
Cocaine (≥ 10 ng/ml)	0.3%	0.3%
Opiates (≥ 10 ng/ml)	0.9%	1.2%

7.2.1.1.3 Germany (German Smartphone Survey)

The prevalence rates in Germany were estimated by the German Smartphone Survey (Walter et al., 2011b). By the present study a new methodological approach was implemented. Instead of detecting drugs in the driving population – like roadside surveys do – a sample of regular drug users out of the regular driving population were daily queried for four weeks about their driving and drug consumption behavior.

The sample consists of 195 drug users and 100 controls out of the normal driving population stratified for sex, age (18-39 years) and residence (rural, urban and city area). The strata sample sizes are about the same size as the strata population sizes – with reference to the general German regularly drug using population that always/sometimes has a car available. To capture real-time data about drug consumption and driving a repeated-entry diary technique was applied. A questionnaire

[10] In the French study the following substances were tested for the group amphetamines: MDMA (ecstasy), MDEA (methylene dioxy-methamphetamines), MDA (methylene dioxy amphetamines) and MBDB (benzodioxazolybutanamine).

was installed on smartphones and was daily filled in for 28 consecutive days. All activities were listed in chronological order with detailed descriptions of drug consumption and driving. Encrypted data were transmitted via GPRS and the internet. To encourage the subjects to fully report their drug use and to be able to validate the reports, all subjects were required to randomly submit to a urine drug testing once within the study period. The subjects' statements about their drug use were found to be reliable since the urine screening results could be explained very well by the previous drug use that got reported.

The reported drug consumption and driving data were comparable to existing drug prevalence rate and mobility data of the general German population. For defining a drive as being under influence, BACs and THC blood plasma levels were calculated using the information given by the subjects in their daily reports about the consumed amount of alcohol and cannabis and the time delay between consumption and driving. For the BAC calculation the Widmark formula was applied (Widmark, 1932), for the calculation of THC blood plasma levels the elimination curve determined by Sticht (Sticht, G., personal communication, December 2009). A drive was classified as under influence if the corresponding BAC was 0.1 g/L or higher and the THC blood plasma level was 1ng/ml or higher, respectively. For all other substances the doubled half life (Passie, Seifert, Schneider, & Emrich, 2002; Prisinzano, 2005; Schulz & Schmoldt, 2003) was used to define a drive as a drive under influence: Drives within the doubled half life time after consumption were classified as drug-positive.

Table 10: Number of drives under influence within the user group and mean percentage by person (N_{User}=195).

		Total sample	By person
		Number (%) of drives	Mean % of drives (95% CI)
All drives		9553 (100%)	
	Sober	7454 (78%)	
	Under influence	2099 (22%)	20.5% (17.4% - 23.5%)
Not separated for single-/poly-drug drives (multiple specifications possible)			
	Cannabis	1521 (15.9%)	14.8% (11.8% - 17.7%)
	Alcohol	546 (5.7%)	5.4% (4.2% - 6.7%)
	Stimulants (Amphetamine, MDMA, Amphetamine & MDMA, Cocaine)	223 (2.3%) (186 / 17 / 19 / 1)	2.2% (1.1% - 3.4%)
	Heroin	5 (0.05%)	0.05% (-)
Separated for single-/poly-drug drives			
Single drug	**Cannabis**	1354 (14.2%)	13.1% (10.5% - 15.8%)
	Alcohol	410 (4.3%)	4.1% (3% - 5.1%)
	Stimulants	147 (1.5%)	1.5% (0.5% - 2.4%)
Multiple drugs	**Total**	188 (2.0%)	1.8% (1.1% - 2.5%)
	Cannabis / Alcohol	107 (1.1%)	1% (0.5% - 1.5%)
	Cannabis / Stimulants	47 (0.5%)	0.4% (0.1% - 0.8%)
	Alcohol / Stimulants	21 (0.2%)	0.2% (0.1% - 0.3%)
	Cannabis / Alcohol / Stimulants	8 (0.1%)	0.1% (-)
	Cannabis / Heroin	5 (0.05%)	0.05% (-)

Averaged per person, 20.5% of the users' drives were under the influence of drugs (Table 10). The most prevalent drug found while driving was cannabis. The mean percentage of drives under the influence of cannabis alone was 13.1% (total: 14.8%). On average, 4.1% of the users' drives were under the influence of alcohol (total: 5.4%) and 1.5% under the influence of stimulants (amphetamine, ecstasy, cocaine –

total: 2.2%). The mean percentage of drives under the influence of multiple drugs was 1.8%, most of which under the influence of alcohol and cannabis (1%). The cut-off values for defining a drive as drive under influence are rather low (BAC>=0.1 g/L, THC blood plasma level>=1 ng/ml). When applying higher cut-off values, like a BAC of 0.5 g/L and a THC blood plasma level of 4 ng/ml[11], the mean percentage of drives under influence within the user sample drops by around 40% from a previous 20.5% to 13.1%.

Via existing mobility measures and prevalence data for drug use in Germany (Follmer et al., 2008; Kraus, Pfeiffer-Gerschel, & Pabst, 2006) the survey results were extrapolated into prevalence rates for the general German driving population. According to this estimation, the prevalence for THC-positive drives (THC blood plasma level>=1ng/ml, substance combinations included) in Germany is 0.14% (95% CI: 0.09% - 0.2%) (Figure 9, left, prevalence rate for different THC blood plasma levels). For drives under the influence of stimulants (cocaine in- or excluded, substance combinations included) the prevalence rate is 0.02% (95% CI: 0.01% - 0.04%), for drives under the influence of multiple drugs (any drug combination, alcohol included) the prevalence rate is 0.02% (95% CI: 0.01% - 0.03%), and for drives under the influence of alcohol in combination with an illegal drug the prevalence rate is 0.01% (95% CI: 0.006% - 0.02%).

The study provides no information about the frequency of BAC-positive drives within the population above 39-year-olds. The high proportion of all drives (Follmer et al., 2008)[12] and the high prevalence rate of risky alcohol consumption in this age group (Kraus et al., 2006), however, led to the suspicion that the prevalence rate of BAC-positive drives is rather high within this age category. Thus, for BAC-positive drives the analysis is reduced to the calculation of prevalence rates for the 18-24- and the 25-39-year-old sub-population. For the 18-24-year-old German population the prevalence rate for alcohol-positive drives (BAC>=0.1 g/L, substance combinations included) is 1.57% (95% CI: 0.52% - 2.7%) and 3.3% (95% CI: 1.63% - 5%) for 25-39-year-olds (Figure 9, right, prevalence rate for different BACs).

[11] According to (Berghaus et al., 2010) a THC blood plasma concentration of 3.8ng/ml corresponds to a BAC of 0.5 g/L concerning the performance impairing effects of the substance.
[12] Proportion of drives of 40+ population of all drives: 66.2% (Follmer et al., 2008).

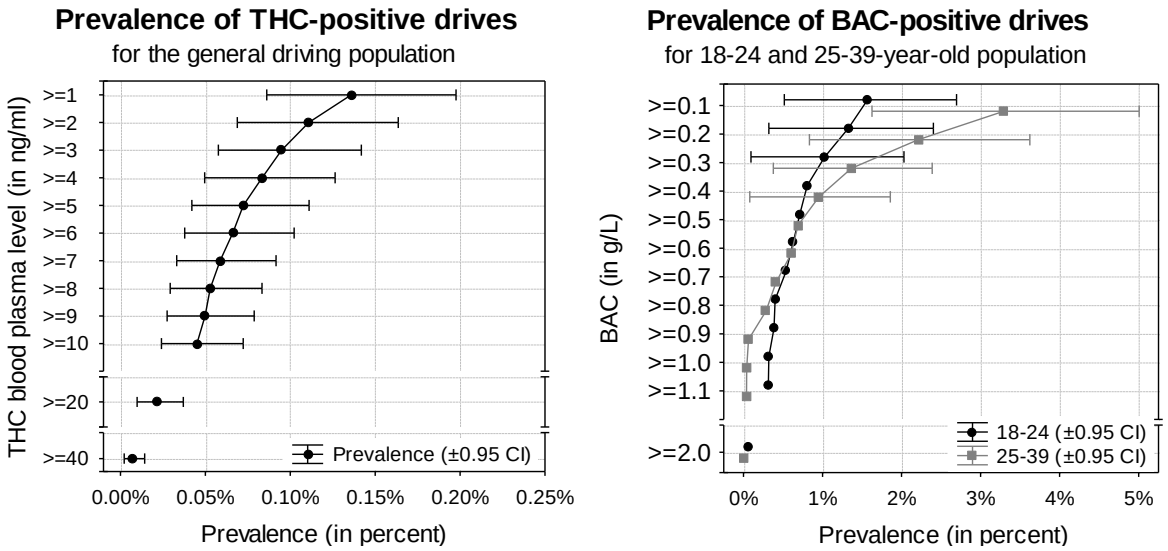


Figure 9: Prevalence rate of THC-positive drives for the general driving population (left) and prevalence rate of BAC-positive drives within the population of 18-24- and 25-29-year-olds (right) calculated from the survey results (in percent ±0.95 CI).

Compared to the results of the German roadside survey (Cannabis: 0.57%; alcohol: 18-24-year-olds: 3.76%; 25-49-year-olds: 5.48%) from 1994 (Krüger, Schulz, & Magerl, 1996) the prevalence rates found within the present study seem fairly low. However, amendments to traffic regulations for drink and drug driving within the last few years might serve as an explanation for a changed prevalence rate of drives under influence in Germany. In 1998, the legal BAC limit for driving a motor vehicle in traffic was lowered from 0.8 g/L to 0.5 g/L. Moreover, the 0.0 g/L BAC limit for novice drivers[13] was introduced in 2007. A positive trend concerning alcohol drives within the last years can also be shown by other traffic related indicators. Alcohol-related accidents (Vorndran, 2009) or alcohol related records at the Central Register of Traffic Offenders (2004, 2009) decreased within the last few years. Furthermore, it was not until 1998 that a law was introduced in Germany that makes driving under the influence of illegal substances prosecutable in the first place. Since then the screening of illegal drugs in traffic has become more prevalent and the detection devices more precise. So, the probability of being detected while driving under the influence of an illegal drug has become higher. Because of the higher deterrence effect, drug users may have altered their drug driving behavior towards more conformity with the law within the last few years.

7.2.1.2 Cases: Hospital studies (Isalberti et al., 2011)

The prevalence rate of psychoactive substances in cases will not be discussed in detail here because the significance of this information is expressed in the relation to the prevalence rate in controls and is reported as risks in chapter 8. Nonetheless there is one specific methodological aspect regarding the cases which should be focused at – the time lag between accident and blood sampling. As explained in chapter 6.3.2 an increasing time-lag between accident and blood sampling must lead – if not corrected for – to certain biases in the risk estimation.

[13] All drivers between the ages of 18 and 21 and newly licensed drivers of any age for the first two years of having a licence.

Within the DRUID sample of cases all time-lags are lower than 3 hours with a median in the different countries around 1.5 hours (see Figure 10) which is rather short. Nonetheless, a time lag of 1.5 hours might be crucial regarding substances with a short half life like THC. Like stated above for THC the half life of the distribution phase is less than 1.4 h ± 0.1 h (Kauert et al., 2007) in plasma. So, consequently much higher THC concentrations might be found in controls than in cases (because in roadside surveys the samples were collected without time delay) yielding the consequences described in chapter 6.3.2.

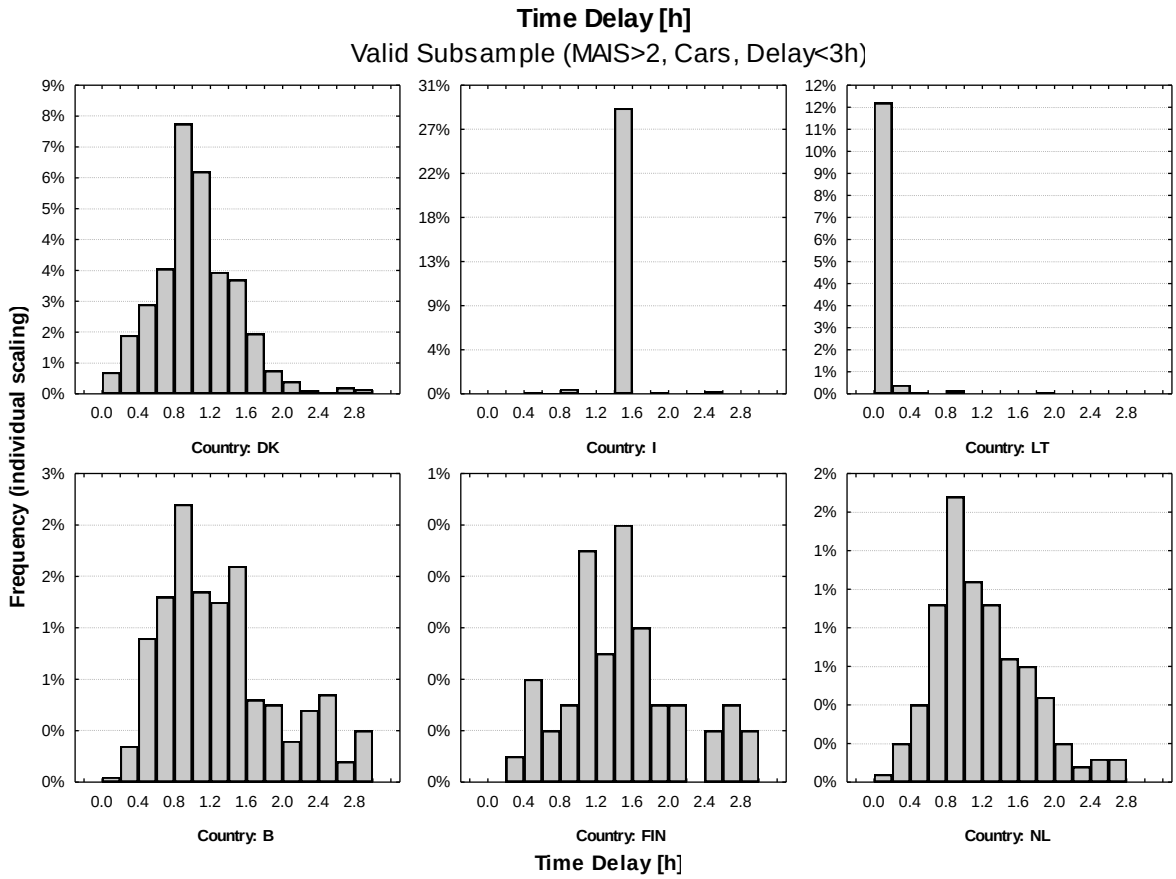


Figure 10: Distribution of time delays between accident and blood sampling in the different countries (all injured drivers = 100%).

7.2.2 Culpability Studies

In DRUID three culpability studies were performed (for details see the related deliverables):

- 2.3.3a (D 2.3.2): IFSTTAR - Relative risk of impaired car drivers involved in fatal accidents in France (Gadegbeku et al., 2010)
- 2.3.3b (D 2.3.3): UTURKU - Relative risk of impaired drivers in fatal motor vehicle accidents in Finland (Laapotti & Keskinen, 2009)

- 2.3.3c (D 2.3.4): LMU - Responsibility study: Psychoactive substances among killed drivers in Germany, Lithuania, Hungary and Slovakia (Thorsteinsdóttir et al., 2011)

Due to the fact that the study of Finland deals with already existing data, many differences in design compared to the other two studies and related difficulties in interpretation exist. Therefore the study of Finland will not be considered for the recommendation of thresholds.

The other two studies (LMU and IFSTTAR) differ also in some aspects. So, a direct comparison is difficult from a methodological point of view.

Table 11: Methodological differences between the two culpability studies of LMU and IFSTTAR.

	LMU (Germany, Lithuania, Hungary, Slovakia)		**IFSTTAR (France)**	
study design	case-control		case-control	
data assessment	retrospective (2008-2009)		retrospective (2000-2003)	
cut off values	Alcohol (Blood):	0.1 g/l	Alcohol (Blood):	0.1 g/l
	Cannabis/THC (Blood)	1 ng/ml	Cannabis/THC (Blood)	1 ng/ml
	Amphetamines (Blood)	20 ng/ml	Amphetamines (Blood)	**50 ng/ml**
	Cocaine (Blood)	10 ng/ml	Cocaine (Blood)	**50 ng/ml**
	Opiates (Blood)	10 ng/ml	Opiates (Blood)	**20 ng/ml**
study pupulation	**Killed** car drivers involved in fatal road crashes		Car drivers involved in fatal road crashes, **whether killed, injured or non-injured**	
included subjects	483		6932	
OR adjustment	no adjustment due to low numbers		adjustment for age, gender and other substances	

Since there are too few cases to calculate ORs for other substances than alcohol or THC in the LMU study, the differences in the cut off values are not critical for comparison. A major difference between the two studies is the study population. Whereas in the French study all involved car drivers of a fatality were screened for substances, in the LMU study only killed drivers of fatalities were screened. The related bias cannot be estimated. Therefore, the two studies have to be reported separately.

7.2.2.1 Germany, Lithuania, Hungary and Slovakia (LMU)

In the LMU study *"...data of killed drivers was sampled prospectively by means of a database established within the DRUID-framework in the years 2008 and 2009 and increased by retrospective data. The analysis included 483 subjects, 18 years and older, killed within 10 hours after being involved in a traffic accident. Responsibility analysis was conducted with the method proposed by Robertson and Drummer (1994) which allocated the 483 subjects in 419 cases and 64 controls. Subsequently a toxicological analysis was carried out where the 23 DRUID-core substances as well as several other additional substances were screened for. (…) Due to in particular a low number of controls the results of OR calculations were in most cases not significantly different from OR=1 and therefore the corresponding analysis did not show an effect of the respective substance on the risk of being responsible for a fatal accident."* (Thorsteinsdóttir et al., 2011).

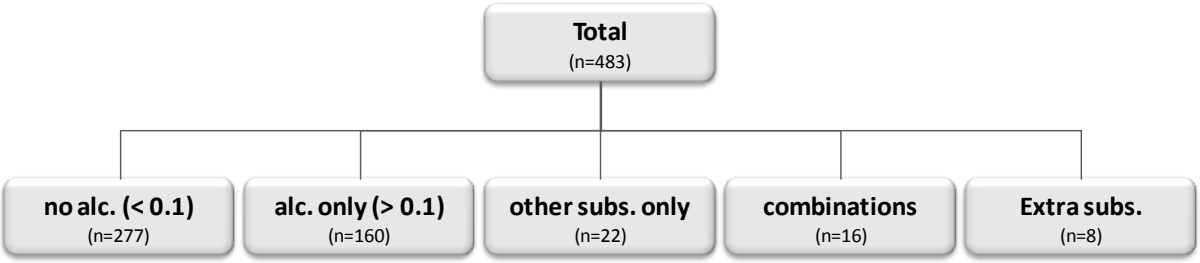


Figure 11: Distribution of the 483 subjects of the culpability studies (all countries merged).

The 483 killed drivers branch in the following exclusive subgroups: 277 drivers (57.3%) without any substance, 160 drivers (33.1%) with only alcohol, 22 drivers (4.6%) with other substances (only), 16 drivers (3.3%) with combinations and 8 drivers (1.7%) with substances not included in the DRUID core list[14] including combinations (see Figure 11).

[14] neuroleptics, opioid (tramadol), antidepressiva, benzodiazepines & antidepressant, non-opiod analgetika, antiepileptika, alcohol & antiepileptika, alcohol & antihistaminika

Table 12: Distribution of the 483 subjects of the culpability studies separated into different countries and into cases (CA) = culpable and controls (CO = not culpable).

	Number of cases (CA) and controls (CO) (n)										
	Germany (n=200)		Lithuania (n=41)		Hungary (n=93)		Slovakia (n=149)		Total (n=483)		Total (n=483)
Explanatory variable	**CA**	**CO**	**CA**	**CO**	**CA**	**CO**	**CA**	**CO**	**CA**	**CO**	**CA+CO**
no substance	***106***	***26***	***12***	***3***	***38***	***5***	***68***	***19***	***224***	***53***	***277***
alcohol (alone)											
0.1 ≤ Alcohol < 0.5 g/L	12	3	0	0	10	2	11	0	33	5	38
0.5 ≤ Alcohol < 0.8 g/L	4	0	0	0	0	0	4	0	8	0	8
0.8 ≤ Alcohol < 1.2 g/L	4	1	1	0	0	0	1	0	6	1	7
1.2 > Alcohol	22	0	24	0	25	0	35	1	106	1	107
substances (alone)											
THC ≥ 1 ng/mL & 0 ng/mL ≤ THC-COOH	0	1	1	0	0	0	1	0	2	1	3
THC-COOH ≥ 5 ng/mL & 0 ng/mL ≤ THC < 1 ng/mL	2	0	0	0	2	0	0	0	4	0	4
Amphetamines ≥ 20 ng/mL	0	1	0	0	0	0	0	1	0	2	2
Opiates ≥ 10 ng/mL	1	0	0	0	0	0	1	0	2	0	2
Benzodiazepines	2	0	0	0	6	1	0	0	8	1	9
Z-drugs	2	0	0	0	0	0	0	0	2	0	2
substances (combination)											
Alcohol + cannabis	1	0	0	0	1	0	1	0	3	0	3
Alcohol + benzodiazepines	1	0	0	0	2	0	1	0	4	0	4
Alcohol + cocaine	0	0	0	0	0	0	1	0	1	0	1
Alcohol + opiates + benzodiazepines	1	0	0	0	1	0	0	0	2	0	2
Cannabis + amphetamines	0	0	0	0	0	0	1	0	1	0	1
Alcohol + amphetamines	1	0	0	0	0	0	1	0	2	0	2
Alcohol + cannabis + amphetamines	0	0	0	0	0	0	1	0	1	0	1
Alcohol + Z-drugs	1	0	0	0	0	0	0	0	1	0	1
Benzodiazepines + antidepressant	1	0	0	0	0	0	0	0	1	0	1
Extra substances (only D/SK)											
Neuroleptics	0	0	0	0	0	0	1	0	1	0	1
Opioid (Tramadol)	1	0	0	0	0	0	0	0	1	0	1
Antidepressiva	1	0	0	0	0	0	0	0	1	0	1
Benzodiazepines + antidepressant	1	0	0	0	0	0	0	0	1	0	1
Non-opiod analgetika	1	0	0	0	0	0	0	0	1	0	1
Antiepileptika	1	0	0	0	0	0	0	0	1	0	1
Alcohol + antiepileptika	1	0	0	0	0	0	0	0	1	0	1
Alcohol + antihistaminika	1	0	0	0	0	0	0	0	1	0	1
Total number	**168**	**32**	**38**	**3**	**85**	**8**	**128**	**21**	**419**	**64**	**483**

The distribution of the examined 483 subjects (Figure 11 and Table 12) shows that

- in 57% of accidents no psychoactive substance was involved,
- even in the "no substance group" (n=277) the ratio of culpable vs. not culpable drivers is 4:1 in most of the countries,
- the majority of accidents happened under the influence of alcohol > 0.1 g/L (33% alcohol only, 36% (33% + 3%) alcohol with combinations),
- the vast majority of all accidents under the single influence of alcohol occurred in all countries with very high BACs of > 1.2 g/L (see Table 12 and Figure 12; 67% of "alcohol alone" accidents),
- for the single use of other substances (without alcohol) only 22 subjects were found, so, a concentration based analysis of risk (OR calculation) is not reasonable.

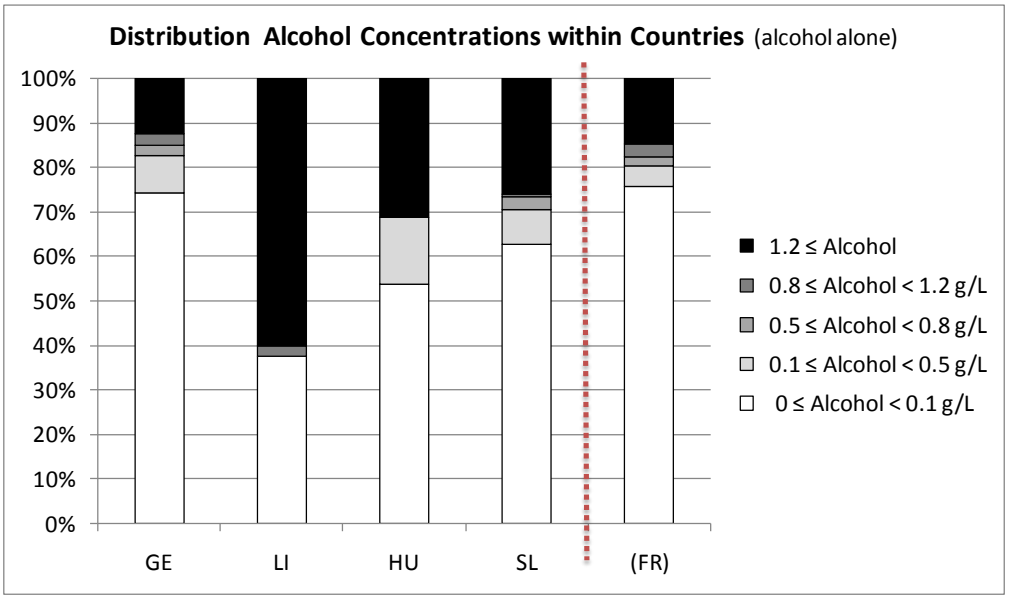


Figure 12: Distribution of alcohol (alone) fatalities in the four countries of the LMU study (Germany, Lithuania, Hungary, Slovakia) and in France (IFSTTAR study).

Looking at the ratio of culpable vs. not culpable drivers within the "no substance group" (n=277) in nearly all countries the ratio is 4:1 which means that having a fatal accident as a driver without being intoxicated implies a 4-fold risk that the fatally injured driver is culpable for the accident. It must be stressed that the judgment of being culpable is not based on a legal judgment but on a classification of accidents regarding mainly the environmental conditions of the accident, e.g. condition of road, condition of the vehicle, driving conditions, task difficulty, etc. (Drummer, 1994). The more difficult these conditions are, the less probable is a culpability assessment of the driver. Following this procedure, it is even possible that the participant of a single vehicle accident is judged as not culpable. Nonetheless, the probability of being culpable is probably higher for a single vehicle accident. So, one reason for the ratio of 4:1 might be the inclusion of single vehicle accidents in the analyses. The ratio of single vs. multiple vehicle accident in the different countries (Table 13) ranges from 1:1 (Slovakia and Lithuania) to approximately 2:1 in Hungary and Germany. So, this seems not to be the (only) reason for the ratio of 4:1 in culpability.

Table 13: Number of subjects and percentages separated for type of crash (single vs. multiple vehicle accident).

	Number of subjects (n) [%]			
Explanatory variable	**Germany (n=200)**	**Lithuania (n=41)**	**Hungary (n=93)**	**Slovakia (n=149)**
Type of crash				
Single vehicle	58 [29.0]	22 [53.7]	36 [38.7]	76 [51.0]
Multi vehicle	142 [71.0]	19 [46.3]	57 [61.3]	73 [49.0]

Since in the study of Drummer (1994) a similar ratio of culpable vs. not culpable within the not intoxicated group was found (Table 14 and Figure 13), it must be assumed that the classification method itself tends to classify accidents as being caused by the fatally injured driver.

Table 14: Number of subjects and percentages separated into gender, age classes, light conditions, location and vehicle type.

Study	**LMU**		**IFSTTAR**		**DRUMMER**	
country	GE, HU, LI, SL		France		Australia	
population	drivers killed		drivers involved in fatalities		drivers killed	
	n	**prevalence**	**n**	**prevalence**	**n**	**prevalence**
population	483	100.00%	10519	100.00%	1045	100.00%
culpable when sober	224	80.87%	3872	52.25%	732	70.00%
culpable	419	86.75%	6620	62.93%	763	73.00%
single vehicle	192	39.75%	3163	30.07%	517	49.50%
benzodiazepines (only & combi)	16	3.31%			32	3.10%
opiates (only & combi)	4	0.83%	91	0.87%	28	2.70%
stimulants (only & combi)	6	1.24%	68	0.65%	39	3.70%
THC (only & combi)	12	2.28%	727	6.91%	112	10.72%
THC only	7	1.45%	343	3.26%	43	4.11%
drugs other alcohol (incl. combi)	38	7.87%	473	4.50%	230	22.00%
Alc > 0.01 & drugs	14	2.90%	381	3.62%	97	9.28%
Alcohol >0.05 only	122	25.26%	1891	17.98%	345	33.00%
Alc > 0.01 only & combi	174	36.02%	2723	25.89%	375	35.89%
Alcohol >0.01 only	160	33.13%	2342	22.26%	278	26.60%
sober	277	57.35%	7323	69.62%	532	50.91%

Looking at the other prevalence rates in the three culpability studies (Table 14 and Figure 13), similar profiles of prevalence rates are found with respect to culpability (upper block), the proportion of single vehicle accidents in the study sample (upper block), drug prevalence rates (middle block), and alcohol prevalence rates (lower block)[15].

[15] Besides the first two lines “culpable when sober” & “culpable” all numbers represent the prevalence rate within the whole study population and are not related to culpability!

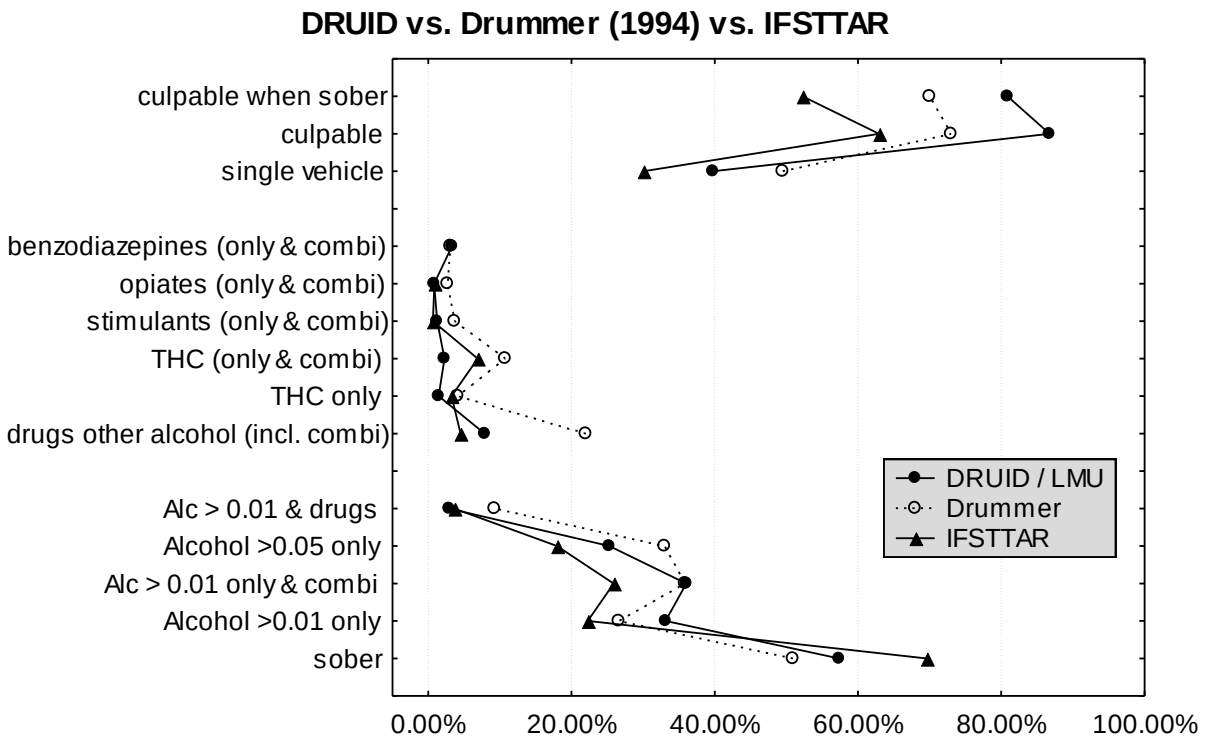


Figure 13: Comparison of basic percentages of the DRUID culpability study and the study of Drummer (1994).

By relating the ratio of culpable vs. not culpable within the sober group compared to different intoxicated groups in order to calculate ORs, it becomes clear that a ratio of 4:1 in the reference group (not intoxicated) makes it difficult to identify increased risks of substances. In order to find a 2-fold risk for a specific substance (concentration), the ratio of culpable vs. not culpable must be 8:1 in the substance group. Nonetheless two significant OR are provided by LMU for the whole sample from all four countries, although the corresponding confidence intervals are wide and therefore the precision of the estimation is poor (Table 15).

- alcohol ≥ 0.1 g/L, i.e. positive (OR=4.57, [2.02-10.38]) and
- alcohol ≥ 1.2 g/L (OR=20.84, [3.10-140.16])[16].

However, bearing the uneven distribution of subjects over the different alcohol categories with proportionally fewer subjects in the categories of lower consumption and many severely intoxicated subjects in mind, these OR values must be interpreted with care. In order to have a clearer picture of the OR of the respective alcohol categories LMU calculated (where possible) the OR for each dosage level. For one category no calculation was possible due to missing controls in this category. For two categories (0.1 ≤ Alcohol < 0.5 g/L and 0.8 ≤ Alcohol < 1.2 g/L) calculations were possible, however the results (OR around 1.5) were not statistically different from value 1 and the analysis does not show an effect of these alcohol concentrations on the risk of being responsible of a fatal crash. In contrast the OR for alcohol concentrations of 1.2 g/L and more are statistically different from 1 and extremely high (adjusted OR around 20), however the confidence intervals are extraordinary wide and therefore the precision of estimate is very poor.

[16] both adjusted for age and gender

Table 15: Whole sample – OR of the risk of a killed driver being responsible for a fatal traffic accident while under influence of alcohol (five dosage levels), THC and benzodiazepines.

Psychoactive substance	Whole sample (OR) (n =440)				
	Nr. of subjects	Crude OR	95% CI	Adjusted OR (§)	95% CI
0 ≤ Alcohol < 0.1 g/L	276	1.00			
0.1 ≤ Alcohol < 0.5 g/L	38	(1.57)	0.59 – 4.21	(1.56)	0.58 – 4.23
0.5 ≤ Alcohol < 0.8 g/L	0	*	*	*	*
0.8 ≤ Alcohol < 1.2 g/L	7	(1.43)	0.17 – 12.01	(1.18)	0.14 – 10.20
1.2 ≤ Alcohol	107	25.19	3.44 – 184.64	20.84	3.10 - 140.16
THC ≥ 1 ng/ml	3	(0.48)	0.04 – 5.34	(0.26)	0.01 – 5.31
Benzodiazepines (y/n)	9	(1.90)	0.23 – 15.53	(1.66)	0.19 – 14.55

§ Adjusted for age and gender
* OR-calculations not possible due to low number of cases vs. controls

Table 15 also shows the results of OR calculations regarding cannabis (THC ≥ 1 ng/ml) and benzodiazepines. The number of subjects was low for those categories, resulting in a low statistical power which is reflected in the respective OR which are not statistically different from the value 1 and the wide confidence intervals. Therefore the analysis does not show an effect of those substances on the risk of being responsible for a fatal accident." (Thorsteinsdóttir et al., 2011)

7.2.2.2 France (IFSTTAR)

In the French study "*drivers involved in fatal road crashes, whether killed, injured or non-injured have been tested for alcohol and illicit drugs. Within the DRUID project, a responsibility analysis restricted to car drivers is conducted. In total, 7455 car drivers, with known drug and alcohol concentrations, are included. The study belongs to the framework of case-control studies in which the health event studied is "being responsible for a fatal crash". Responsibility is assessed with a method adapted from Robertson and Drummer. Cases are thus the 4946 car drivers who are responsible for the crash; the controls are 1986 car drivers selected from the 2509 non-responsible car drivers. The control group is chosen in order to be as close as possible to the driving population."* (Gadegbeku et al., 2010).

Due to the different cut-off values in the French study only the prevalence rates and risks for alcohol and THC are reported here. In the French study 70.44% of drivers were not intoxicated (see Table 16). From the remaining 30%, nearly 14% were drivers with an alcohol (only) concentration of > 1.2 g/L, followed by alcohol (only) higher than 0.1 g/L and lower than 0.5 g/L, alcohol (only) higher than 0.5 g/L and lower than 0.8 g/L, etc.

Table 16: Prevalence rates of alcohol and cannabis by dose, all drivers over 18 years old involved in fatal crashes, France, 2001-2003.

	Alcohol [g/L]	0	0.5	0.8	1.2	>1.2	TOTAL
THC [ng/ml]	**0**	70.44% (7410)	4.33% (455)	2.02% (212)	2.63% (277)	13.67% (1438)	**93.09% (9792)**
	3	1.76% (185)	0.17% (18)	0.10% (10)	0.19% (20)	0.79% (83)	**3.00% (316)**
	5	0.76% (80)	0.08% (8)	0.02% (2)	0.11% (12)	0.46% (48)	**1.43% (150)**
	>5	1.15% (121)	0.22% (23)	0.12% (13)	0.14% (15)	0.85% (89)	**2.48% (261)**
	TOTAL	**74.11% (7796)**	**4.79% (504)**	**2.25% (237)**	**3.08% (324)**	**15.76% (1658)**	**100.00% (10591)**

Within the intoxicated group (i.e. ignoring the 70% sober drivers) the group with an alcohol concentration above 1.2 g/L comprises nearly 50% (see Figure 14). The first four groups (in descending order) consist of the four alcohol concentrations without THC and sum up to 76.62%.

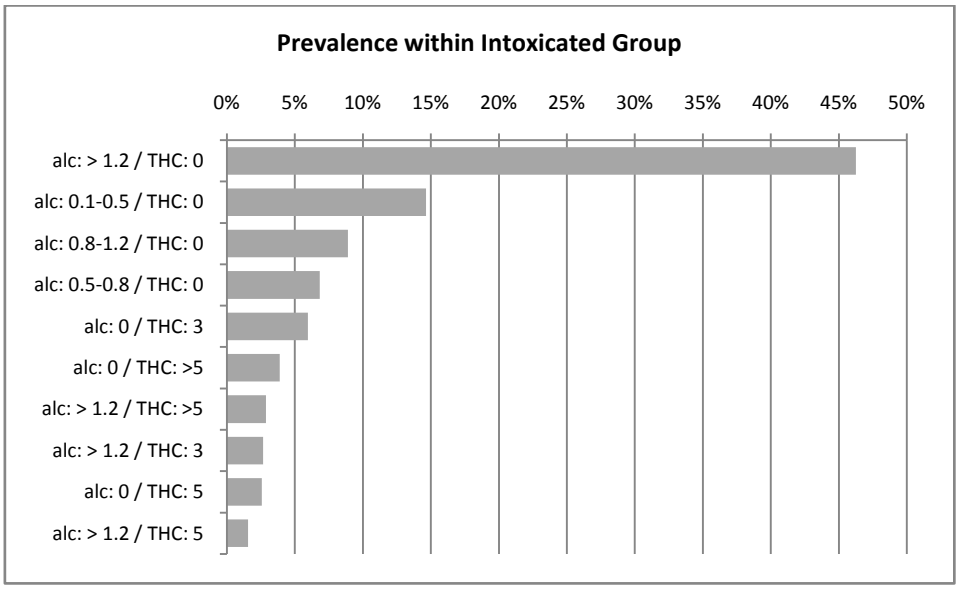


Figure 14: Proportion of different alcohol / THC concentrations within intoxicated drivers involved in fatal crashes (cases and controls) in France.

7.3 Experimental Studies

Within task 1.2 15 experiments (see Table 17) with 8 alcohol calibration experiments (one of each partner or setting) were planned according Annex I (revision 04). They comprise both “within designs” for different substance concentrations or substance combinations in the same subjects and “between designs” with a comparison between different groups of subjects (usually patients and healthy controls). Both approaches require different methodologies for the OR calculation, which are explained in (Krüger et al., 2008).

Table 17: Overview of planned experiments in task 1.2.

Institute	Experiment	Subjects	n
Umaas	*Alcohol Calibration (0.5 g/L)*	healthy volunteers	18
	Sleep Deprivation & MDMA	recreational MDMA user	16
	MDMA & alcohol vs. placebo	recreational MDMA user	18
	Zopiclone (zopliclone 7.5mg) vs. placebo → within comparison (groups against placebo)	patients: (1) treated & (2) untreated insomniacs controls: (3) healthy volunteers	16
	Hypnotics (var. dosages, var. substances) → between comparison of 3 groups	patients: (1) treated & (2) untreated insomniacs controls: (3) healthy volunteers	16
	Dronabinol vs. Placebo	light & heavy THC user	12
CERTH/HIT	*Alcohol Calibration (0.5 g/L)*	healthy volunteers	18
	CPAP vs. noCPAP	patients (sleep apnea)	16
	Aprazolam	patients (anxiety)	18
IFSTTAR	*Alcohol Calibration (0.3, 0.5, 0.8 g/L)*	healthy volunteers	16
	Codoliprane (20, 40, 60mg) vs. placebo	healthy volunteers	16
	Benzodiazepines & Insomniacs	DELAYED	
	Benzodiazepines & Analgetics	patients	16
VTI	*Alcohol Calibration (0.5 g/L)*	MISSING	8
	Dextroamphetamin (10mg & 40 mg) vs. Placebo	recreational user	18
RugPsy	*Alcohol Calibration (0.3, 0.5, 0.8 g/L))*	healthy volunteers	17
	MDMA & Alcohol	recreational user	19
TNO	*NO ALCOHOL CALIBRATION*	MISSING	
	Alcohol (0.08 g/L), Amph. 10mg, Alc. & Amph 10mg	recreational user	14/15
SIPSiVi	*Alcohol Calibration (0.5 g/L)*	healthy volunteers	16
	Risperidone (0.3-0.4mg)	psychotic patients	16
BASt	*Alcohol Calibration (0.5 g/L)*	healthy volunteers	20
	Opiods	pain patients	20

7.3.1 Problematic experiments

Within the DRUID project an alcohol reference condition was established in all methodological approaches (meta-analysis, epidemiology, and experiments) in order to be able to compare the results. Even if only regarding one approach, there are major differences concerning the sensitivity of different scenarios (e.g. driving simulators) for different substances or different groups of people.

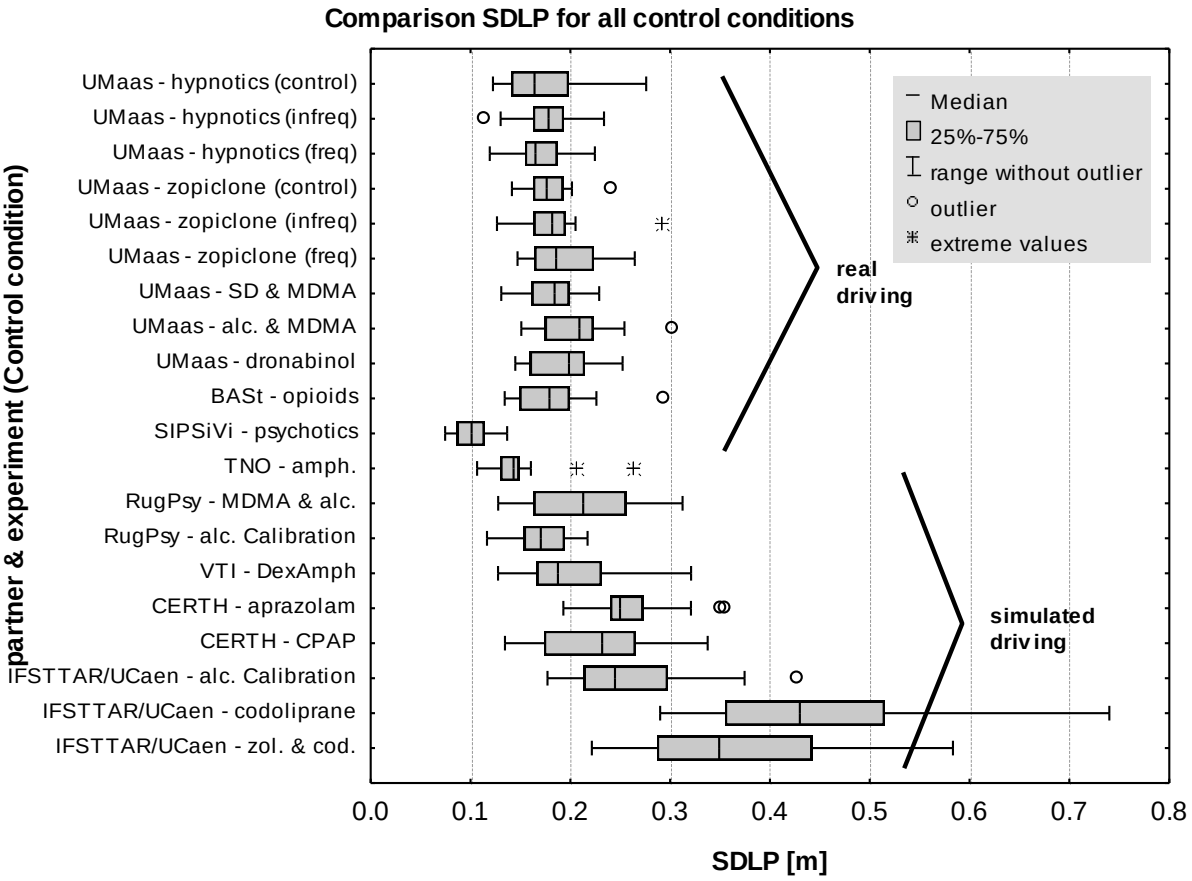


Figure 15: Distribution (Box-Plots) of the SDLP values from all control conditions.

The variation in the main parameter SDLP is illustrated in Figure 15, where all control conditions (either placebo in within-designs or healthy controls in between-designs) are compared. It is evident that:

- there are both lower mean SDLP values and a lower variation of SDLP values in real driving than in simulated driving;
- the study of SIPSiVi reveals remarkable low SDLP values (which is based on the fact, that they were driving in a closed circuit with a low speed of 30 km/h compared to 100 km/h in the other real driving experiment);
- there are extremely and unrealistic high SDLP values in the experiments of UCaen (codoliprane / zolpidem & codein), but not for the simulation of IFSTTAR in Salon de Provence (alcohol calibration).

7.3.1.1 The problem of IFSTTAR/UCaen

So, there is a problem with the experiments of IFSTTAR/UCaen. Within the DRUID project IFSTTAR/UCaen was charged with four experiments. According to Annex I (Revision 4) the experiments were:

Table 18: Overview over the experiments of IFSTTAR/UCaen.

Question	Groups	Institute
Alcohol Calibration Study	Alcohol [1] placebo / [2] 0.3 g/L / [3] 0.5 g/L / [4] 0.8 g/L	IFSTTAR (Salon de Provence)
Acute effects of 3 doses of analgesics on simulated driving performance in healthy volunteers	codoliprane (codeine, paracetamol) [1] placebo / [2] codoliprane 20mg [3] codoliprane 40mg / [4] codoliprane 60mg	University of Caen
Effects of benzodiazepines on simulated driving performance in insomniac patients	Benzodiazepines [1] insomniacs and frequent users of benzodiazepines [2] insomniacs and users of benzodiazepines [3] controls	University of Caen (delayed and not reported here)
Benzodiazepine and analgesic effects alone and in combination on simulated driving in healthy volunteers	zolpidem & codoliprane (codeine+ paracetamol) [1] placebo & placebo / [2] placebo & zolpidem [3] placebo & codoliprane / [4] zolpidem & codoliprane	University of Caen

Problems arise because the studies were indeed performed with the same scenario and the same software and basically the same hardware, but at different locations (University of Caen, IFSTTAR Salon). The main difference between the two simulators is that the simulator in Caen only has one front screen whereas the simulator in Salon de Provence has three screens. Thus, the very high SDLP values of the Caen simulation might be attributed to the different simulator cabins. Additionally, the alcohol calibration study for BAC of 0.3, 0.5 and 0.8 g/L was conducted in Salon de Provence which means that a direct comparison between the single drug conditions of the Caen experiments and the reference of the 0.5 g/L alcohol condition from Salon does not make sense. Due to the fact that all four experiments were performed by different samples, the attempt of establishing a transfer function in order to compensate for the bias in SDLP was not successful.

7.3.1.2 The problem of SIPSiVi

SIPSiVi has planned to examine the effect of different dosages of risperidone (patients under treatment) in a real driving scenario and compare the driving performance with healthy volunteers (between-design). Additionally, the alcohol calibration was done as a within design experiment with the healthy subjects group. Although the quality of the raw data was fine, these data must be excluded from OR calculations because

- a reliable control group is lacking;
- measures of SDLP were taken under conditions that deviate significantly from other partners (mainly at very low speeds of 30 km/h). Maybe therefore
- there was no alcohol effect in the primary measure (SDLP) which makes it difficult to interpret other effects with regard to the alcohol reference.

7.3.1.3 The problem of VTI

VTI was charged to look at the effects of dextroamphetamine (10 mg & 40 mg) vs. Placebo in the driving simulation. Although these data are fine as well, they provided an alcohol calibration experiment that was done with only 8 subjects before the DRUID project. Since the OR calculation from experimental data is based on a frequency approach using a 2x2 matrix (see Krüger et al., 2008), 8 subjects are far

too few to apply this methodology. Thus, the VTI data must be excluded from the OR calculation as well.

7.3.1.4 The problem of TNO

TNO was charged to examine the effects of alcohol (0.8 g/L), amphetamine (10 mg), and the combination against placebo. TNO did not do the alcohol calibration, but they use the same simulation as RugPsy. So, the alcohol calibration of RugPsy is used to calculate the OR's. Unfortunately, no Car-Follow task was implemented in the setting of TNO. Therefore, these parameters are not available.

7.3.2 Main dependent variables[17]

All partners adhered to a standard set of driving parameters to increase comparability between studies. These driving parameters basically covered 3 core levels of driving behaviours:

- automated behaviours – well-learned (over-learned) skills,
- controlled behaviours – controlled manoeuvres in traffic, and
- executive, strategic behaviours - interactive functions with ongoing traffic, planning, risk taking.

Dependent on the research question and the study setting, partners agreed on including 2-3 driving scenarios in each and every study. These scenarios represent the behavioral levels above and constituted the primary driving measures over all studies.

Road tracking scenario (automated behaviors): 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, Haak, Blaauw, & Riemersma, 1982). Participants are required to drive a 100 km course maintaining a constant speed of 95 km/h and a steady lateral position in traffic lanes. The primary driving measure is the standard deviation of lateral position or **SDLP**. SDLP is an index of road tracking error or weaving, swerving, and overcorrecting. SDLP is measured using an electro-optical device mounted on the rear of the vehicle that continuously records lateral position relative to the traffic lane. An increase in SDLP, measured in centimeters, indicates driver impairment, as the driver's ability to hold the car in a steady lateral position is diminished.

Car-Following scenario (controlled behaviors): 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 are 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 is the "car following reaction time" (or **CF-RT**) to lead vehicle's speed decelerations. This test assesses the driver's ability to adapt to manoeuvres of other motorists (Brookhuis & de Waard, 1993; Ramaekers & O'Hanlon, 1994).

[17] mainly cited from (Ramaekers et al., 2010).

Risk taking scenario (strategic behaviours): Risk taking scenarios were only embedded in studies using a driving simulator. Standard parameters that were used by respective partners were gap acceptance, number of crashes, number of red light crossings, and number of crashes during sudden event scenarios.

Simple reaction time: A simple reaction time task was embedded in some studies and was mostly realized as a sudden breaking reaction to a hazardous event.

In addition, all partners included 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 driving parameters.

Table 19: Overview of the number of experiments ("n experim."), that have assessed parameters belonging to the different driving scenarios; the number of experiments in which the parameters are evaluable regarding the data quality ("evaluable experim."); and the number of experiments in which the OR calculation against the alcohol reference can be done ("OR vs. alc."). Partners for which the OR calculation can be done are marked in bold.

scenario	parameter	partners who assessed these parameter	n experim.	evaluable experim.	OR vs. alc.
Road tracking scenario	SDLP	all:**Umaas, CERTH**, VTI, **RugPsy, TNO,** IFSTTAR/UCaen, SIPSiVi, **BASt**	15	15	**10**
Car-Following (CF)	CF RT = CF delay	**Umaas, CERTH**, IFSTTAR/UCaen[18], VTI, **RugPsy, BASt**	12	10	**9**
	CF coherence	**BASt**, VTI	2	2	**1**
	CF gain	**BASt**, VTI	2	2	**1**
Risk Taking	gap acceptance	**RugPsy, TNO**	2	2	**2**
	gap time	**RugPsy, TNO**	2	2	**2**
	gap distance (Y vs. LR)	**TNO**	1	1	**1**
Simple reaction time	RT urban circuit	IFSTTAR/UCaen	1	1	**0**
	sudden event RT	SIPSiVi	1	1	**0**
	simple RT	**BASt**	1	1	**1**

7.3.3 What's left?

In Table 19 it becomes obvious that a comparison of OR between the different experiments (i.e. substances) is only reasonable for

- the road tracking scenario (parameter SDLP), which can be done for 10 experiments[19], and for
- the car following (CF) scenario, which can be done for 9 experiments.

All other parameters are skipped for the OR calculation against the alcohol reference but are reported in the single reports of the partners in task 1.2. The remaining data for the risk comparison are listed in Table 20.

[18] IFSTTAR/UCaen only implements the Car Follow task in the experiment with "benzodiazepine and analgesic effects alone and in combination on simulated driving in healthy volunteers"

[19] 15 planned experiments – 5 excluded experiments (3 from IFSTTAR/UCaen, 1 from VTI and one from SIPSiVi = 10).

Table 20: Experiments and parameters for which a risk calculation against the alcohol reference of 0.5 g/L can be done.

Institute	Experiment	BAC 0.5 comparison	parameters
Umaas	Sleep Deprivation & MDMA	YES	SDLP, CF reaction time
	MDMA & alcohol vs. placebo	YES	SDLP, CF reaction time
	Hypnotics (zopliclone 7.5mg) vs. placebo	YES	SDLP, CF reaction time
	Hypnotics (var. dosages, var. substances) vs. placebo	YES	SDLP, CF reaction time
	Dronabinol vs. Placebo		SDLP[20]
CERTH/HIT	CPAP vs. noCPAP	YES	SDLP, CF reaction time
	Aprazolam	YES	SDLP, CF reaction time
IFSTTAR	Codoliprane (20, 40, 60mg) vs. placebo	NO	
	Benzodiazepines & Insomniacs	NO	
	Benzodiazepines & Analgetics	NO	
VTI	Dextroamphetamin (10mg & 40mg) vs. Placebo	NO	
RugPsy	MDMA & Alcohol	YES	SDLP, CF reaction time
TNO	Alcohol (0.8 g/L), Amph. 10mg, Alc 0.8 g/L & Amph. 10mg	YES	SDLP
SIPSiVi	Risperidone (0.3-0.4mg)	NO	
BASt	Opiods	YES	SDLP, CF reaction time

7.4 Meta-Analysis

7.4.1 Data

The meta-analytic approach was conducted by two different institutes because the number of substances was too big to be screened by only one research group (see Figure 16).

(1) In the meta-analysis of (Morland & Strand, 2010) opiods (including morphine, methadone, and buprenorphine), narcoanalgetics, and hallucinogens were analysed.

(2) In the meta-analysis of (Berghaus et al., 2010) antipsychotics, anxiolytics, hypnotics and sedatives, antidepressants, antihistamines, and illegal drugs were examined.

In the part of Morland (group 1) there were not sufficient studies/effects in literature in order to evaluate them meta-analytically and to estimate any kind of risk. Thus, these substances could not be considered in this report (for further information see Morland & Strand, 2010).

In Table 21 all substances (group 2) are listed that were basically analyzed by (Berghaus et al., 2010). Only studies with single dose oral administrations to healthy subjects were used. This decision shrinks the validity of the sample because usually patients are taking medicaments for a longer time which leads to habituation to and/or tolerance for the substance. But studies with either multiple administrations to healthy subjects or with administrations to patients are rare and difficult to conduct. Consequently, these results cannot be summarized in a meta-analytical approach but only by means of a review (Berghaus et al., 2010).

[20] In the dronabinol Study of UMaas there were too much missing values in the Car-Following task to evaluate this parameter.

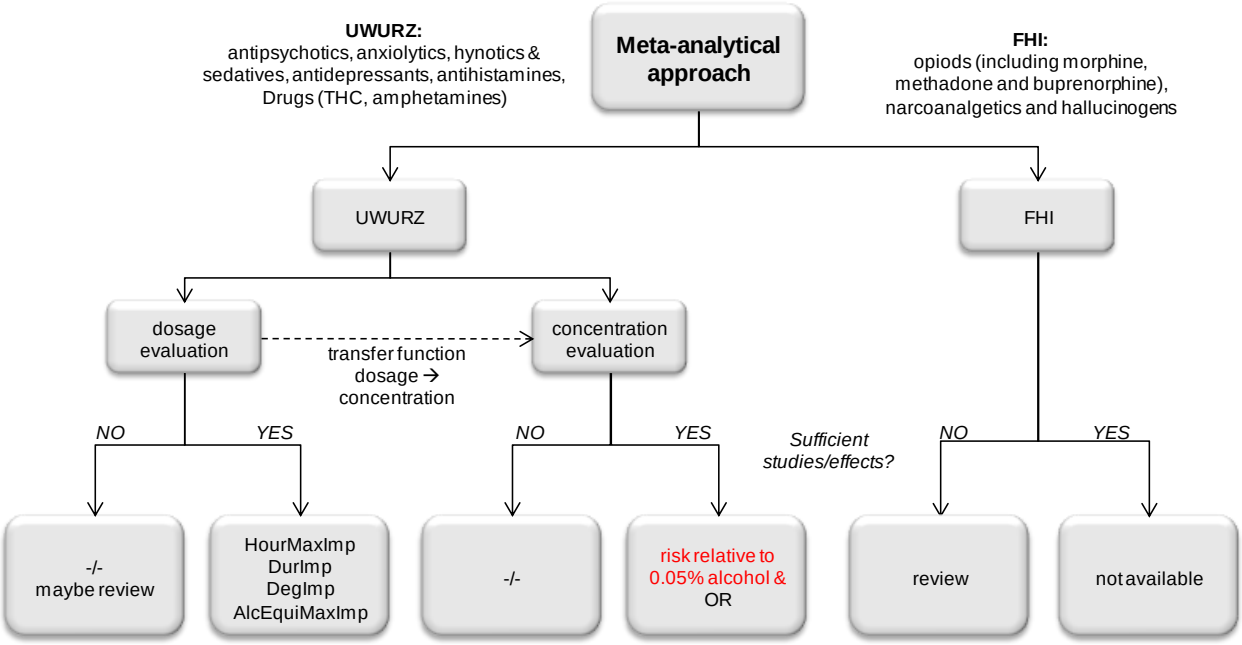


Figure 16: Output of meta-analytical evaluations dependent on substances and number of studies/effects in literature (the parameters "HourMaxImp" etc. are explained later).

Regarding the rest of the substances that were analysed meta-analytically one shortcoming should be mentioned: Due to the elaborate methodology of medicament studies, for economic reasons most of the authors assess a huge amount of dependent variables which is illustrated in the right column of Table 21, where the quotient "number of reported effects divided by the number of studies" is shown. This quotient varies from 10.8 (sulpiride) to 34 (fexofenadine) which means that e.g. for fexofenadine within one study 34 parameters were tested. From a strict statistically point of view only one decision is allowed. This problem is called "alpha inflation" and describes the fact that the more dependent variables are tested for significance within one study using the same sample, the bigger is the chance of indentifying effects as significant just by random (i.e. without being actually significant). Unfortunately, no procedure exists to correct this bias afterwards. Thus, (Berghaus et al., 2010) used all information and took the reported significances as heuristic significances (in contrast to confirmatory significances).

Table 21: Meta-analytically evaluated substance groups of Berghaus (sorted by number of studies per substance group in descending order). Substances that were for some reasons not evaluable[21] with respect to dose are written in italic.

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
	buspirone	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*
	zolpidem	31	857	27.6
	temazepam	30	695	23.2
	flunitrazepam	29	491	16.9
	flurazepam	*22*	*203*	*9.2*
	zopiclone	21	331	15.8
	lormetazepam	13	161	12.4
	zaleplon	12	350	29.2
	brotizolam	*6*	*78*	*13*

Class	Substance Name	n studies	n effects	n effects/ n studies
Anti-psych.	promethazine	11	236	22.8
	haloperidol	10	228	21.5
	sulpiride	8	86	10.8
Antide-pressants	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	56	962	17.2
	terfenadine	16	259	16.2
	triprolidine	14	233	16.6
	loratadine	13	213	16.4
	fexofenadine	5	170	34
Drugs	THC smoking	234	2664	11.4
	THC oral admin.	63	1446	23
	d-amphetamine[22]	20	416	20.8

7.4.2 Evaluation

For all of these substances basically two further evaluation approaches exist regarding the independent variable:

7.4.2.1 Dose related evaluation

Dose related information is highly relevant for medical doctors and patients because they need to know which substance in which dose might have an impact on traffic safety or not. So first the effects are evaluated with respect to the studied dosages and the respective percentage of significantly impaired effects.

[21] For Flurazepam, Nitrazepam and Brotizolam no curve fitting was possible.
[22] For MDMA and cocain there were not enough studies to apply a meta-analytical approach. Results of the review are shortly outlined in chapter 8.4.5.1

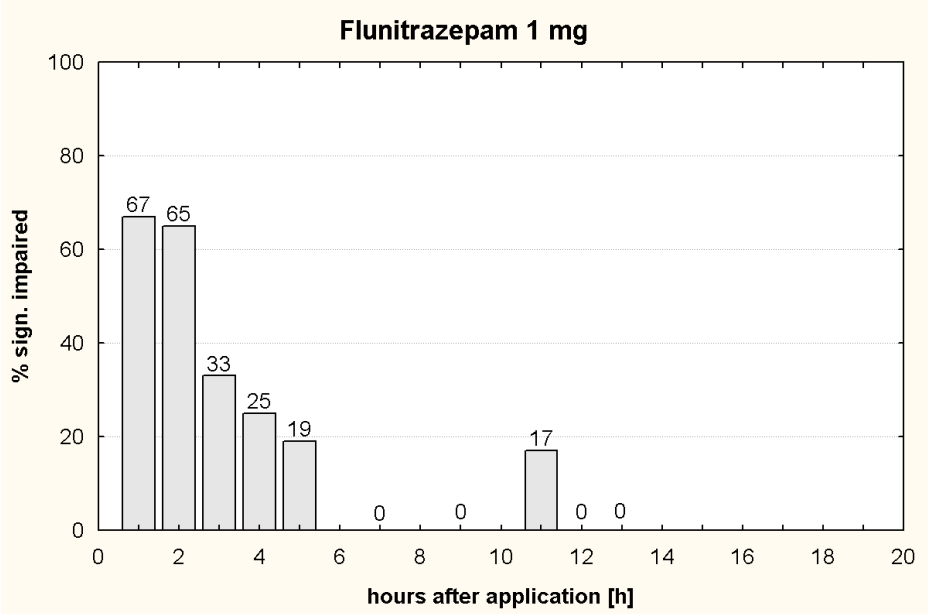


Figure 17: Example Flunitrazepam: Time-dependent impairment for 1 mg (Berghaus et al., 2010).

Additionally the impairing effect of different dosages varies (due to pharmacodynamic and -kinetic aspects) with the time after application. Therefore, the number of evaluable effects must be divided up in hours after application[23]. The result is the percentage of reported significant (impairing) effects in relation to not significant effects for each specific substance and for a specific time after application (Figure 17).

Although single categories are only evaluated if sufficient effects exist in the meta-analysis, there are certain variations in the course of time that are not very likely with respect to the pharmacodynamic and -kinetic characteristics of psychoactive substances. In order to get “smoother” results, an approximation procedure[24] in line with these pharmacodynamic and -kinetic characteristics was applied (Figure 18) and different parameters (Table 22) were calculated.

[23] In Berghaus et al. (2010) the time after application is categorized in hourly classes up to 12 hours. After this time span hardly any results are reported. If so, broader categories are defined.

[24] The quality of the approximation depends (apart from other influencing factors) on the number of studies and effects that can be integrated in an analysis: The higher the number of studies and effects the better in general the approximation

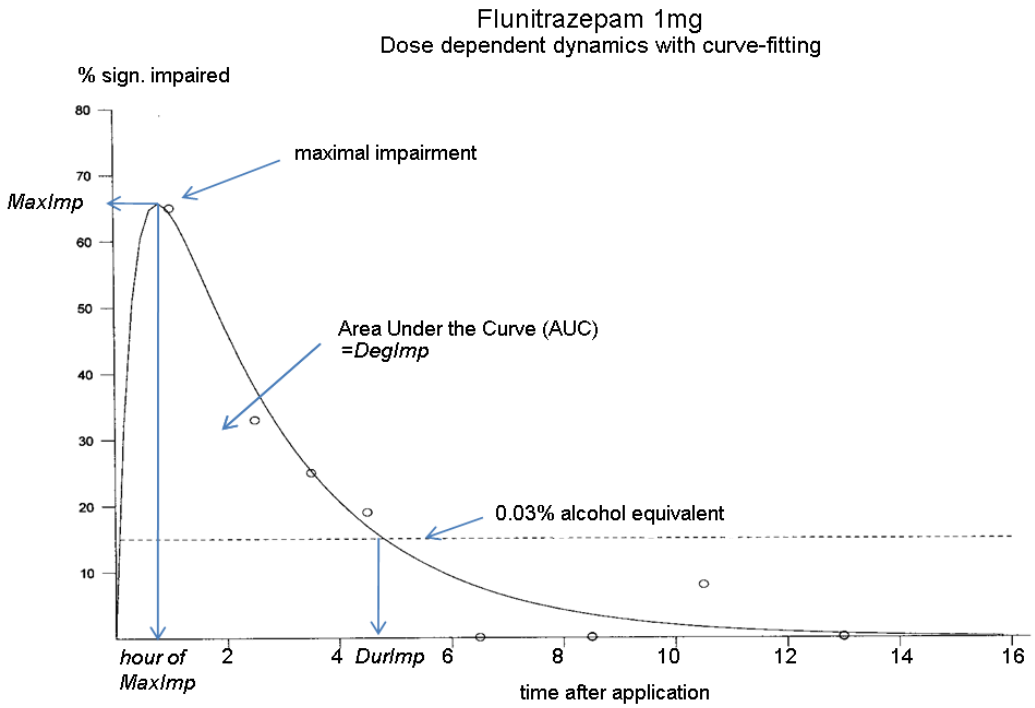


Figure 18: Example Flunitrazepam: Approximation with resulting parameters for time-dependent impairment for 1 mg (Berghaus et al., 2010).

The variables "MaxImp", "Hour of MaxImp" refer to the maximum impairment and are not very meaningful due to the following reason: If a substance shows a very high impairment that lasts very shortly (e.g. THC), these two variables will show very high values suggesting a very critical impairment, even if the duration of this impairment is very short. The "alcohol equivalence of max imp. (%)" also refers to the peak (maximum) of impairment and must therefore also be interpreted with care, because it only indicates a potential hazard.

Table 22: Definitions of the calculated variables of Berghaus et al. (2010).

Variable	Explanation
MaxImp	% of significant impaired effects at the maximum (peak) of the approximation
Hour of MaxImp	Time point (hour) when the maximum of impairment emerges.
Alcohol equivalence of max. imp.(%)	equivalent alcohol class based on the percentage of maximum impairment.
DurImp	Duration of impairment = time period in hours until the approximation will be lower than 15% significantly impaired effects (corresponding to 0.3 g/L BAC).
DegImp	Degree of impairment = area between the approximation curve and the 15% impairment line, which is a parameter for the impairment of a medicament (Area Under the Curve AUC).

The best variables to compare the different substances and dosages are "duration of impairment" and "degree of impairment". The duration of impairment ("DurImp") indicates the time period in hours until the approximated curve crosses the threshold of 15% significant effects, which is the equivalent percentage of significant effects for 0.3 g/L BAC (derived from the meta-analysis of the reference substance alcohol in (Schnabel et al., 2010). The degree of impairment ("DegImp") is calculated as the area under the curve (AUC),

> *"…which is the integral (summation) of impairment > 15% over time. Agents that show a long period of impairment under 15% in the late*

elimination phase are not overestimated using this modification. Hence, in the context of traffic safety of medicaments, the AUC enables a comparison of the degree of impairment within an agent (dose) and between different substances: The higher the value of this parameter the larger the degree of impairment in terms of sum of impairment over time. Thus, this parameter tries to represent in one single parameter what is normally represented by the intensity (magnitude of significantly impaired effects) and the time period of impairment." (Berghaus et al., 2010).

As supposed, the duration and degree of impairment are strongly correlated (r=0.79, p<0.0001) because a longer duration of impairment generally leads to a higher AUC and thus to a higher degree of impairment. Consequently, one of the parameters is sufficient to describe the potential hazard of the substance/dose combination. Basically, higher dosages are related to a higher degree of impairment (Figure 20).

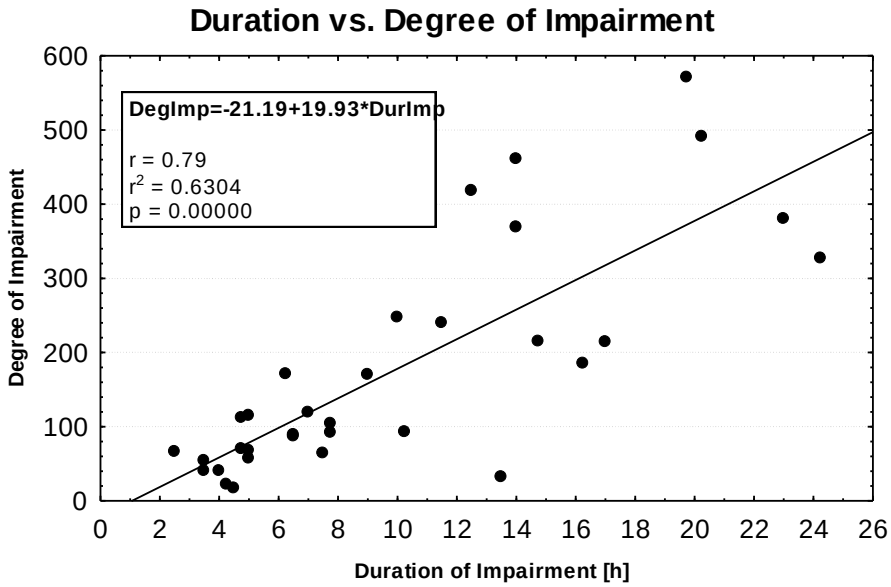


Figure 19: Correlation between the duration and degree of impairment.

Class	Substance/Dose [mg]	Degree of Impairment
Anxiolytics	Buspirone (10)	0
	Buspirone (20)	0
	Clobazam (10)	0
	Clobazam (20)	0
	Meprobamate (400)	0
	Meprobamate (800)	0
	Diazepam (5)	17
	Diazepam (10)	57
	Lorazepam (1)	64
	Oxazepam (15)	104
	Diazepam (15)	112
	Oxazepam (30)	170
	Diazepam (20)	171
	Alprazolam (1)	369
	Lorazepam (2)	418
	Lorazepam (2.5)	571
Hypnotics & Sedatives	Temazepam (10)	0
	Zolpidem (5)	0
	Lormetazepam (1)	22
	Temazepam (20)	40
	Zaleplon (10)	40
	Triazolam (0.25)	89
	Flunitrazepam (1)	115
	Zolpidem (10)	119
	Zolpidem (20)	214
	Zopiclone (7.5)	240
	Triazolam (0.5)	247
	Flunitrazepam (2)	461

Class	Substance/Dose [mg	Degree of Impairment
Anti-psych.	Sulpiride (400)	0
	Haloperidol (3)	93
	Promethazine (27)	491
Antide-pressants	Fluoxetine (60)	0
	Paroxetine (30)	0
	Imipramine (75)	32
	Trazodone (100)	87
	Mianserin (10)	185
	Amitriptyline (25)	327
	Amitriptyline (50)	380
Antihista-mines	Fexofenadine ()	0
	Loratadine (10)	0
	Terfenadine (60)	0
	Diphenhydramine (25)	54
	Diphenhydramine (50)	92
Drugs	d-amphetamine (24.75)	0
	d-amphetamine (4.25)	0
	THC oral admin. (8.25)	0
	THC smoking (5)	66
	THC oral admin. (13.5)	68
	THC smoking (13.5)	70
	THC oral admin. (24.5)	215

Figure 20: Degree of impairment sorted in ascending order within the different substance classes. (For missing substance/dose combinations no degree of impairment exists).

High impairment in terms of AUC (> 150[25]) is shown for:

- 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 amitryptiline (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 drugs[26] show a comparable high potential of impairment. For further information regarding the dose related evaluation please look at (Berghaus et al., 2010).

7.4.2.2 Concentration related evaluation

To transfer the dose-dependent information in concentration-based information, a special meta-analysis of pharmacokinetic studies was done (for details see Berghaus et al., 2010; page 407 ff.). The result is an approximated concentration curve over time for different substances and different concentrations. Using this approximation,

[25] The degree of impairment is not an absolute interpretable value. It serves only for a comparison within the substance/dose combinations. By visual inspection there is a pretty clear cut between values below and above 150, therefore this value is chosen.

[26] Besides THC with an oral administration of 24.5 mg

the blood plasma concentration of a substance could be estimated by knowing the given dose of the substance and the relevant time after application (i.e. when the performance test was done) – both pieces of information that are available in the studies. All effects of all substances could now be listed in a table sorted by concentration classes and not only by dosages. So, the independent variable changes by means of transformation from dose to concentration, whereas the dependent variable remains the percentage of significant effects (per concentration category).

By comparing the relation of the chance to show a significant impairment (i.e. effect) under a certain substance concentration (number of significant effects divided by the number of non significant effects) with the chance to show a significant impairment when being sober, a risk measure called odds ratio (OR) is calculated. This OR describes the x-fold risk of impairment for a specific substance concentration compared to the reference of being sober. Usually, this parameter is only used in epidemiology by evaluating the number of accidents. In our case the "population" consists not of traffic accidents but of all effects in the meta-analysis. An effect can show significant impairment (i.e. "accident") or not (i.e. "no accident"). Whereas in epidemiology normally the reference are the number of accidents without any substance, in the meta-analytical approach there is no "number of effects without substance" available, because in experimental studies every single effect is defined as being different from placebo (or no substance). So, another reference category must be defined. As in the experimental and the epidemiological approach, the 0.5 g/L BAC reference is chosen when possible. So, every OR represents the x-fold risk of a substance to show a significant impairment in an experimental study compared to 0.5 g/L BAC[27].

Thus, for calculating these ORs the substance concentration that matches the percentage of significant effects of 0.5 g/L BAC is chosen as reference. Table 23 shows an overview over the substances for which

- no 0.5 g/L BAC equivalent was calculable because not sufficient effects were reported to calculate a reliable approximation ("not calculable", for which concentrations ORs are calculated depends on the total number of effects),
- the 0.5 g/L BAC equivalent was not exceeded by any concentration of the substance, which means that no substance concentration shows an impairment comparable to 0.5 g/L alcohol or higher ("not reached"), and
- the 0.5 g/L BAC equivalent was calculable and therefore ORs can be calculated for different concentrations ("calculable").

[27] i.e. the BAC class from 0.45-0.55 g/L. For a detailed description as well as pros and cons of this calculation see Krüger et al. (2008).

Table 23: Overview of the 0.5 g/L BAC reference. There are substances for which not enough data exist to calculate the 0.5 g/L BAC reference ("not calculable"), substances that show never impairment worse than the 0.5 g/L BAC reference ("not reached"), and substances for which the 0.5 g/L BAC reference is calculable and therefore the OR against the alcohol reference can be evaluated.

not calculable	
class	**substance**
antidepressant	imipramine
antidepressant	amitryptiline
antipsychotic	haloperidol
anxiolytic	bromazepam
anxiolytic	chlordiazepoxide
anxiolytic	clobazam
hypnotic/sedative	flurazepam
hypnotic/sedative	nitrazepam

not reached	
antidepressant	fluoxetine
antidepressant	paroxetine
antihistamine	terfenadine
antihistamine	loratadine
antihistamine	fexofenadine
antipsychotic	sulpiride
anxiolytic	buspirone
drug	amphetamine
drug	*cocaine*

calculable		
class	**substance**	**conc. [ng/ml]**
antidepressant	mianserin	8.9
antidepressant	trazodone	1240
antihistamine	diphenhydramine	60
antihistamine	triprolidine	5.7
antipsychotic	promethazine	4.5
anxiolytic	oxazepam	330
anxiolytic	lorazepam	9
anxiolytic	alprazolam	9
anxiolytic	diazepam	320
anxiolytic	meprobamate	29000
drug	THC oral	3.7
drug	THC smok	3.8
hypnotic/sedative	triazolam	1.6
hypnotic/sedative	brotizolam	2.8
hypnotic/sedative	lormetazepam	9.2
hypnotic/sedative	temazepam	450
hypnotic/sedative	flunitrazepam	5.4
hypnotic/sedative	zopiclone	26
hypnotic/sedative	zolpidem	71
hypnotic/sedative	zalepon	17

Concentration classes with less than 5 effects are ignored and will be indicated in the graphs by the label "*invalid*". For example the substance flunitrazepam shows a 0.5 g/L BAC equivalent percentage of significant impaired effects at 5.4 ng/ml[28] (Berghaus et al., 2010). Therefore, this concentration class (5 < x <6 ng/ml) is chosen as reference. The OR for a concentration of 6 < x <7 ng/ml is 3.27 (see Table 24).

Table 24. Example of the OR calculation for single substance concentration. The reference categories for the OR calculation are marked in grey.

FLUNITRAZEPAM					**OR**
blood conc. [ng/ml]	**n not sign.**	**n sign.**	**% not sign.**	**% sign.**	**(vs. 5.4 ng/ml)**
1	3	0	100.00%	0.00%	
2	19	1	95.00%	5.00%	0.12
3	43	4	91.49%	8.51%	0.21
4	37	1	97.37%	2.63%	0.06
5	24	10	70.59%	29.41%	0.95
6	32	14	69.57%	30.43%	1.00
7	14	20	41.18%	58.82%	3.27
8	21	12	63.64%	36.36%	1.31
9	9	20	31.03%	68.97%	5.08
10	3	19	13.64%	86.36%	14.48
22	4	47	7.84%	92.16%	26.86
	209	148			

[28] This value is calculated by inspecting the approximated impairment function of a substance for the concentration, that produces the same percentage of significant effects as 0.5 g/L alcohol, i.e. 30% (see Figure 25 and Berghaus et al., 2010).

This means that a concentration of 6-7 ng/ml of flunitrazepam in blood plasma has a 3.2-fold “risk” of producing impairing performance effects compared to the concentration of 5-6 ng/ml, which corresponds to the 0.5 g/L BAC reference. The so calculated ORs are presented in chapter 10 as final result of the meta-analysis and will be compared with the results from the other methodological approaches.

But it has to be stressed, that the OR calculated by this method are highly dependent on the % significant results in the reference (0.05 g/L alcohol) concentration class. Moreover it was decided not to “smooth” the results (i.e. the OR of the different concentrations) by applying any kind of approximation but to report the empirical results as the present from the single studies. As consequence an OR of a lower concentration might be higher than the OR of a higher concentration.

Although the results of the single substances should not be discussed here in detail, it should be outlined that **THC shows (by means of meta-analysis) a comparable level of impairment with a concentration of 3.7 (oral) – 3.8 (smoking) ng/ml in serum as alcohol with 0.5 g/L**. This value is in line with the findings of (Grotenhermen et al., 2005) who stated:

> *“Epidemiological studies on DUI examine the association between rare events (traffic crashes, injury or death) and a risk factor, such as the consumption of alcohol or a drug. The results of some 20 studies on cannabis and driving are somewhat inconsistent. The most meaningful recent culpability studies indicate that drivers with THC concentrations in whole blood of less than 5 ng/mL have a crash risk no higher than that of drug-free users. The crash risk apparently begins to exceed that of sober drivers as THC concentrations in whole blood reach 5–10 ng/mL (corresponding to about 10–20 ng/mL in blood serum or plasma). Because recent studies involved only a few drivers with THC concentrations in that critical range, a reliable assessment of the associated crash risk is still lacking.*
>
> *Following several rounds of discussion, panel members agreed that a legal limit for THC in the 7–10 ng/mL range (measured in blood serum or plasma, equivalent to about 3.5–5 ng/mL measured in whole blood) may achieve a reasonable separation of unimpaired from impaired drivers, who pose a higher risk of causing accidents. The panel further arrived at the following findings and conclusions.*

The difference of the proposed legal limit of Grotenhermen et al. (2005) of 3.5 ng/ml in whole blood and the value of 3.7 ng/ml in serum of (Berghaus et al., 2010) bases on the addition of confidence intervals and the inaccuracy of measurement. Regarding this fact the value of 3.7 ng/ml of Berghaus would also end up at a value of approximately of 7-10 ng/ml in blood serum.

8 RISK ESTIMATIONS

8.1 Comments to the calculation of odds ratios (OR)

The basic rationale behind the OR estimation is to relate the odd (chance) for being exposed (intoxicated) in the accident group and the odd (chance) for being exposed (intoxicated) in the control group.

Table 25: Basic taxonomy of case-control studies.

Case-control study		**First:** select cases			
		Cases (accidents)	**Controls (accident-free)**	Sums	
Second: determine exposition	**Exposed (alcohol positive)**	A	B	A+B	
	Not exposed (sober)	C	D	C+D	
	Sums	A+C	B+D	A+B+C+D	
	Proportion of exposed	A / (A+C)	B / (B+D)		

Therefore, the odds for being exposed (intoxicated) in the accident group will be A/C and in the control group B/D. If alcohol is a cause for accidents, the odds for the accident group should be higher than for the control group. As a measure, the odds ratio is defined as

Odds ratio = odds accident / odds control = (A/C) / (B/D) = (A*D) / (B*C)

It is important to note that the odds ratio is based on a rationale that is different from the concept of relative risk. However, in the case of seldom events, the OR may be used as an estimate of the relative risk (for further explanations see (Krüger et al., 2008).

8.1.1 Biases from study procedure

From a theoretical point of view the risk for an injury or a fatality due to a psychoactive substance should be comparable in different countries. Of course there are:

- different risks in every country (even without substance) for having an accident, which might be attributed to the traffic volume, infrastructure, driving style of the inhabitants, etc.,
- different risks in every country (even without substance) for being injured, which might be attributed to the safety measures in cars (e.g. antilock breaking system, etc.) or the willingness of drivers to wear safety belts, etc.
- and different risks in every country (even without substance) for being killed, which might be attributed to the efficacy of the different emergency call systems (see Figure 21).

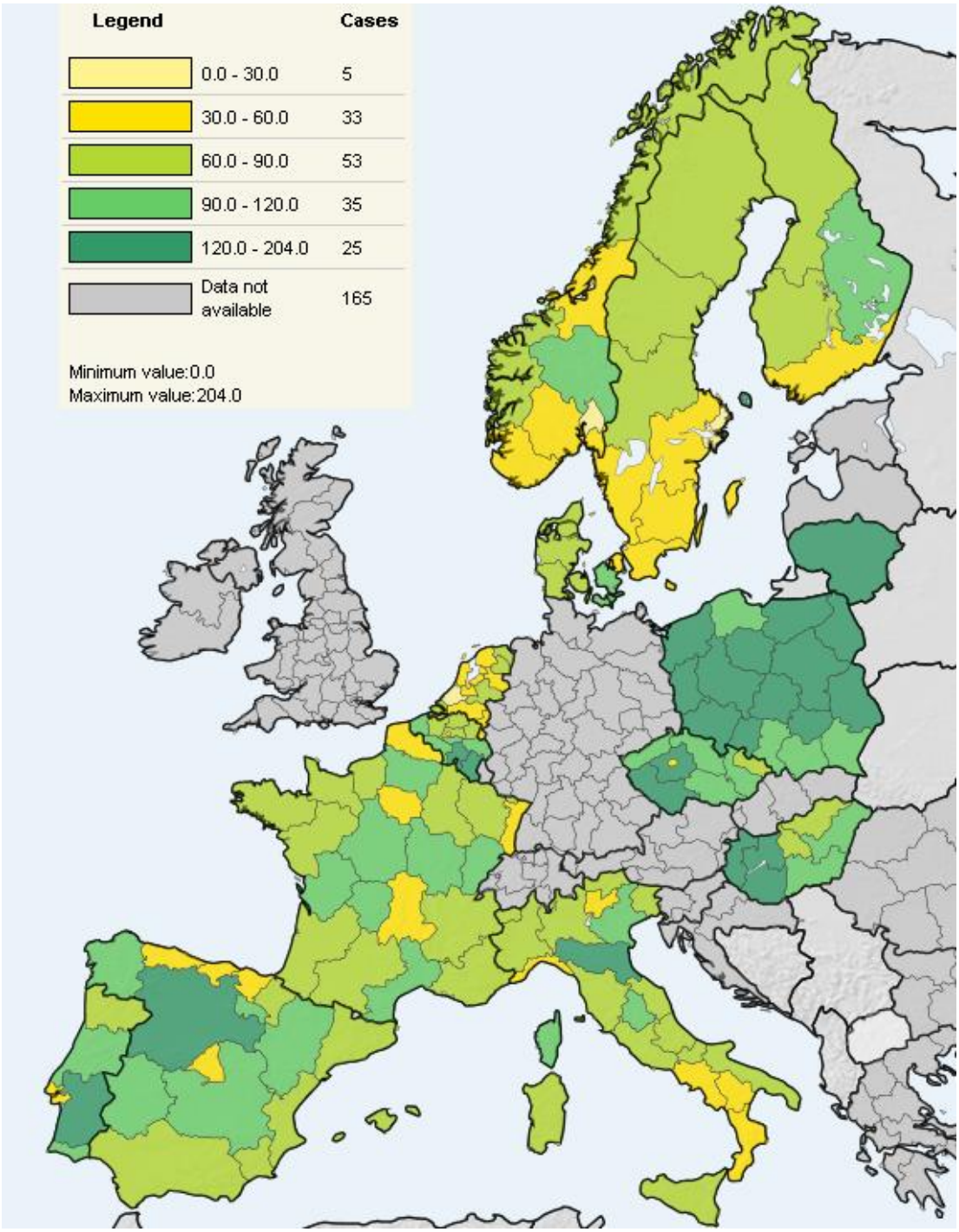


Figure 21: Victims in road accidents, by NUTS 2 regions[29] - Number of deaths per million inhabitants (2008)

Besides these differences, there might be differences in the study procedures of each country with great impact on the calculated risk. None of these biases can be fully corrected. **Therefore, it is highly recommendable to keep these possible biases in mind when interpreting the epidemiological odds ratios.**

[29] NUTS (fr. Nomenclature des unités territoriales statistiques“) hierarchical system for an unambigous indentification and classification of territorial areas for official statistics in the EU. (NUTS 2 = medium scaled regions/areas).

A systematic selection bias within the hospital cases is not probable (Isalberti et al., 2011) because usually all injured or killed drivers, who meet the in- and exclusion criteria, are included in the study. So biases mostly are related to the relation of the exposed and non exposed controls. To illustrate the problem Table 26 shows a fictive distribution of cases and controls. For reasons of explanation we assume the resulting OR=6 is the true.

Table 26: Fictive distribution of exposed and non exposed cases and controls.

	Cases injured	**Controls** accident-free	sum
exposed (substance)	30	50	80
not exposed (no substance)	100	1000	1100
sum	130	1050	1180

OR = 6

If the police would apply not a completely random stopping procedure but a stopping procedure guided by suspicion with respect to substance use, they would find more exposed controls. Because the total number of controls must remain stable, the number of not exposed controls is reduced in the same way. So, increasing the number of exposed controls for 20% (Table 27) leads to a decreased OR=5.

Table 27: Changed distribution of exposed and non exposed cases and controls in the case of a suspicious guided stopping procedure.

	Cases injured	**Controls** accident-free	sum
exposed (substance)	30	60 ↑	110
not exposed (no substance)	100	990 ↓	1070
sum	130	1050	1180

OR = 5 ↓

An increased non-response rate would lead to the opposite effect. Assuming that especially exposed drivers refuse the participation in the survey, the number of exposed controls would decrease (Table 28). As a consequence, the OR would increase to 7.6. This case also accounts for situations in which not all drivers positive for alcohol were allowed by the police to take part in the road side survey because they were taken into police custody. This is e.g. the case for Finland (Houwing, Hagenzieker, Mathijssen, Bernhoft, Hels, & Kira, 2011). Thus, alcohol prevalence rate in the Finnish driving population was underestimated and the risk consequently overestimated since there was not the same bias in the case population of injured drivers.

Table 28: Changed distribution of exposed and non exposed cases and controls in the case of a high non-responder rate.

	Cases injured	**Controls** accident-free	sum
exposed (substance)	30	40 ↓	110
not exposed (no substance)	100	1010 ↑	1070
sum	130	1050	1180

OR = 7.6 ↑

8.1.2 Biases from low cell counts

Unfortunately, in most countries the distribution of cases and controls in the 2x2 matrix is very skew. Usually, there is a very high number of not-exposed controls (D) and a very low number of exposed cases (A). Remember the formula for the crude OR calculation:

Odds ratio = odds accident / odds control = (A*D) / (B*C).

Obviously this constellation is highly prone to a bias in the term A*D. If there is one case less or more in the low frequented cell A, the term A*D will extremely change because D usually includes a high number of cases. To give an example, the frequencies of cases/controls with or without amphetamines from NL are used.

Table 29: Example of a very skew distribution of cases and controls (based on the numbers for amphetamine in NL)

	Cases injured	**Controls** accident-free	sum
exposed (substance)	2	13	15
not exposed (no substance)	126	4425	4551
sum	128	4438	4566

OR = 5.4

This matrix would result in a crude OR of 5.4 (without weighting or adjustment procedures). Due to the fact that the equation for the crude OR calculation is (2*4425) / (126*13), it is obvious that the cell A with the lowest cell size of 2 is mostly prone to a random bias because it is multiplied with the cell D (highest cell size = 4425). Therefore, one case less or more in cell A will change the OR considerably (see the following tables).

Table 30 and Table 31 show the effect of in- or decreasing the number of exposed cases by one case. A decrease results in an OR = 2.7, an increase in an OR = 8.2. So, with such a skewed distribution in the 2x2 matrix one exposed case less or more can lead to halved or nearly doubled OR's.

Table 30: Effect of decreasing the number of exposed cases by one case.

	Cases injured	**Controls** accident-free	sum
exposed (substance)	**1** ↓	13	15
not exposed (no substance)	127	4425	4551
sum	128	4438	4566

OR = 2.7 ↓

Table 31: Effect of increasing the number of exposed cases by one case.

	Cases injured	**Controls** accident-free	sum
exposed (substance)	**3** ↑	13	15
not exposed (no substance)	125	4425	4551
sum	128	4438	4566

OR = 8.2 ↑

Therefore, the procedure of in- and decreasing the number of the exposed cases/controls by one is introduced by Hels et al. (2011) to get an impression of the liability of the OR of the single countries to a random bias. This will be important in particular when looking for an appropriate method for merging the different countries.

8.1.3 Odds ratio calculations based on data from more than one country[30]

In order to get more reliable relative risk results, one could argue that data from all countries be pooled and odds ratio estimates should be calculated based on data from all countries in the survey.

However, the number of subjects with positive concentrations of substances is sparse in both the case samples and the control samples. Even though this is fortunate from at road safety point of view, it results in imprecise odds ratio estimates with broad confidence intervals.

This chapter includes three different methods for pooling data from various countries ("multinational estimation"). Each of the methods is correct in its own right; still they produce different results. To give a comprehensive overview, all risks for injury and fatality are shown in the results chapter in three different ways:

(1) A risk estimations for the single countries

(2) A multinational estimation for a subset of countries, for which a merging procedure was assessed to be reasonable. The merging was done following all three different criteria (see below) one by one.

(3) A risk estimation against the reference of 0.5 g/L alcohol

The three different merging methods for the multinational estimation were as follows.

[30] This chapter is mainly cited from Hels et al. (2011).

8.1.3.1 Method 1

Data from all countries were included in common risk estimates, irrespective of differences in the various countries' odds ratio estimates and their precision (measured by the size of the confidence intervals). Odds ratios were estimated both as crude odds ratios and odds ratios adjusted for age and gender.

8.1.3.2 Method 2

The rationale of the second method was to pool data from countries with similar odds ratio estimates and leave out data from countries with odds ratio estimates that were very different. This rationale was implemented as follows (all three criteria should be met for the data to be pooled):

- The highest odds ratio estimate among the countries which data were pooled was as a maximum four times higher than the lowest one.
- The confidence intervals of the odds ratio estimates for all the countries which data were pooled overlapped.
- If there were several solutions of pooling countries' data, the one which included most countries was chosen.

8.1.3.3 Method 3

The rationale of the third method was to include data from countries where the odds ratio estimates were most precise and leave out data from countries where the odds ratio estimates were very imprecise. The precision of the odds ratio estimates for each country is evaluated as follows:

The evaluation is based on the crude odds ratio: OR = (a*d)/(b*c) (see Table 25). The procedure is to find the smallest value in any of the cells a,b,c,d and compute the modified odds ratio estimate when 1 is either added ('OR+1') or subtracted ('OR-1') from the value in the cell. The rationale is that the smallest value of the four (a,b,c,d) will be the one where a change has the largest effect on the size of the odds ratio estimate.

If the value of 'OR+1' is at least twice as big as 'OR-1', it is a sign that the odds ratio estimate is too susceptible to be influenced by very small changes in the data, and data from that country were left out of the pooled odds ratio estimate.

Example:

a=4, b=8, c=400, d=2000 (for the meaning of a,b,c,d, see Table 25).

OR = (4*2000)/(8*400) = 2.5

'OR-1' = (3*2000)/(8*400) = 1.9

'OR+1' = (5*2000)/(8*400) = 3.1

Since 'OR+1' (=3.1) is not greater than twice the value of 'OR-1' (2x1.9=3.8), data from this (fictitious) country should be included in the pooled odds ratio estimate. For alcohol, the odd ratio estimate for each interval of alcohol concentration was considered.

8.2 The Risk of alcohol

Alcohol is the sole substance for which on the one hand reliable risks for different concentrations could be calculated and on the other hand data exist from all three methodological approaches.

8.2.1 Epidemiological risk of injury

8.2.1.1 Single countries

Table 32: Crude odds ratios[31] for injury against the reference "no substance" for the single countries (different alcohol concentrations without combinations).

Substance / Country	BE	DK	FI	IT	LT	NL
Negative (ref.)	1.00	1.00	1.00	1.00	1.00	1.00
0.1 g/L ≤ alcohol < 0.5 g/L	(0.95)	(1.25)	(7.09)	(0.67)	(1.36)	(1.33)
0.5 g/L ≤ alcohol < 0.8 g/L	(2.17)	5.86	34.81	(0.67)	(3.06)	10.81
0.8 g/L ≤alcohol < 1.2 g/L	12.75	19.67	81.11	(1.45)	6.83	40.30
Alcohol ≥ 1.2 g/L	98.42	255.96	172.11	15.01	11.74	102.69

OR in brackets = not sign. different from 1

The injury risk for alcohol compared to "no substance" is increasing with increasing alcohol concentration in each country. Obviously FI shows consistently much higher risk than the rest of the countries as IT shows much lower risks, which can be explained by the biases mentioned in chapter 8.1.

"The Finnish odds ratios for alcohol are much higher than those of the other participating countries, and the confidence interval much larger. This is a result of the sampling procedure of the controls, where the police in Finland allowed only a(n) (unknown) fraction of the alcohol positives to be sampled.

The results from Italy are highly atypical compared to the results of the other participating countries. The odds ratios for alcohol and alcohol-drug combinations were very low and only high concentrations of alcohol (≥ 1.2 g/L) and alcohol-drug combinations were associated with increased risk of injury (odds ratios 15.0 and 5.7, respectively). The low risk connected to alcohol is most probably due to skewness in the control sampling procedure. In Italy, there was skewness in the driving population sampled towards drivers exhibiting signs of alcohol impairment (Favretto, pers.com)." (Hels et al., 2011).

Because of the sampling procedures in Finland and Italy, both results were not included in the aggregated alcohol and alcohol-drugs odds ratio calculations. Moreover all OR calculations against the alcohol reference 0.5 g/L includes only BE, DK, LT and NL. These four countries show

- no significantly elevated risk for alcohol concentrations of 0.1-0.5 g/L
- a marked elevated risk (range OR=2-10) for concentrations of 0.5-0.8 g/L
- a high elevated risk (range OR=6-40) for concentrations of 0.8-1.2 g/L, and
- an extreme risk (range OR=11-250) for concentrations above 1.2 g/L.

[31] Although confidence intervals are crucial for the estimation of reliability, they are ignored in chapter 10 for reasons of clarity and comprehensibility.

8.2.1.2 Multinational estimation

Table 33: Crude odds ratios for injury against the reference "no substance" for all merged countries and adjusted odds ratios of the countries, which are accepted for merging by the different merging methods (different alcohol concentrations without combinations).

Merging method		**1**	**2**	**3**
Merged countries	**all**	**BE, DK, LT, NL**	**BE, DK, LT, NL**	**BE, DK, LT, NL**
Substance	**OR (crude)**	**OR (adj.)**	**OR (adj.)**	**OR (adj.)**
Negative (ref.)	1.00	1.00	1.00	1.00
All alcohol concentrations	7.55	8.27	8.27	8.27
0.1 g/L ≤ alcohol < 0.5 g/L	(1.05)	(1.18)	(1.18)	(1.18)
0.5 g/L ≤ alcohol < 0.8 g/L	3.80	3.64	3.64	3.64
0.8 g/L ≤alcohol < 1.2 g/L	13.97	13.35	13.35	13.35
Alcohol ≥ 1.2 g/L	55.27	62.79	62.79	62.79

OR in brackets = not sign. different from 1

Due to sufficient numbers of cases and controls all countries (BE, DK, LT, NL) could be included for all three merging methods and so the result is similar for all of them:

- no significantly elevated risk for alcohol concentrations of 0.1-0.5 g/L
- a marked elevated risk (OR ≈ 3.5) for concentrations of 0.5-0.8 g/L
- a high elevated risk (OR ≈ 13) for concentrations of 0.8-1.2 g/L
- and an extreme risk (OR ≈ 60) for concentrations above 1.2 g/L.

8.2.1.3 Estimation vs. 0.5 g/L alcohol

In order to compare the epidemiological results for alcohol with the experimental results and those from the meta-analysis, the ORs are additionally calculated against the reference group of 0.5 g/L alcohol (0.4-0.6 g/L). As a consequence the alcohol concentration classes of 0.1-0.5 and 0.5-0.8 g/L change to 0.1-0.4 and 0.6-0.8 g/L.

Table 34: Crude odds ratios for injury against the reference 0.5 g/L alcohol (different alcohol concentrations without combinations).

Merged countries	**BE,DK,LT,NL**[32]
Substance	**OR (crude) vs. 0.5 g/L alc.**
0.4 g/L ≤ alcohol < 0.6 g/L (ref)	1.00
0.1 g/L ≤ alcohol < 0.4 g/L	(0.5)**
0.4 g/L ≤ alcohol < 0.6 g/L	(1.0)
0.6 g/L ≤ alcohol < 0.8 g/L	2.4**
0.8 g/L ≤ alcohol < 1.2 g/L	6.9
alcohol ≥ 1.2 g/L	27.2**

OR in brackets = not sign. different from 1
** correction of 0.5 in one or more countries included in the computation (for methodological details of this procedure see (Hels et al., 2011))

[32] For all calculations against the reference of 0.5 g/L alcohol (injured and fatality) FI and IT are excluded because the validity of their alcohol data were doubtful (see chapter 8.2.1.1).

8.2.2 Epidemiological risk of fatality

8.2.2.1 Single countries

When it comes to the risk of fatality (Table 35) the different alcohol concentrations show the following risks:

- A marked elevated risk (range OR = 4-6) for concentrations of 0.1-0.5 g/L
- a high elevated risk (range OR = 18-40) for concentrations of 0.5-0.8 g/L
- an extreme elevated risk for concentrations above 0.8-1.2 g/L

Table 35: Crude odds ratios for fatality against the reference "no substance" for the single countries (different alcohol concentrations without combinations).

Substance / Country	FI	NO	PT
Negative (ref.)	1.00	1.00	1.00
0.1 g/L ≤ alcohol < 0.5 g/L	6.30	9.47	3.77
0.5 g/L ≤ alcohol < 0.8 g/L	(1.47)*	39.88	18.14
0.8 g/L ≤alcohol < 1.2 g/L	86.69	248.76	8.47
Alcohol ≥ 1.2 g/L	285.55	2123.20	136.65

OR in brackets = not sign. different from 1
* correction of 0.5 in every cell due to a cell with zero count

Obviously the risk of fatality increases exponentially with concentrations and is somewhat higher than the risk of injury, a result which is also known from other epidemiological studies.

8.2.2.2 Multinational estimation

Table 36: Crude odds ratios for fatality against the reference "no substance" for all merged countries and adjusted odds ratios of the countries, which are accepted for merging by the different merging methods (different alcohol concentrations without combinations).

Merging method		1	2	3
Merged countries	NO, FI, PT	NO, FI, PT	N	PT
Substance	OR (crude)	OR (adj.)	OR (adj.)	OR (adj.)
Negative (ref.)	1.00	1.00	1.00	1.00
All alcohol concentrations	37.64	34.9	92.89	12.06
0.1 g/L ≤ alcohol < 0.5 g/L	9.23	8.01	9.35	3.26
0.5 g/L ≤ alcohol < 0.8 g/L	42.94	45.93	46.10	19.16
0.8 g/L ≤alcohol < 1.2 g/L	34.81	35.69	278.70	8.21
Alcohol ≥ 1.2 g/L	450.37	500.04		144.43

As shown in Table 36 the different merging methods result in different risks. However it can be stated *"that for drivers with a BAC of 0.1 g/L and above there is a significantly increased odds ratio of getting killed in an accident. Moreover, it is indicated to be extremely risky to drive when positive for alcohol in higher concentrations." (Hels et al., 2011).*

8.2.2.3 Estimation vs. 0.5 g/L alcohol

Compared to the reference of 0.5 g/L alcohol, only the alcohol concentrations of 0.6 - 0.8 g/L and > 1.2 g/L show a significant elevated risk (Table 37).

Table 37: Crude odds ratios for fatality against the reference 0.5 g/L alcohol (different alcohol concentrations without combinations).

Merged countries	**NO, PT**
Substance	**OR (crude)**
0.4 g/L ≤ alcohol < 0.6 g/L (ref)	1
0.1 g/L ≤ alcohol < 0.4 g/L	(0.32)
0.6 g/L ≤ alcohol < 0.8 g/L	4.89
0.8 g/L ≤ alcohol < 1.2 g/L	(1.55)
alcohol ≥ 1.2 g/L	20.07

OR in brackets = not sign. different from 1

8.2.3 Epidemiological risk of culpability

Different from the risk calculation for an injury/fatality, the risk of being culpable for a fatality is only available compared to being sober and not compared to the epidemiological alcohol reference of 0.4-0.6 g/L.

8.2.3.1 Germany, Lithuania, Hungary and Slovakia (LMU)

In the LMU study the single samples of the involved countries (Germany, Lithuania, Hungary, and Slovakia) are too small to calculate reasonable ORs. So, the samples were merged. For the merged sample only two significant ORs could be identified (see Table 38, bold numbers). The OR of being culpable for a fatality is 4.57 (2.02-10.38) with alcohol, regardless in which concentration. The OR is 20.84 (3.10-140.16) for alcohol higher than 1.2 g/L. Both ORs are adjusted for age and gender.

Table 38: Whole sample – ORs of the risk of a killed driver being responsible for a fatal traffic accident while under influence of alcohol (five dosage levels) (Thorsteinsdóttir et al., 2011).

Psychoactive substance	**Whole sample (OR) (n =440)**				
	Nr. of subjects	**Crude OR**	**95% CI**	**Adjusted OR (§)**	**95% CI**
0 ≤ Alcohol < 0.1 g/L	276	1.00			
0.1 ≤ Alcohol < 0.5 g/L	38	(1.57)	0.59 – 4.21	(1.56)	0.58 – 4.23
0.5 ≤ Alcohol < 0.8 g/L	0	*	*	*	*
0.8 ≤ Alcohol < 1.2 g/L	7	(1.43)	0.17 – 12.01	(1.18)	0.14 – 10.20
1.2 ≤ Alcohol	**107**	**25.19**	**3.44 – 184.64**	**20.84**	**3.10 - 140.16**
Alcohol positive (> 0.1 g/L)	**152**	**4.92**	**2.18 - 11.13**	**4.57**	**2.02 – 10.38**
THC ≥ 1 ng/ml	3	(0.48)	0.04 – 5.34	(0.26)	0.01 – 5.31
Benzodiazepines (y/n)	9	(1.90)	0.23 – 15.53	(1.66)	0.19 – 14.55

§ Adjusted for age and gender
* OR-calculations not possible due to low number of cases or controls

Looking at these data from Germany, Lithuania, Hungary and Slovakia the risk of being culpable for a fatality seems to be much lower than the risk of injury of fatality. Even rather high alcohol concentrations of 0.8-1.2 g/L show no significantly increased risk for being culpable. Again reasons for that must remain unclear.

8.2.3.2 France

In France the sample size was much higher so that ORs for being culpable could be calculated for different alcohol concentrations (see Table 39). The French study also finds the highest risk[33] (OR = 19.32 [13.99-26.69]) for the most intoxicated group (> 1.2 g/L), followed by the alcohol groups between 0.8-1.2 g/L and 0.5-0.8 g/L at nearly the same level (OR = 6.92 [4.3-11.13] and OR = 6.14 [3.52-10.69] respectively).

Table 39: OR for alcohol consumption (5 dose categories) of the risk of being responsible of a fatal crash for car drivers above 18 years old, France, 2001-2003, n=6932 (Gadegbeku et al., 2010).

Psychoactive substance	Number of drivers	Crude OR	95% CI	Adjusted OR	95% CI
0 ≤ Alcohol < 0.1 g/l	4935	1.00		1.00	
0.1 ≤ Alcohol < 0.5 g/l	327	2.57	1.93-3.40	2.45	1.84-3.26
0.5 ≤ Alcohol < 0.8 g/l	162	6.35	3.66-11.01	6.14	3.52-10.69
0.8 ≤ Alcohol < 1.2 g/l	251	7.33	4.58-11.74	6.92	4.30-11.13
1.2 ≤ Alcohol	1257	18.26	13.26-25.15	19.32	13.99-26.69

adjusted for THC (in 4 dose categories), age, gender

8.2.4 Experimental studies

In a first step, the different alcohol conditions are compared in order to get an impression of the sensitivity of the different settings (Figure 22).

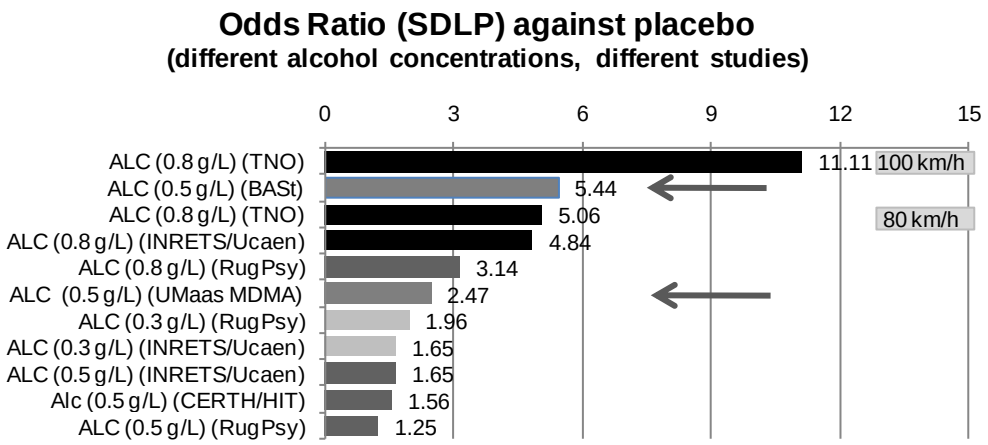


Figure 22: The risk (OR) of bad performance (SDLP) in the experimental studies for different alcohol concentrations (0.3 g/L = light grey, 0.5 g/L = dark grey, 0.8 g/L = black). Arrows are indicating real-driving experiments; all others are driving simulation experiments.

Obviously a high BAC of 0.8 g/L results in the severest performance impairment (SDLP), regardless if tested in real driving scenarios or in the simulation (see Figure 22). These are followed by the 0.5 g/L BAC condition, which was tested in a real driving scenario (from UMaas in the MDMA study). The OR´s of the 0.5 g/L BAC conditions (from simulation studies) and all 0.3 g/L conditions range without much difference between 1.25 and 1.96. Thus, with respect to SDLP the following main result can be drawn from the experiments:

[33] adjusted for THC (in 4 dose categories), age, gender.

(1) higher alcohol concentrations lead to higher performance impairment,
(2) a BAC of 0.8 g/L or 0.5 g/L in real driving leads to OR's between 3 to 5 (11 for TNO[34]),
(3) real driving scenarios seem to be more sensitive to alcohol induced impairment measured by SDLP,
(4) BACs of 0.3 g/L and 0.5 g/L (in the simulation) result in minor impairment, which is usually indicated by OR's lower than 2.

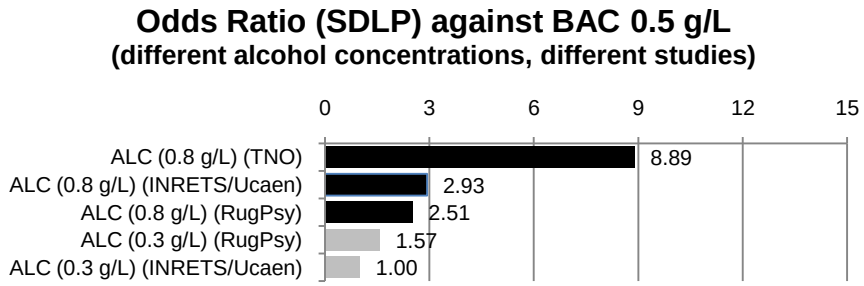


Figure 23: The risk (OR) of bad performance (SDLP) in the experimental studies for different alcohol concentrations (0.3 g/L = light grey, 0.8 g/L = black) compared to the alcohol reference of 0.5 g/L.

For the reaction time in the Car-Follow (CF) scenario, a different picture emerges (see Figure 24). The only BAC 0.8 g/L condition shows the least impairment whereas the BAC 0.5 g/L condition of UMaas shows with an OR of 4 the highest impairment. So, at a first glance the CF-reaction time does not seem to describe the alcohol induced impairment very well. Nonetheless, it is apparent that the two real-driving scenarios seem to be much more sensitive to the CF-parameters than the simulation setting. Due to the fact that neither TNO nor IFSTTAR had used a CF-scenario, only the alcohol calibration study of RugPsy is appropriate to compare different alcohol levels. With the BAC 0.8 g/L condition showing the lowest risk against placebo (OR=1.25, see Figure 24) and slightly higher risks for the BAC 0.5 g/L and 0.3 g/L condition, a more detailed evaluation of this parameter (also for the other experiments with medicines and illicit drugs) is resigned to because of lacking validity and sensitivity to different alcohol levels. The same accounts for the gap-distance scenario.

[34] In the TNO experiment only 15 subjects could be evaluated. 5 subjects show a better performance with respect to SDLP in the 0.8 g/L alcohol condition than in the placebo condition which is very unusual and might be attributed to special conditions in the experimental setting. Therefore the resulting OR of 11 is treated with care.

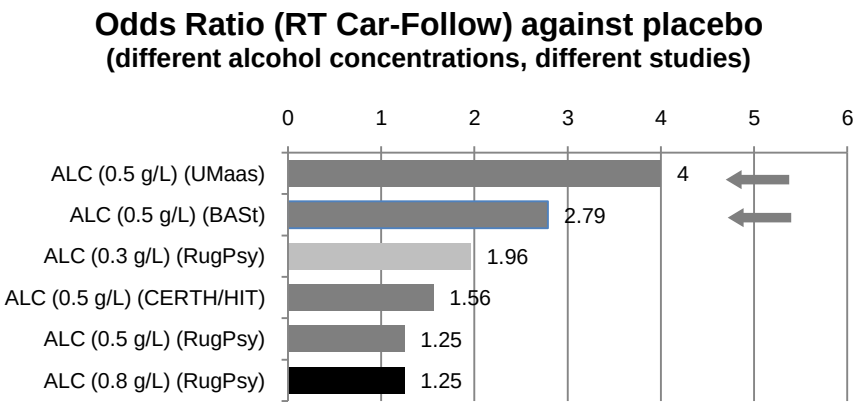
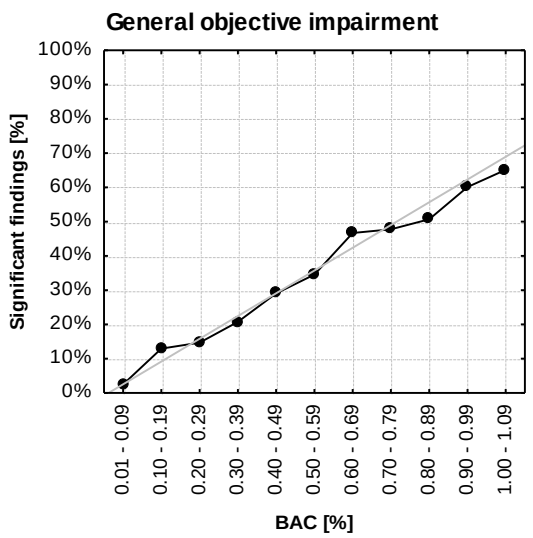


Figure 24: The risk (OR) of bad performance (reaction time Car-Follow) in the experimental studies for different alcohol concentrations (0.3 g/L = light grey, 0.5 g/L = dark grey, 0.8 g/L = black). Arrows are indicating real-driving experiments; all others are driving simulation experiments.

8.2.5 Meta-Analysis

As described in 7.4.2 Figure 25 shows the percentage of significant findings for all performance categories (Schnabel et al., 2010). 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 0.5 g/L, 30% of the findings are significant, while at a BAC of 0.8 g/L, about 50% of the findings are significant. With every BAC group the percentage of significant findings increases by 6.6%.



BAC [g/L]	% sign. findings
0.01 – 0.09	2.53
0.10 – 0.19	12.96
0.20 – 0.29	14.71
0.30 – 0.39	20.75
0.40 – 0.49	29.04
0.50 – 0.59	34.54
0.60 – 0.69	46.70
0.70 – 0.79	47.76
0.80 – 0.89	50.70
0.90 – 0.99	60.11
0.10 – 1.09	65.13

Figure 25: General objective impairment – percentage of significant findings.

Obviously, there is no substantial difference between the two types of analyses. However, some of the mean values of the single categories could not be considered because of their doubtful reliability (too low number of findings). Therefore, the original values are used for calculating risk measures against the reference of 0.5 g/L

alcohol (0.45-0.55 g/L) in order to compare the effects of alcohol with those of drugs and medicines[35].

Table 40: Number of significant impaired findings and non-significant findings for different alcohol concentrations and OR vs. BAC= 0.1 g/L and the alcohol reference (=0.4 < BAC < 0.6).

GENERAL PERFORMANCE				
BAC [g/L]	**n (not significant)**	**n (significant)**	**OR (vs. < 0.1 g/L)**	**OR (vs.0.5 g/L)**
0.01 – 0.09	77	2	**1.0**	0.1
0.10 – 0.19	94	14	5.7	0.4
0.20 – 0.29	145	25	6.6	0.4
0.30 – 0.39	252	66	10.1	0.6
0.40 – 0.49	215	88	15.8	**1.0**
0.50 – 0.59	254	134	20.3	1.3
0.60 – 0.69	234	205	33.7	2.1
0.70 – 0.79	198	181	35.2	2.2
0.80 – 0.89	176	181	39.6	2.5
0.90 – 0.99	73	110	58.0	3.7
0.10 – 1.09	53	99	71.9	4.6
0.11 – 1.19	6	31	198.9	12.6

Compared to 0.5 g/L alcohol a double risk (see Table 40 and Figure 26) is found at concentrations of around 0.6-0.8 g/L, an approximately 4-fold risk at concentrations of 0.9-1.1 g/L. From there on the risk seems to increase exponentially. Higher concentrations than 1.2 g/L were not evaluated due to a limited number of studies examining those high concentrations.

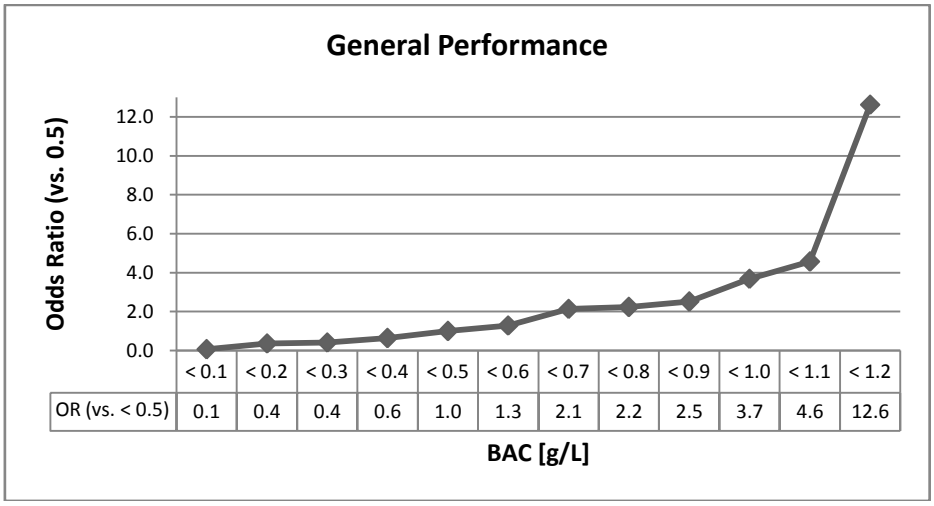


Figure 26: OR calculated from the meta-analytical results compared to the reference concentration of 0.5 g/L (0.45-0.55 g/L).

8.2.6 Prevalence rate alcohol

In order to get a more profound impression about the influence of alcohol in traffic, the information about risk should be combined with the information about prevalence.

[35] For further methodological information see Krüger et al. (2008).

The weighted European mean for the single use of alcohol is 3.48%, for the combined use with illicit drugs/medicines is 0.37%.

Table 41: Prevalence rate of alcohol alone by BAC (g/L) category and country; prevalence rate in percentages (Houwing, Hagenzieker, Mathijssen, Bernhoft, Hels, & Kira, 2011).

	substance /country	Nothern				Eastern				Southern			Western		
		DK	FI	SE	NO	PO	HU	LT	CZ	IT	PT	ES	BE	NL	Europe
	negative	95.5	97.1		97.0	97.6	97.6	94.4	97.2	84.9	90.0	85.1	89.3	94.4	92.57
	alcohol alone	2.53	0.64		0.32	1.47	0.15	3.86	0.99	8.59	4.93	3.92	6.42	2.10	3.48
	alcohol combi	0.10	0.08		0.07	0.00	0.00	0.03	0.05	1.01	0.42	1.14	0.34	0.28	0.37
only	alcohol 0,1-0,5	2.05	0.38		0.26	0.89	0.05	1.55	0.54	3.35	3.71	2.31	4.27	1.54	1.96
only	alcohol 0,5-0,8	0.28	0.10		0.04	0.18	0.02	0.43	0.24	2.02	0.44	0.90	1.33	0.26	0.68
only	alcohol 0,8-1,2	0.18	0.02		0.02	0.27	0.00	0.41	0.15	1.81	0.47	0.23	0.42	0.14	0.42
only	alcohol > 1,2	0.02	0.13		0.01	0.14	0.08	1.47	0.06	1.40	0.31	0.49	0.41	0.21	0.39
combi	alcohol 0,1-0,5	0.09	0.02		0.07	0.00	0.00	0.03	0.05	0.47	0.26	0.71	0.13	0.17	
combi	alcohol 0,5-0,8	0.00	0.02		0.00	0.00	0.00	0.00	0.00	0.01	0.12	0.14	0.02	0.05	
combi	alcohol 0,8-1,2	0.01	0.03		0.00	0.00	0.00	0.00	0.00	0.49	0.03	0.22	0.02	0.00	
combi	alcohol > 1,2	0.00	0.00		0.00	0.00	0.00	0.00	0.00	0.04	0.00	0.08	0.14	0.02	

Obviously 1 out of 10 drives under the influence of alcohol is additionally under the influence of medicines/illicit drugs. Other substances are mainly combined with low alcohol concentrations (0.1-0.5 g/L and particularly in southern and western Europe. In general the highest prevalence is found for lower BAC categories. However, in Lithuania a large number of alcohol-intoxicated drivers had a BAC level of 1.2 g/L or higher. The distribution of the alcohol prevalence over age groups shows no obvious effects whereas alcohol is in nearly all countries more prevalent in male drivers. The combination of age and gender reveals that in most countries the percentage of alcohol positive male drivers is the highest for the two oldest age groups: 35-49 and 50+ (Houwing, Hagenzieker, Mathijssen, Bernhoft, Hels, & Kira, 2011).

The use of alcohol in combination with other substances is definitely lower than for illicit drugs and medicines. As a rule in most countries the percentage of combined use of alcohol is below 10% of all alcohol positive drivers in the respective category, whereas higher amounts are found in ES.

8.2.7 Summary alcohol

In Table 42 all alcohol related ORs against being sober are listed. Unfortunately the ORs from experiments and epidemiology are attributed to different concentration classes so that a direct comparison is difficult. Moreover the meta-analysis reveals a monotonous increase of risk compared to the reference of < 0.1 g/L alcohol, but risks are much higher than the risks calculated from the other two approaches.

Table 42: Alcohol related risks from all methodological approaches against a reference of no other substance (for meta-analysis reference = 0-0.1 g/L).

BAC[36] [g/L]	Meta-analysis	Experiments (SDLP)	Epidemiology Injury (Europe)	Epidemiology Fatality (Europe)	Epidemiology Culp. / fatal crash	
					IFSTTAR	LMU
0.05	**1.00**					
0.15	5.7					
0.25	6.6		1.1	9.2	2.5	
0.35	10.1	1.7[3] / 2.0[2]				
0.45	15.8					
0.55	20.3	1.3[2] / 1.7[3] / 2.5[4] / 5.4[5] / 1.6[6]				
0.65	33.7		3.8	20-46	6.1	
0.75	35.2					
0.85	39.6	(11.1[1]) / 3.1[2] / 4.8[3]				
0.95	58.0					
1.05	71.9		14.0	8-278	6.9	
1.15	198.9					
1.25			55.3	144-500	19.3	20.8
1.35						

[1]TNO, [2] RugPsy, [3] IFSTTAR, [4] UMaas, [5] BASt, [6] CERTH/HIT

For reasons of comparability all ORs are transferred to the risk against the alcohol reference of 0.5 g/L (Table 43). This is done within each approach so that the different sensitivities of the approaches are regarded.

Table 43: Alcohol related risks from all methodological approaches against a reference BAC of 0.05%.

BAC [g/L]	Meta-analysis	Experiments (SDLP)	Epidemiology Injury (Europe)	Epidemiology Fatality (Europe)
0.05	0.06			
0.15	0.36			
0.25	0.42		0.5	0.3
0.35	0.64	1.57[2] / 1.0[3]		
0.45	**1.00**			
0.55	1.29			
0.65	2.14		2.4	4.9
0.75	2.23			
0.85	2.51	(8.9[1]) / 2.5[2] / 2.9[3]		
0.95	3.68			
0.105	4.56		6.9	1.6
0.115	12.62			
0.125			27.2	20.1
0.135				

[1]TNO, [2] RugPsy, [3] IFSTTAR, [4] UMaas, [5] BASt, [6] CERTH/HIT

[36] BAC categories are not totally comparable between the three methodological approaches. The BAC categories from meta-analysis are calculated for classes, e.g. from 0.8-0.9 g/L and thus allocated to the BAC category 0.85 (i.e. 0.75-0.85 g/L). In the experimental studies the OR should be allocated to exactly 0.8 g/L because this concentration was produced by the given dosages, but are allocated to 0.85 g/L because of the chosen categories for the table. The ORs for alcohol >1.2 g/L are allocated to the category 1.25 g/L.

Moreover these results are compared with former epidemiological studies (Blomberg, Peck, Moskowitz, Burns, & Fiorentino, 2005; Borkenstein, Crowther, Shumate, & Zylman, 1974; Krüger, Kazenwadel, & Vollrath, 1995) because epidemiology is still the golden yardstick for the measurement of risk in traffic. Like described in (Krüger et al., 2008) all three studies are combined to calculate a “mean risk” for “being involved in an accident” (all severities) and two of them (Krüger and Borkenstein) additionally calculated a risk for being responsible for an accident. Both curves are quite similar up to alcohol concentrations of 1.0 g/L. After that the risk of being responsible for an accident seems to increase much faster than the risk of being involved in an accident.

Thus, the risks are slightly different from the ones in DRUID because DRUID looks at the risk of being injured or of being killed in an accident and for being culpable for an fatal accident. However, the three studies of Borkenstein, Krüger and Blomberg are the sole studies from which equidistant alcohol concentration classes are calculable.

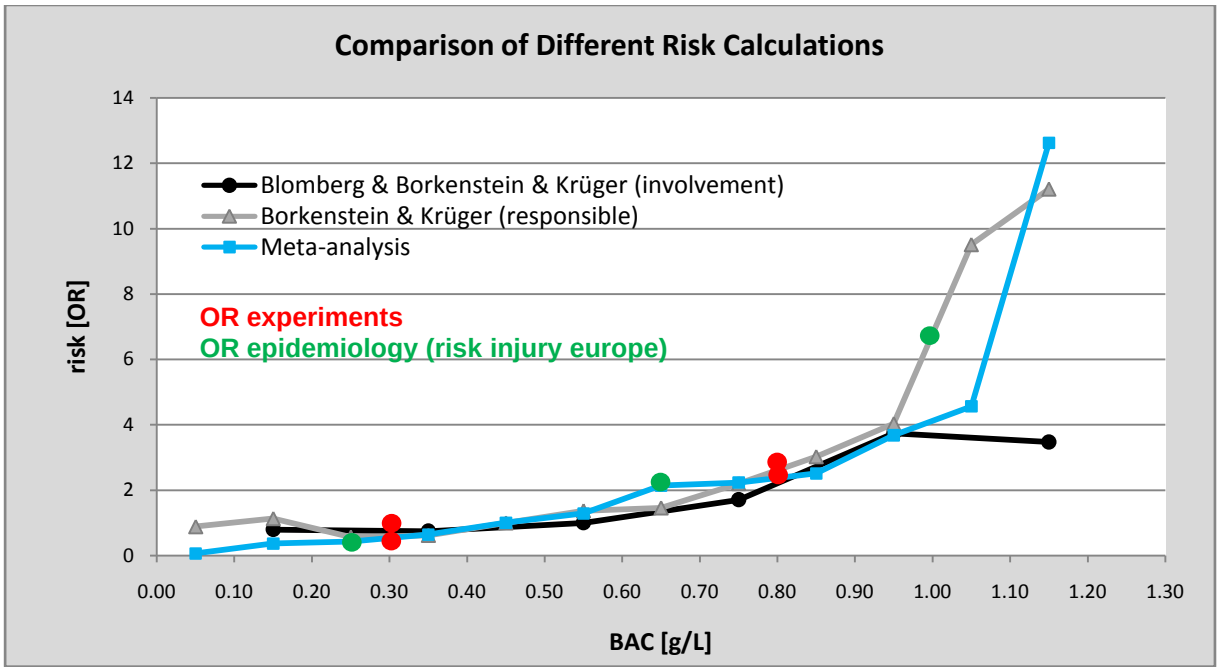


Figure 27: Comparison of different risk calculations (black line: geometric mean of the risks of (Blomberg et al., 2005; Borkenstein et al., 1974; Krüger et al., 1995) (risk involvement in accident); grey line: OR from DRUID meta-analysis (Schnabel et al., 2010); red dots: OR from DRUID experiments; green dots: OR from DRUID epidemiology (risk injury).

When inserting the DRUID risk compared to 0.5 g/L alcohol in the three big epidemiological studies (also referenced to 0.5 g/L alcohol) Figure 27 emerges:

- The DRUID risk (green dots) of being injured in an accident are approximately comparable to the risk of both established studies (involvement and responsible).
- At higher alcohol concentrations (1.0 g/L) the DRUID risk seems to more at a level with the established risk of being responsible for an accident.

- The risk calculated from meta-analysis is quite in line with the establishes studies and seems to be between the risk of involvement and of being responsible above concentrations of 1.0 g/L.
- Even the risks calculated from experiments are comparable to the established risk functions.

The main issue of this comparison was not to define a new risk function or threshold for alcohol, but to validate the highly pragmatic approach to calculate risk measures from meta-analysis and experiments. Of course the so estimated "risk-alike values" are not meant to be interpreted on a very exact level. But it seems, that the risks calculated from meta-analysis and experiments using the 0.5 g/L alcohol reference lead to roughly comparable risks as well established studies. This is a very important result for interpreting concentration based risks for illicit drugs and particularly medicines, for which mainly meta-analytical results are available.

8.3 The Risk of Medicines

8.3.1 Epidemiological risk of injury

8.3.1.1 Single countries

Table 44: Crude odds ratios for injury against the reference "no substance" for the single countries (different alcohol concentrations without combinations).

Substance / Country	BE	DK	FI	IT	LT	NL
Negative (ref.)	1.00	1.00	1.00	1.00	1.00	1.00
Benzos and Z-drugs	(1.89)	3.23	(2.49)	(0.30)	(1.50)	(1.76)
Medicinal opioids	4.22	4.22	(5.11)	9.41	186.5*	(4.17)

OR in brackets = not sign. different from 1
* correction of 0.5 in every cell due to a cell with zero count

When it comes to medicines, risks are only available for two substance categories (Table 44). For benzodiazepines the risk varies between 0.3 and 3 and only the risk in DK is significantly different from 1. For medicinal opioids the risk seems to be higher, namely between 4 and 9 (ignoring the value of LT), but also not too different between countries.

8.3.1.2 Multinational estimation

The estimation for Europe comes to slightly different risks using the three different merging procedures (Table 45). Based on all results, the odds ratio estimate is assessed to be significantly above 1 and of the order of about 2-3 for benzo-diazepines and z-drugs. For medicinal opioids the risk estimation for Europe is assessed to be significantly above 1 and approximately between 5 and 8. Both results are calculated without knowledge of the underlying substance concentrations.

Table 45: Crude odds ratios for injury against the reference "no substance" for all merged countries and adjusted odds ratios of the countries, which are accepted for merging by the different merging methods (different medicines).

Merging method		**1**	**2**	**3**
Merged countries	**BE,DK,FI,IT,LT,NL**	**BE,DK,FI,IT,LT,NL**	**see footnote**	**see footnote**
Substance	**OR (crude)**	**OR (adj.)**	**OR (adj.)**	**OR (adj.)**
Negative (ref.)	1.00	1.00	1.00	1.00
Benzos and Z-drugs	1.73	1.99	3.04 [1]	2.41 [3]
Medicinal opioids	7.99**	9.06	6.96 [2]	5.14 [4]

** correction of 0.5 in one or more countries included in the computation, see overview table

1: BE, DK, FI, LT, NL
2: BE, DK, FI, IT, NL
3: BE, DK, LT
4: BE, DK

With a view to the results from meta-analysis (chapter 8.3.4) it becomes clear, that the impairing effect of benzodiazepines and z-drugs varies considerably for different substances and different concentrations. Thus it might be questionable, in how far a risk estimate for a category like "benzodiazepines and z-drugs" is reasonable at all. Moreover not all benzodiazepines were screened in epidemiology so that this risk should not be overrated.

8.3.1.3 Estimation vs. 0.5 g/L alcohol

Compared to the reference of 0.5 g/L alcohol (Table 46) benzodiazepines and z-drugs lead to no significant elevated risk, whereas the risk of medicinal opioids is still increased with an OR around 4.

Table 46: Crude odds ratios for injury against the reference 0.5 g/L alcohol (different medicines).

Merged countries	**BE,DK,LT,NL**
Substance	**OR (crude) vs. 0.5 g/L alc.**
Negative (ref.)	
Benzos and Z-drugs	(1.2)**
Medicinal opioids	4.2**

OR in brackets = not sign. different from 1
** correction of 0.5 in one or more countries included in the computation

8.3.2 Epidemiological risk of fatality

8.3.2.1 Single countries

For benzodiazepines and z-drugs the risk for a fatal accident in the single country evaluation (Table 47) seems to be higher than the OR's for injury (OR from 0.5 to 8) whereas the risk for medicinal opioids seems to be comparable to the injury with ORs between 4 and 10.

Table 47: Crude odds ratios for fatality against the reference "no substance" for the single countries (different alcohol concentrations without combinations).

Substance / Country	FI	NO	PT	SE
Negative (ref.)	1.00	1.00	1.00	1.00
Benzos and Z-drugs	8.37	4.15	(0.46)	8.86
Medicinal opioids	4.31	(4.94)	7.66	2.87

OR in brackets = not sign. different from 1

8.3.2.2 Multinational estimation

The estimation for Europe (Table 48) comes to comparable risks using the three different merging procedures. Based on all results, the odds ratio estimate is assessed to be significantly above 1 and of the order of about 5-7 for benzo-diazepines and z-drugs. For medicinal opioids the risk estimation for Europe is assessed to significantly above 1 and is approximately 5 and 8. Thus the risk for benzodiazepines and z-drugs is slightly higher for a fatality than for an injury. The opposite is the case for medicinal opioids.

Table 48: Crude odds ratios for fatality against the reference "no substance" for all merged countries and adjusted odds ratios of the countries, which are accepted for merging by the different merging methods (different medicines).

Merging method		1	2	3
Merged countries	FI,NO,PT,SE	FI,NO,PT,SE	see footnote	see footnote
Substance	OR (crude)	OR (adj.)	OR (adj.)	OR (adj.)
Negative (ref.)	1.00	1.00	1.00	1.00
All medicines	5.05	5.29		
Benzos and Z-drugs	5.11	5.40	7.42 [1]	7.42 [1]
Medicinal opioids	4.82	4.82	4.82 [2]	

1: FI, NO, SE
2: FI, PT, NO, SE

8.3.2.3 Estimation vs. 0.5 g/L alcohol

Compared to the reference of 0.5 g/L alcohol neither "benzodiazepines and z-drugs" nor "medicinal opioids" lead to a significant elevated fatality risk (Table 49).

Table 49: Crude odds ratios for fatality against the reference 0.5 g/L alcohol (different medicinces).

Merged countries	NO, PT
Substance	OR (crude) vs. 0.5 g/L alc.
Negative (ref.)	
Benzos and Z-drugs	(0.09)
Medicinal opioids	(0.29)

OR in brackets = not sign. different from 1

8.3.3 Experimental studies

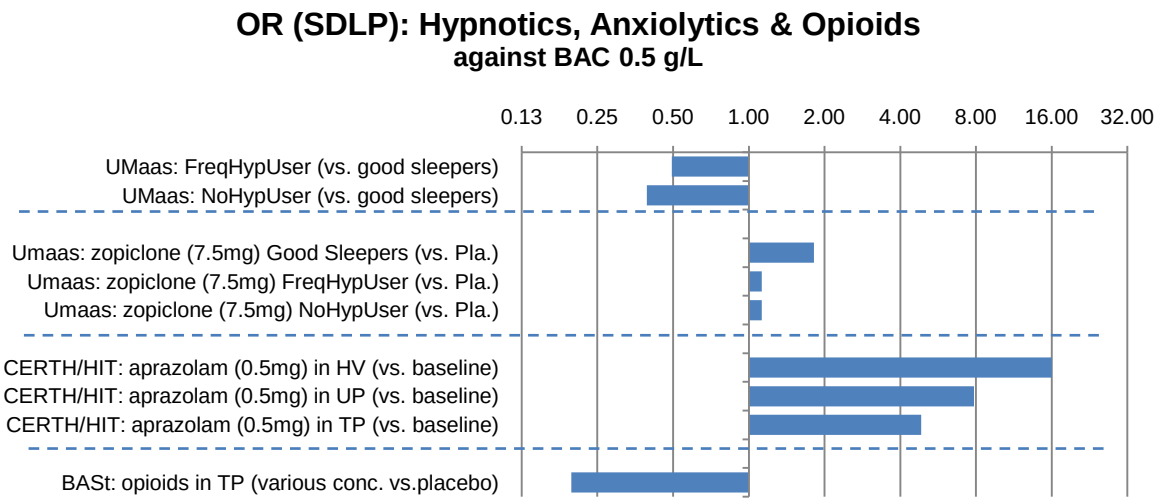


Figure 28: The risk (OR) of bad performance (SDLP) in the experimental studies from different studies (separated by dashed lines). HV=healthy volunteers, UP=untreated patients, TP=treated patients.

In the first study (Figure 28, top) three groups of subjects were compared in a between design.

(1) insomnia patients frequently using hypnotics
(2) insomnia patients not or infrequently using hypnotics
(3) healthy, self-defined good sleepers

The group of good sleepers was also participating in the alcohol calibration study. As the ORs indicate, both the regular hypnotic users and the insomniacs without treatment show less impairment than the good sleepers (reference) under 0.5 g/L alcohol. The same accounts for the experiment from BASt (, in which pain patients under regular treatment of different opiods were compared in an on-road experiment to healthy volunteers. Zopiclone in dosages of 7.5mg[37] seem to show similar effects as 0.5 g/L alcohol in all three study groups: (1) Good Sleepers, (2) insomniacs who are frequently using hypnotics and (3) insomniacs without treatment. By far the marked impairment with up to 4-16 fold risk compared to 0.5 g/L alcohol shows the benzodiazepine alprazolam, which was given to anxiety patients and healthy volunteers in a dosage of 0.5 mg[38]. By tendency the least impairment was shown by treated patients, possibly because of habituation effects. The worst impairment was shown by healthy volunteers. Although habituated patients are less impaired than non-habituated patients and healthy volunteers, the impairment seems to be considerable.

[37] According to Berghaus et al. (2010) a dose of 7.5 mg zopiclone leads 2-4 hours after oral application to concentrations of 30-50 ng/ml in plasma (supposed a body weight of 70 kg).
[38] According to Berghaus et al. (2010) a dose of 1.0 mg alprazolam leads 0.5-8 hours after oral application approximately to concentrations of 10-15 ng/ml in plasma (supposed a body weight of 70 kg).

8.3.4 Meta-Analysis / Review

The rational of the OR calculation from the meta-analytical data is described in chapter 7.4.2.2. All reported OR's are calculated against the concentration class of the respective substance that meets approximately the same percentage of significant impaired findings as it was found for a BAC of 0.5 g/L in the meta-analysis. Therefore, the reported risks represent a x-fold risk of an significantly impaired finding in experimental studies compared to a reference of a BAC of 0.5 g/L. Concentration classes with less than five effects are ignored and will be indicated in the graphs by the label "*invalid".* Substances for which this calculation cannot be done and the reasons for this are listed in Table 23 in Chapter 7.4.2.2.

Again it should be stressed, that all results are based on studies which used single administration of the respective substance to healthy volunteers. Thus, the calculated risks mainly account for the first period of medicament use until a habituation occurs. Also effects of performance increment due to the relieving effect of a substance cannot be described. Although these risks should not be interpreted absolutely, the reported risks should be appropriate to indicate the relationship of risks between different substances or different substance concentration in a quasi-ordinal manner.

8.3.4.1 N05A Antipsychotics

Within the class of antipsychotics, **promethazine** is the only evaluable substance. Concentrations higher than 6 ng/ml show a marked increase in risk compared to a BAC 0.5 g/L (Figure 29). At concentrations higher than 6 or 7 ng/ml the risk is 10-fold or more.

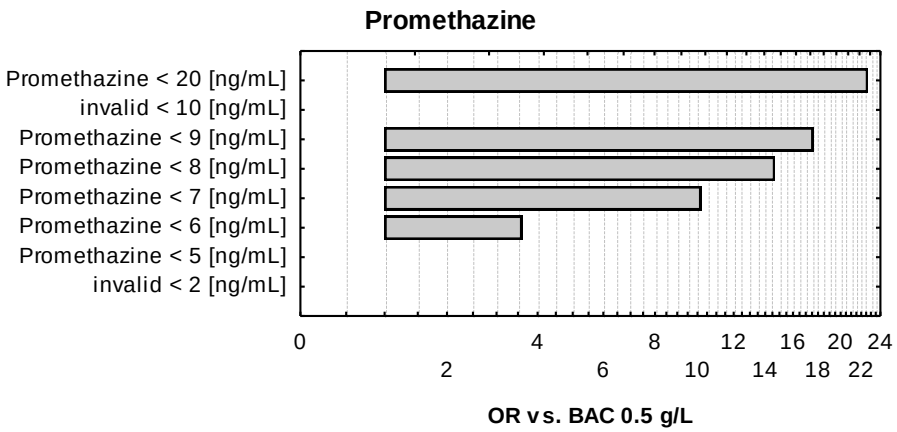


Figure 29: Risk of significantly impaired findings of different concentration classes of promethazine compared to the reference of BAC 0.5 g/L[39].

[39] The substance concentration labeling "< 6 [ng/mL]" means in that context "higher than the category below (i.e. 5 ng/mL) and < 6 [ng/mL]", i.e. from 5-6 [ng/mL]. This accounts for all other concentrations and all comparable figures in this chapter, too.

8.3.4.2 N05B Anxiolytics

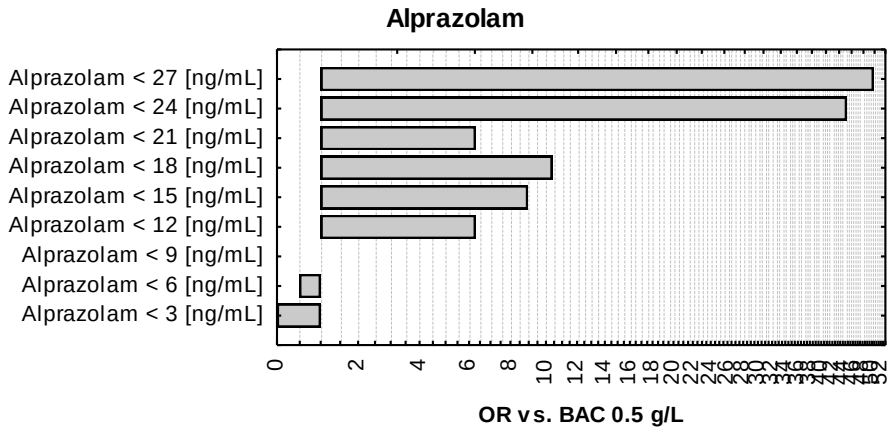


Figure 30: Risk of significantly impaired findings of different concentration classes of alprazolam compared to the reference of BAC 0.5 g/L.

Within the class of anxiolytics, **alprazolam** shows the highest risk (Figure 30). At concentrations higher than 21 ng/ml the risk is 40-fold compared to a BAC of 0.5 g/L. Concentrations of 9 to 21 ng/ml show a risk of approximately 8. Concentrations lower than 9 ng/ml are less impairing than 0.5 g/L alcohol. Thus a clear relation exists for alprazolam between concentration and level of impairment.

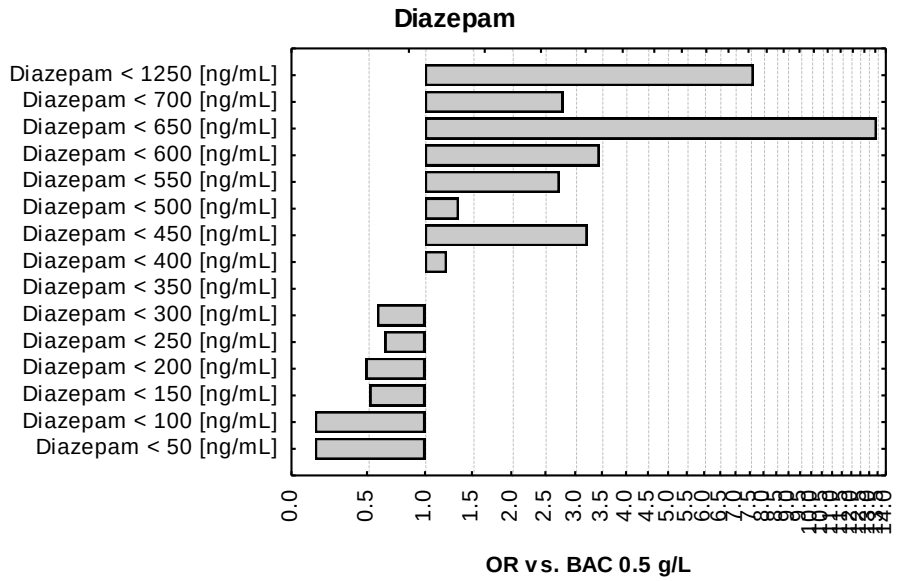


Figure 31: Risk of significantly impaired findings of different concentration classes of diazepam compared to the reference of BAC 0.5 g/L.

Diazepam (Figure 31) seems to be highly impairing (5- to 10-fold) at concentrations of 400 ng/ml and higher (compared to BAC 0.5 g/L). Concentrations lower than 300 ng/ml seem to be much less impairing. Again the values clearly reflect a relation between concentration and impairment.

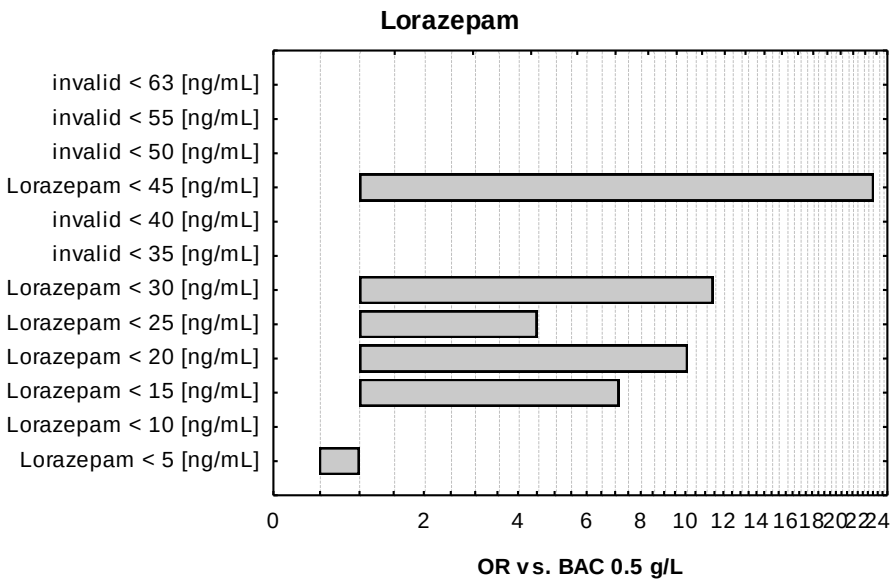


Figure 32: Risk of significantly impaired findings of different concentration classes of lorazapam compared to the reference of BAC 0.5 g/L.

Lorezepam at concentrations of 10 ng/ml and higher is more impairing than BAC 0.5 g/L. Already 15 ng/ml show an 8-fold risk compared to a BAC of 0.5 g/L. This risk is increasing with higher concentrations up to a more than 20-fold risk at a concentration of 45 ng/ml.

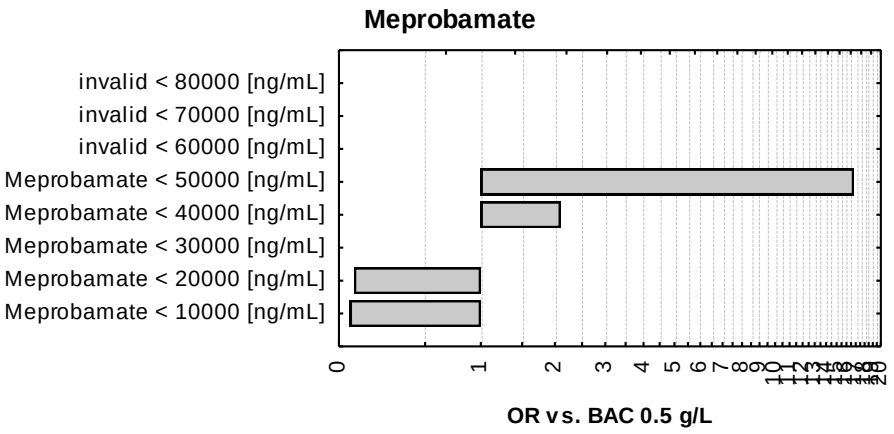


Figure 33: Risk of significantly impaired findings of different concentration classes of meprobamate compared to the reference of BAC 0.5 g/L.

Meprobamate shows a marked increase in risk of 16.8 at 50000 ng/ml. Higher concentrations were not evaluable due to the low number of findings.

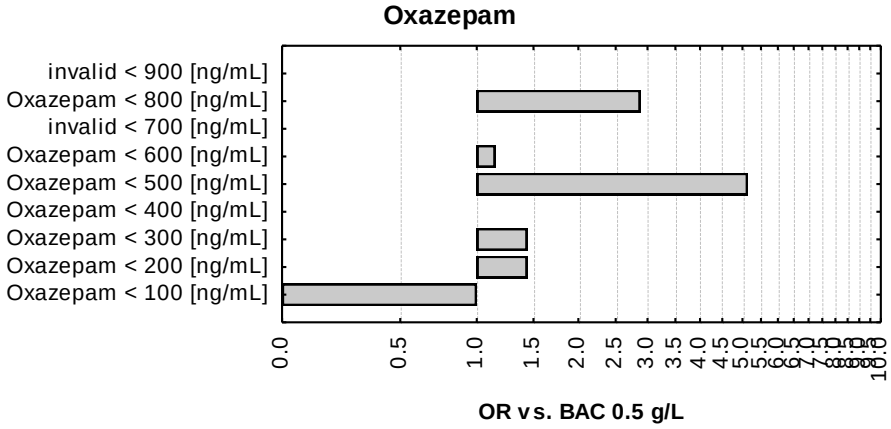


Figure 34: Risk of significantly impaired findings of different concentration classes of oxazepam compared to the reference of BAC 0.5 g/L.

The results for **oxazepam** are somehow inconsistent. Despite there is no clear concentration effect, it seems to be apparent that there is much lower impairment than that of 0.5 g/L alcohol at concentrations lower than 100 ng/ml.

8.3.4.3 N05C Hypnotics and Sedatives

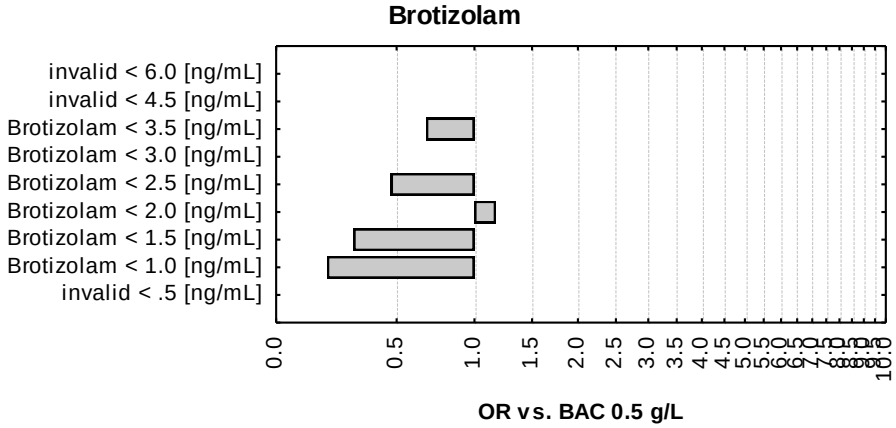


Figure 35: Risk of significantly impaired findings of different concentration classes of brotizolam compared to the reference of BAC 0.05 g/L.

Brotizolam seems in all examined concentrations (lower than 3.5 ng/ml) less impairing than a BAC of 0.5 g/L.

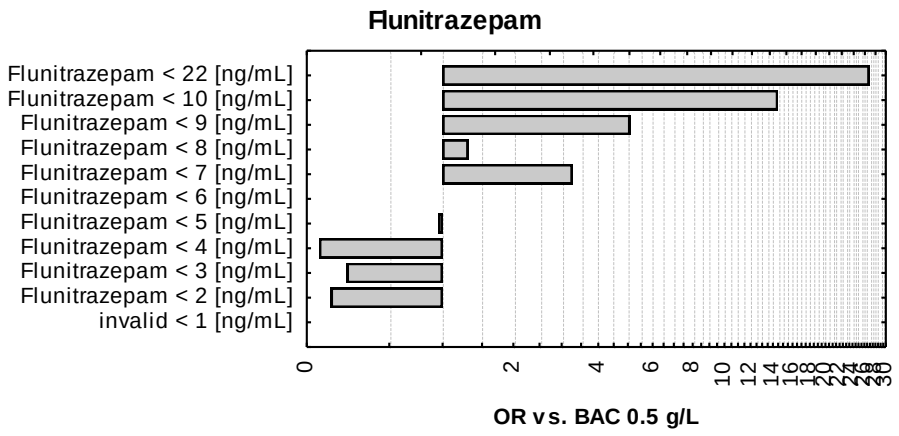


Figure 36: Risk of significantly impaired findings of different concentration classes of flunitrazepam compared to the reference of BAC 0.5 g/L.

Flunitrazepam shows lower risks than a BAC of 0.5 g/L at concentrations up to 5 ng/ml. At concentrations higher than 7 ng/ml, the risk is increasing to a 27-fold risk at concentrations around 20 ng/ml. A clear relationship between concentration and risk is present.

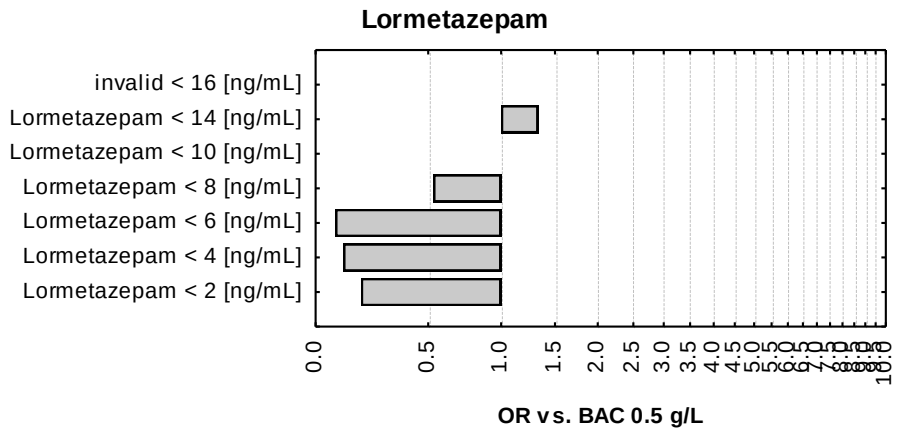


Figure 37: Risk of significantly impaired findings of different concentration classes of lormetazepam compared to the reference of BAC 0.5 g/L.

Lormetazepam seems at concentration lower than 14 ng/ml less impairing as a BAC of 0.5 g/L.

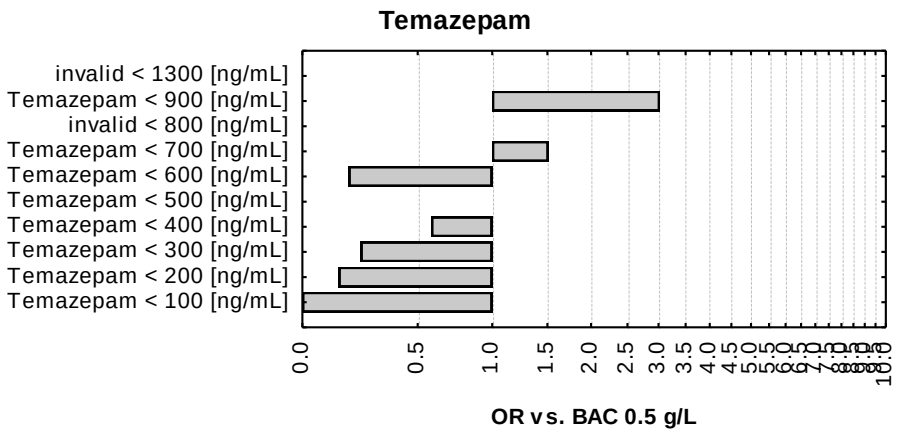


Figure 38: Risk of significantly impaired findings of different concentration classes of temazapem compared to the reference of BAC 0.5 g/L.

Temazepam shows a lower risk as a BAC of 0.5 g/L at concentrations lower than 500 ng/ml. Only at concentrations of 900 ng/ml there seems to be a marked increase of risk compared to the alcohol reference.

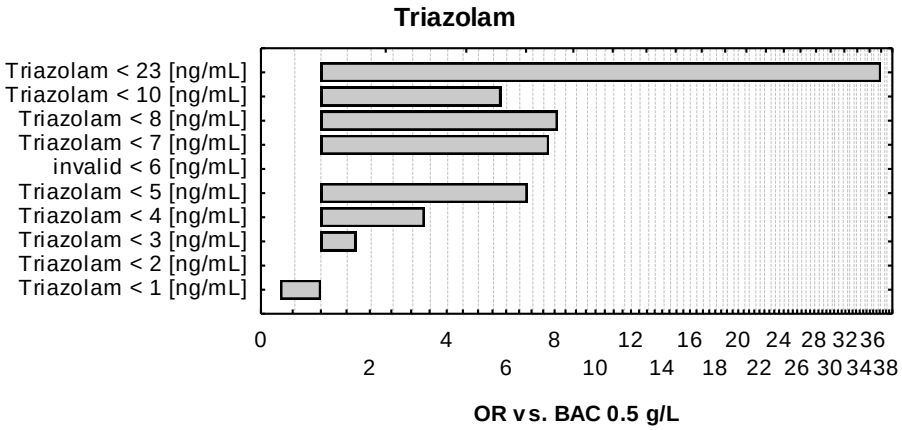


Figure 39: Risk of significantly impaired findings of different concentration classes of triazolam compared to the reference of BAC 0.5 g/L.

Triazolam reveals a quite high risk potential. Only concentrations lower than 1 ng/ml are less risky than a BAC of 0.5 g/L. At concentrations up to 10 ng/ml, the risk is approximately 5-10-fold. Higher concentrations, like 20 ng/ml, seem to have a manifest increase in risk up to 30- to 40-fold.

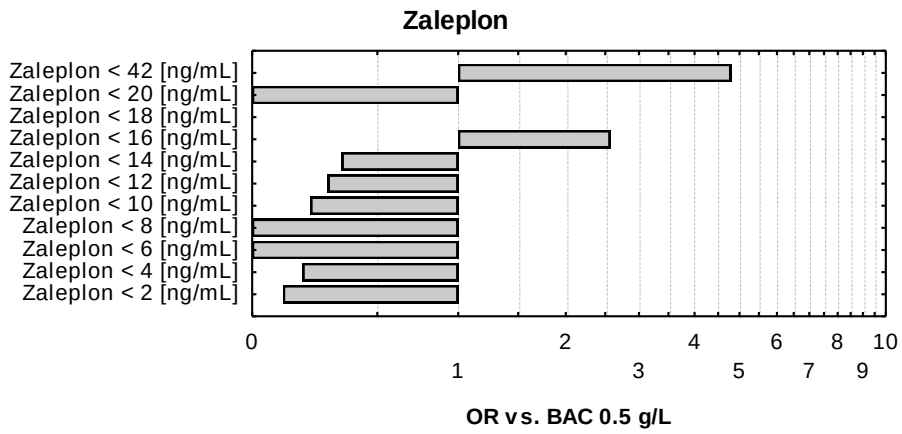


Figure 40: Risk of significantly impaired findings of different concentration classes of zalepon compared to the reference of BAC 0.5 g/L.

The risk of **zalepon** does not change very consistently at different concentrations. But at most concentrations, the risk seems to be lower than the reference of a BAC of 0.5 g/L.

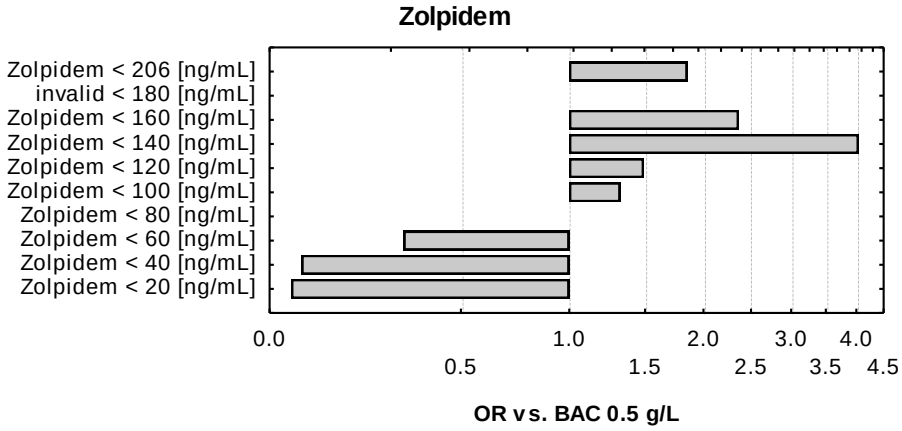


Figure 41: Risk of significantly impaired findings of different concentration classes of zolpidem compared to the reference of BAC 0.5 g/L.

Zolpidem reveals lower risks than a BAC of 0.5 g/L at concentrations below 80 ng/ml. At concentrations up to 200 ng/ml the risk still is below 5. Again a unambiguous relationship between concentration and risk is found.

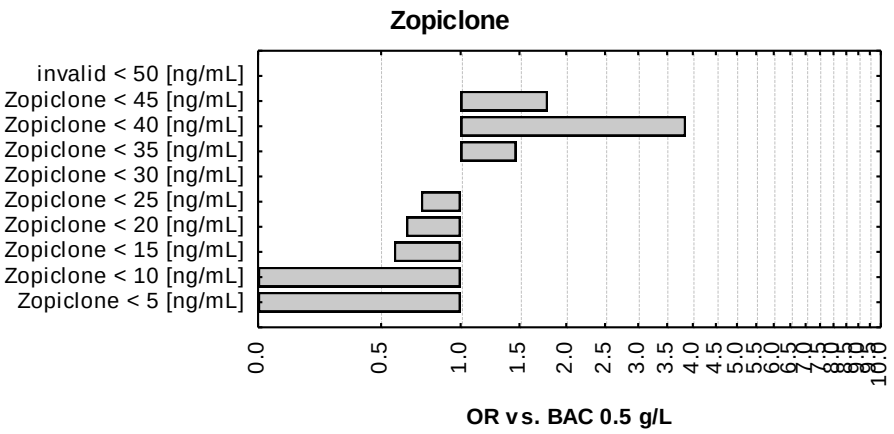


Figure 42: Risk of significantly impaired findings of different concentration classes of zopiclone compared to the reference of BAC 0.5 g/L.

For Zopiclone also a relationship between concentration and risk is apparent. Zopiclone shows lower risks than a BAC of 0.5 g/L at concentrations below 25 ng/ml. From 30 to 45 ng/ml the risk is still below 5, comparable to the maximum risk of all examined concentrations of “z-drugs”.

8.3.4.4 N06 Antidepressants

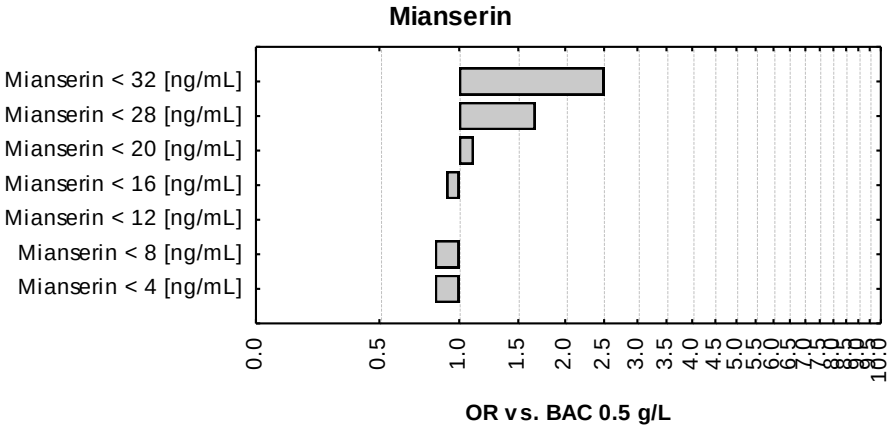


Figure 43: Risk of significantly impaired findings of different concentration classes of mianserin compared to the reference of BAC 0.5 g/L.

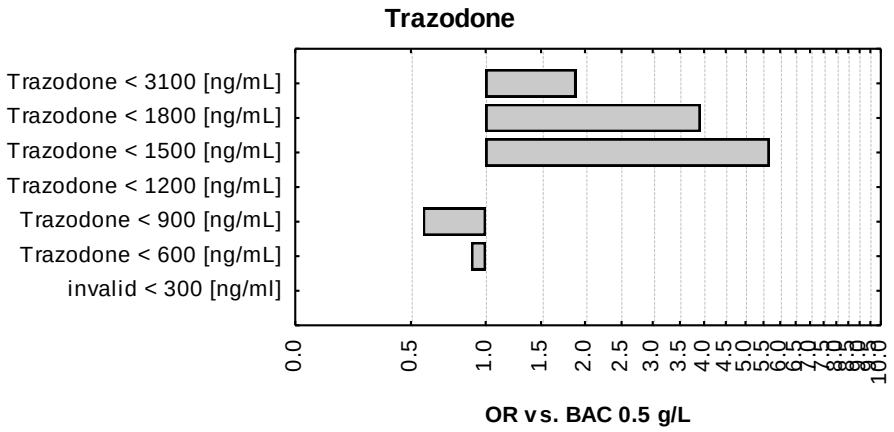


Figure 44: Risk of significantly impaired findings of different concentration classes of trazodone compared to the reference of BAC 0.5 g/L.

IN the groups of antidepressants, **mianserin** seems to be critical at concentrations above 20 ng/ml, **trazodone** at concentrations above 1200 ng/ml. Both substances reveal an association between concentration and risk.

8.3.4.5 R06 Antihistamines

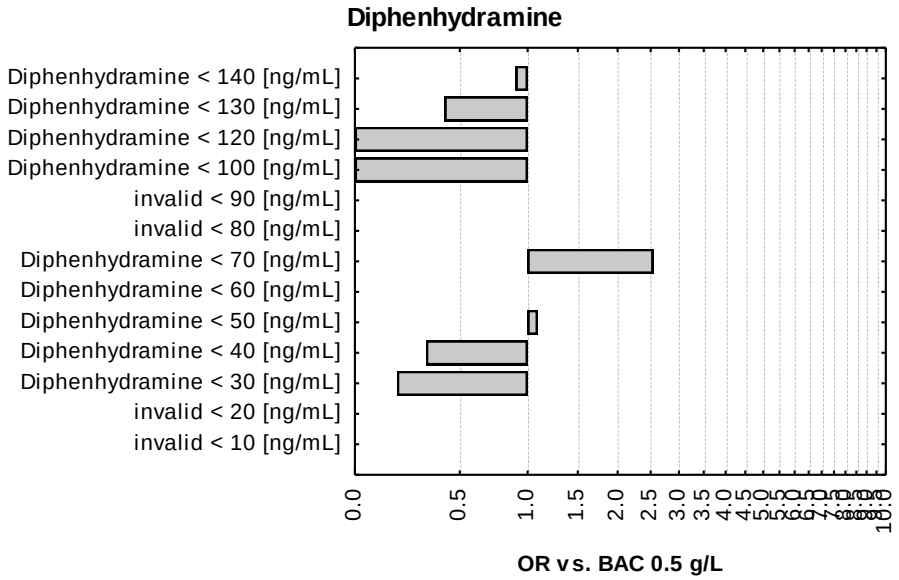


Figure 45: Risk of significantly impaired findings of different concentration classes of diphenhydramine compared to the reference of BAC 0.5 g/L.

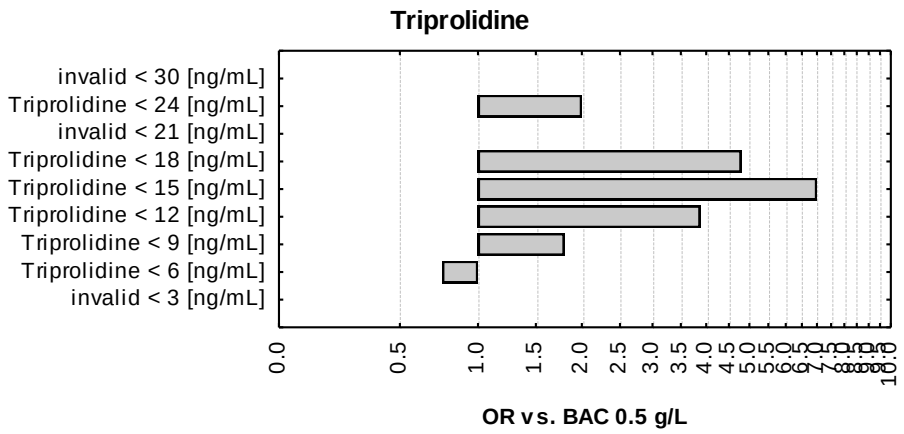


Figure 46: Risk of significantly impaired findings of different concentration classes of triprolidine compared to the reference of BAC 0.5 g/L.

Of the antihistamines, **diphenhydramine** seems not to be critical at all, whereas **triprolidine** shows slightly higher risks than a BAC of 0.5 g/L at concentrations above 6 ng/ml.

8.3.4.6 Opiates and Opioids

Like stated in chapter 7.4.2.1, there are too few studies to apply a meta-analysis to the effects of opiates and opioids. Nonetheless, Morland & Strand (2010) have reviewed the respective studies for the different opiates and opioids and comes to the following recommendations:

Table 50: The lowest impairing dose/concentration after single dose intake for different drugs in relation to dosages/concentrations related to treatment and drug half life (Morland & Strand, 2010).

Drug	Lowest impairing dose	Regular dosages in treatment	Lowest impairing concentration	Regular concentrations in treatment	Half life
Group 1					
Alfentanil	0.5 mg	0.56 mg	40 ng/ml	40-90 ng/ml	1.5 h
Fentanyl	0.014 mg	3.5 mg	2.5 ng/ml	Up to 10 ng/ml	1-6 h
Remifentanil			1.5 ng/ml	1-40 ng/ml	Up to 15 min
Butorphanol	0.5 mg i.v.	1 mg i.v.			2-4 h
Codeine	25 mg p.o.	25-50 mg p.o.			2-4 h
Dextro-propoxyphene Propoxyphene	65 mg	65-130 mg			8-24 h
Hydrocodone (HC)	7.5 mg i.v. 20 mg p.o.	5-10 mg p.o. 3-6 times/day			3-4.5 h
Hydromorphone (HM)	1 mg i.v.	0.2-0.6 mg i.v. 6-8 times/day			1-3 h
Meperidine (Pethidine)	70 mg i.v. 75 mg i.m.	50-100 mg p.o.			
Meptazinol	50 mg i.v. 100 mg i.m.	50 mg i.m.			~ 2 h
Nalbuphine	2.5 mg i.v. ~ 10 mg i.m.	10-20 mg parenteral			2-4 h
Oxycodone	20 mg p.o.	2.25-20 mg p.o.			2-3 h
Pentazocine	7.5 mg i.v. 30 mg p.o.	20-60 mg parenteral 25-100 mg p.o.			~ 2 h
Group 2					
Tramadol	No impairment seen up to 100 mg p.o.	50-100 mg p.o.			~ 6-8 h
Group 3					
Ketamine	0.1 mg/kg i.v. (~ 7 mg)	0.5-4.5 mg/kg i.v. (~ 35-315 mg)	113 ng/ml		α-phase: 10-15 min β-phase: 2.5 h

For a more detailed discussion see (Morland & Strand, 2010).

8.3.4.7 Substitutes (Methadone and Buprenorphine)

Again, there are too few studies available to apply a meta-analytical approach to Methadone and Buprenorphine. After reviewing the respective studies, (Morland & Strand, 2010) come to the following conclusion:

The literature in this field is too limited to draw clear conclusions regarding maintenance use of methadone/buprenorphine and driving. It seems, however, quite clear that low doses of both methadone and buprenorphine cause impairment in performance tasks related to driving in drug naïve as all of the studies in these groups show some level of impairment. It can thus be stated that both drugs have an impairing potential, but that the scientific literature so far does not allow us to draw any firm conclusions on whether this group or certain subgroups of maintenance patients should be allowed a driving license.

But it can be recommended at least not to drive at the beginning of a therapy. In regard of maintenance treatment an evaluation of individual performance of such patients seems to be the only useful procedure to approach the question of fitness for driving. Further on concomitant substance abuse should be controlled in this specific patient group.

8.3.4.8 Morphine

For morphine too few studies are on-hand for a meta-analysis. A review of (Morland & Strand, 2010) reveals a lot of methodological problems when examining the impairing effects of morphine which leads to the following conclusions:

Single dose administration of morphine *in doses up to 5 mg appears to cause very few effects in traffic relevant performance tasks. At higher doses impairment is found in various tasks, but with no clear dose-effect relationship except for DSST. Probably blood morphine concentrations < 50 nmol/L are accompanied by few effects in traffic relevant performance tasks. Therefore this level, 50 nmol/L, could represent a level with little accompanying traffic risk.*

The literature is too limited to draw clear conclusions regarding the effects of ***long-term medical use of morphine*** *and driving. It is, however, possible that drug effects of relevance to driving are not marked in such patients. Therefore evaluation of individual performance of such patients seems with the present knowledge to be the only useful procedure to approach the question of fitness for driving.*

For further details see again Morland & Strand (2010).

8.3.4.9 Special Consideration: Patients under medication (Berghaus et al., 2010)

Usually, multiple administration of a psychoactive substance to **naïve subjects** leads to adaptation after some time of use. This means that after some days of use of a psychoactive substance, the degree of performance impairment decreases. The degree of adaption depends on many factors, especially the dose and the frequency of use.

The condition in **patients** is by far even more complex than the situation during adaption of healthy subjects, because the disease itself might have impairing effects on performance that might be decreased by the medicament itself. Thus, the impairing effects are determined by an interaction of these factors. For further discussion of this problem see (Berghaus et al., 2010).

8.3.5 Prevalence rate medicines

The characteristic of the prevalence rates of medicines (Table 51) can be described as follows:

- *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 present.*
- *The medicinal drugs Z-drugs, medicinal opiates and opioids were in general relatively frequently detected in Northern European countries (Houwing, Hagenzieker, Mathijssen, Bernhoft, Hels, & Kira, 2011).*

Table 51: Prevalence rates medicines.

		Northern				Eastern				Southern			Western		
	country / substance	DK	FI	SE	NO	PO	HU	LT	CZ	IT	PT	ES	BE	NL	Europe
only	negative	95.5	97.1		97.0	97.6	97.6	94.4	97.2	84.9	90.0	85.1	89.3	94.4	92.5
	benzodia-zepines	0.47	0.79	0.19	0.84	0.14	1.50	1.41	0.62	0.97	2.73	1.40	2.01	0.40	0.90
	z-drugs	0.32	0.36	0.31	0.69	0.00	0.07	0.00	0.00	0.00	0.00	0.00	0.22	0.04	0.12
	opiates / opioids	0.79	0.56	0.63	0.16	0.03	0.11	0.00	0.21	0.53	0.11	0.19	0.75	0.16	0.35
combi	benzodia-zepines	0.04	0.29	0.02	0.20	0.00	0.25	0.03	0.04	0.75	0.22	0.32	0.27	0.04	
	z-drugs	0.00	0.22	0.11	0.07	0.00	0.08	0.00	0.00	0.00	0.00	0.00	0.07	0.01	
	opiates / opioids	0.01	0.09	0.11	0.08	0.00	0.19	0.00	0.00	0.70	0.09	0.00	0.23	0.05	

Looking at the absolute numbers of medicine positive drivers in the general driving population (and ignoring countries with less than 5 positive drivers) it becomes obvious, that approximately 10-30% of the benzodiazepine positive drivers were positive for combined use with a pretty low rate of combined use the eastern countries (PO: 0%, LT: 2%, CZ 6%) and rather high rates in IT (44%), FI (27%), NO (19%) and ES (19%). For z-drugs there is a marked combined use in FI (38%), SE (26%) and also BE (24%). For opiates and opioids there is a high combined use in HU (63%), IT (57%) and also PT (45%) and a medium use in NO (33%), NL (24%) and BE (23%). So in total the combined use should not be ignored when talking about the prevalence of substances in European traffic.

8.3.6 Summary Medicines

In experiments also alprazolam (0.5mg) was related to a significant decrease of driving performance. Epidemiology reveals a low risk for injury (1.5-3) and a higher fatality risk (5-7) for the group of “benzodiazepines and z-drugs”. The risk of medicinal opioids is high for injury (5-8) but lower for a fatality (≈5).

Most of the information regarding medicines can be derived from meta-analysis. On the one hand the risks of the single medicines calculated from meta-analytical data show in most of the cases a clear relation between concentration and risk. On the other hand one has to be aware of the fact, that the OR are only a very crude estimation of the real risk and therefore have to be interpreted with care.

In order to get a rough impression of low, high, and very high risk, the different concentrations of medicaments were classified based on their OR in relation to 0.5 g/L alcohol:

- LOW in the case of an OR below the OR of 0.5 g/L alcohol,

- MEDIUM in the case of an OR lower than 5-fold compared to the OR of 0.5 g/L alcohol,
- HIGH in the case of an OR higher than 5-fold compared to the OR of 0.5 g/L alcohol.

The respective concentrations are listed in Table 52.

Table 52: Overview of the evaluable medicines in different concentrations with respect to three different risk levels: OR > BAC 0.5 g/L, OR > than 5-fold compared to BAC 0.5 g/L and OR >= 5-fold compared to BAC 0.5 g/L.

Risk Class	Antipsychotics	Anxiolytics	Hypnotics & Sedatives	Antidepressants	Antihistamines
OR < 1 compared to 0.05 g/L alcohol **LOW**		Alprazolam (<= 6) Diazepam (<=300) Lorazepam (<=5) Meprobamate (<= 20000) Oxazepam (< 100)	Brotizolam (0.5-3.5) Flunitrazepam (< 4) Lormetazepam (< 10) Temazepam (< 500) Triazolam (< 1) Zalepon (< 14) Zolpidem (< 60) Zopiclone (< 25)	Mianserin (<16) Tradozone (< 900)	Diphenhydr. (< 130) Triprolidine (< 6)
1 < OR < 5 compared to 0.05 g/L alcohol **MEDIUM**	Promethazine (5-6)	Diazepam (350-600) Meprobamate (30000) Oxazepam (> 200)	Flunitrazepam (6-9) Temazepam (800-900) Triazolam (2-4) Zolpidem (100-200) Zopiclone (35-45)	Mianserin (> 20) Tradozone (> 1500)	Triprolidine (< 6)
OR >= 5 compared to 0.05 g/L alcohol **HIGH**	Promethazine (> 6)	Alprazolam (>9) Diazepam (> 600) Lorazepam (>10) Meprobamate (> 40000)	Triazolam (> 7) Flunitrazepam (> 9)		

The results go in line with the outcome of the pharmacoepidemiological approach (Ravera & de Gier, 2010), which is estimating the accident risk by linking pharmacy prescription data, police traffic accident data, and driving license data. The crude ORs of this special case-control study show a positive association between the risk of having a traffic accident and the exposure to at least one psychotropic medication of opioids, antipsychotics, anxiolytics, hypnotics and sedatives, antidepressants and antihistamines [Crude OR=1.28 (95% CI: 1.12-1.46)]. This association was found to be higher in combination therapy users [Crude OR=1.55 (95% CI: 1.20-2.02)] and SSRI[40] users [Crude OR=1.76 (95% CI: 1.38-2.24)]. The highest risk groups were new users (although the association was not statistically significant), intermediate and long half-life benzodiazepine users (the association was statistically significant only for hypnotic intermediate half-life users), female users (the association was statistically significant only for hypnotic, antidepressant, and SSRIs users), and young/middle-aged users (the association was statistically significant only for anxiolytics, antidepressant, and SSRIs users).

In general the risk estimations of the different studies indicate that psychoactive medications can constitute a problem in traffic 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.

[40] Selective Serotonin Reuptake Inhibitor

8.4 The Risk of Illicit drugs

8.4.1 Epidemiological risk of injury

8.4.1.1 Single countries

Table 53: Crude odds ratios for injury against the reference "no substance" for the single countries (different illicit drugs).

Substance / Country	BE	DK	FI	IT	LT	NL
Negative (ref.)	1.00	1.00	1.00	1.00	1.00	1.00
Stimulants	110.26*	86.43	(18.10)*		(1.60)	8.27
Benzoylecgonine	(1.42)*		(22.72)*	(2.54)	(12.44)*	18.08
Cocaine	(4.99)*	(14.33)*		(0.85)	(12.44)*	(1.80)*
Cannabis	6.78	4.00	(51.02)	(1.47)	(12.44)*	(0.44)
Illicit opiates	(2.47)*			(0.98)		(15.3)*
All alcohol-drug combinations	63.20	56.35	143.33	5.73	(270.02)	18.00
All multiple drug combinations	11.87	58.75	40.00	(1.76)	29.02*	(0.93)*

OR in brackets = not sign. different from 1
* correction of 0.5 in every cell due to a cell with zero count

For illicit drugs in general most values are not significantly different from one (values in brackets). This indicates in case of a high OR a rather imprecise estimation of risk and therefore large confidence intervals due to a small number of cases and or controls whereas in case of a low OR this might mean a really low OR. As a consequence the ORs vary to an extreme extent within most of the substances. ORs indicated with a (*) are calculated by adding 0.5 cases or controls for the calculation of the OF due to zero cells, which also can lead to estimations which are based on chance on a great extent (for details of this procedure see Hels et al., 2011).

So for stimulants only DK, LT and NL give rather precise (without *) estimations with OR for injury varying between 1.6 and 86, for cannabis the valid estimations lie between 0.4 and 51 from NL and FI. A similar picture with large variations is found for benzoylecgonine, illicit opiates and cocaine.

Nonetheless the OR for the combination of alcohol with any other screened substance is consistently much higher with risks between 5 for IT and 143 for FI. As explained in chapter 8.2.1.1 there were some sampling problems in IT and FI for controls leading to a overestimation of risk in FI and a underestimation in IT. Even by ignoring these two countries the risk for combined alcohol-substance use lies between 18 and 63, which is considerable. The risk for the combined use of substances besides alcohol is also high (between 11 and 60).

8.4.1.2 Multinational estimation

For the European estimation there are two substances for which all three merging methods lead to a result. The risk for benzoylecgonine seems to be around 4-5 compared to being sober, the risk of cannabis is not significant for method 1 and 2.4 (BE, DK, IT) for method 2 and 3.

Table 54: Crude odds ratios for injury against the reference "no substance" for all merged countries and adjusted odds ratios of the countries, which are accepted for merging by the different merging methods (different illicit drugs).

Merging method		**1**	**2**	**3**
Merged countries	**BE,DK,FI,IT,LT,NL**	**BE,DK,FI,IT,LT,NL**	**see footnote**	**see footnote**
Substance	**OR (crude)**	**OR (adj.)**	**OR (adj.)**	**OR (adj.)**
Negative (ref.)	1.00	1.00	1.00	1.00
Stimulants	9.66	8.35		
Benzoylecgonine	5.36	3.70	5.93 [1]	5.93 [1]
Cocaine	3.41	3.30		
Cannabis	1.86	(1.38)	2.41 [2]	2.41 [2]
Illicit opiates	4.03	(2.47)		
All alc-drug combinations	32.0	28.8	36.8 [3]	29.1 [5]
All multiple drug combinations.	8.64	8.01	35.01 [4]	4.48 [6]

OR in brackets = not sign. different from 1

1: IT, NL
2: BE, DK, IT
3: BE, DK
4: DK, FI
5: BE, DK, NL
6: BE, IT

Reflecting the big variations in risk for single countries the merging methods 2 and 3, which are skipping extreme values or rather imprecise estimations, cannot be applied to amphetamines, cocaine and illicit opiates which rises some suspicion concerning the validity of theses OR from merging all countries. Nonetheless the estimated DRUID-European risk is 8 for amphetamines, 3 for cocaine and 3-4 for illicit opiates.

As also seen in the single countries the risk for injury in Europe is significantly increased for the combinations of various substances besides alcohol ranging between 4 and 35, but even higher for the combination of alcohol with other substances with an approximately 30-fold risk for all merging methods.

8.4.1.3 Estimation vs. 0.5 g/L alcohol

Table 55: Crude odds ratios for injury against the reference 0.5 g/L alcohol (different illicit drugs).

Merged countries	**BE,DK,LT,NL**
Substance	**OR (crude) vs. 0.5 g/L alc.**
0.4 g/L ≤ alcohol < 0.6 g/L (ref)	1.00
Stimulants	5.8**
Benzoylecgonine	(2.1)**
Cocaine	(1.4)**
Cannabis	(0.6)**
Illicit opiates	(1.7)**
All alc-drug combinations	15.6**
All multiple drug combinations	5.1**

OR in brackets = not sign. different from 1
** correction of 0.5 in one or more countries included in the computation

By comparing the respective risks for illicit drugs categories to the reference of 0.5 g/L alcohol, only stimulants, alcohol-drug and multiple drug combinations show significant ORs (Table 55).

8.4.1.4 Concentration based estimation for Cannabis

The odds ratios for getting injured when positive for cannabis (THC) in different concentrations were calculated based on blood data from Belgium, Italy, Lithuania and the Netherlands. As controls only results from blood samples were included. The controls were weighted by time period. The results are shown in Table 56

Table 56: Crude odds ratios against the reference "no substance" for all countries and adjusted odds ratios of the countries, which are accepted for merging by the different merging methods (different THC concentrations without combinations).

Merging method		**1**	**2**	**3**
Merged countries	**BE,IT,LT,NL**	**BE,IT,LT,NL**	**see footnote**	**see footnote**
Substance	**OR (crude)**	**OR (adj.)**	**OR (adj.)**	**OR (adj.)**
Negative (ref.)	1	1	1	1
1 ng/mL ≤ THC < 3 ng/mL	2.65	2.83	3.54 [1]	3.54 [1]
3 ng/mL ≤ THC < 5 ng/mL	1.75	1.44	8.01 [1]	8.01 [1]
THC ≥ 5 ng/mL	0.66	0.55	1.59 [1]	1.59 [1]
All THC concentrations, BE, IT	1.64	1.38	3.48 [1]	3.48 [1]

OR in brackets = not sign. different from 1

1: BE, IT

Regardless of the merging method a surprising picture emerges. The risk for injury seems to decrease with increasing concentration. Since this result contradicts psychopharmacological knowledge it is supposed to reflect a methodological bias. Remembering the theoretical deliberations in chapter 6.3.2 the THC concentrations of cases are inspected in more detail. Figure 47 left illustrates the different THC concentrations of a subsample of injured cases at the time point of blood sampling, for which the exact time lag between accident and blood sampling was known. These THC-concentration were therefore used for the risk estimation. By knowing the pharmacokinetic of THC with a very high peak of concentration after 30 min and an also very fast elimination, the THC concentrations of these 43 injured subjects were estimated for the time of the accident by using the half-life of THC (Figure 47 right).

As expected the THC concentrations at the time of the accident are more frequent in higher concentrations than at the time of blood sampling, although the median time lag was only 1.5 hours. Consequently the real accident risk was caused by higher concentrations but with an increasing time-lag between accident and blood sampling the THC concentration decreases and thus the risk is attributed to lower THC concentrations. This is of course not the only explanation for the increasing epidemiological injury risk for THC with decreasing concentrations, but a feasible one. Of course also habituation in subjects consuming higher amounts of THC is also possible.

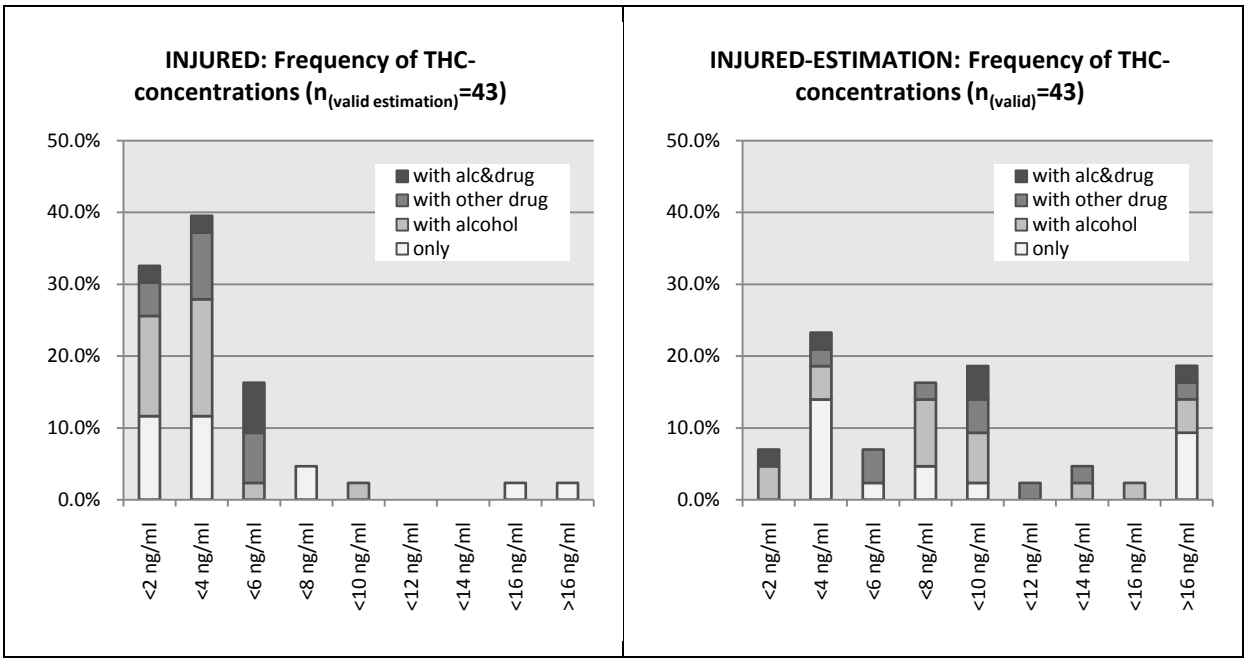


Figure 47: Frequency of different THC concentration classes differentiated by kind of use (single use, combined with alcohol, combined with other substances, combined with other substances and alcohol). Left: THC concentrations at the time of blood sampling. Right: THC concentrations as estimated for the time of the accident.

8.4.2 Epidemiological risk of fatality

8.4.2.1 Single countries

When it comes to the risk of fatality (Table 57) the different substances show the following risks in the single countries:

- A high elevated risk (range OR=19-53) for stimulants,
- A high elevation of risk (range OR=5-29) for cannabis,
- A high elevation of risk (range OR=2-39) for multiple substances, and
- an extreme elevated risk (range OR=8-153) for alcohol-drug combinations.

The risk estimations for benzoylecgonine, cocaine and illicit opiates are rather imprecise and therefore will not be discussed here.

Table 57: Crude odds ratios for fatality against the reference "no substance" for the single countries (different illicit drugs).

Substance / Country	FI	NO	PO	S
Negative (ref.)	1.0	1.0	1.0	
Stimulants	19.2	28.7		53.9
Benzoylecgonine	(3.8)*	(5.7)*		
Cocaine			(5.8)*	
Cannabis	(3.1)*	5.1	(0.2)*	29.2
Illicit opiates		24.9*	(2.0)*	
All alc-drug combination	132.7	153.8	8.8	
All multiple drug combination	16.7	31.8	(2.4)	39.5

* correction of 0.5 in every cell due to a cell with zero count

8.4.2.2 Multinational estimation

Regarding the estimations for the fatality risk of different illicit drugs in Europe it is obvious (Table 58) that for most of the substances the estimations are valid for all three merging methods. Similar to the injury risk the risk of fatality seems higher for the combination of alcohol with other substances (OR range 30-100) than for the combination of various substances besides alcohol (OR range 15-24), but nonetheless both are considerable high.

Table 58: Crude odds ratios for fatality against the reference "no substance" for all merged countries and adjusted odds ratios of the countries, which are accepted for merging by the different merging methods (different illicit drugs).

Merging method		**1**	**2**	**3**
Merged countries	**NO, FI, PT**	**NO, FI, PT**	**see footnote**	**see footnote**
Substance	**OR (crude)**	**OR (adj.)**	**OR (adj.)**	**OR (adj.)**
Negative (ref.)	1.0	1.0	1.0	1.0
All illicit drugs	3.9	3.6		
Amphetamine	25.4	24.1	28.2 [1]	
Benzoylecgonine	6.9			
Cocaine	22.3			
Cannabis	(1.8)	1.3		
Illicit opiates	10.0			
All alc-drug combin.	41.2	31.5	104.7 [2]	31.5 [3]
All multiple drug combin.	18.5	18.5	24.9 [1]	15.1 [4]

OR in brackets = not sign. different from 1
1: FI, NO, SE
2: NO
3: NO, PT
4: FI, NO, PT

The risk for stimulants is 25 for all countries and 28 for merging method 2, which allows the combination of FI, NO and SE. The rest of the OR seems to be very prone for different biases and are not discussed in detail. But looking at the crude OR for all countries cannabis seems to show the lowest and therefore not significant elevated risk (OR=1.8) for fatality compared to the other substances.

8.4.2.3 Estimation vs. 0.5 g/L alcohol

The estimations of the fatality risk against the reference of 0.5 g/L alcohol are all based on corrected calculations due to low cell counts and therefore not discussed in detail here.

Table 59: Crude odds ratios for fatality against the reference 0.5 g/L alcohol (different illicit drugs).

NO, PT	**OR (crude) vs. 0.5 g/L**
0.4-0.6 (ref)	1
Amphetamine	(0.8)**
Benzoylecgonine	(0.3)**
Cocaine	(1.0)**
Cannabis	(0.1)**
Illicit opiates	(0.3)**
All alcohol-drug combinations	1.8
All multiple drug combinations	0.7

** correction of 0.5 in one or more countries included in the computation

8.4.3 Epidemiological risk of culpability (Germany/France)

In the German culpability study were not enough controls/cases to calculate an OR for THC. In the French study, the adjusted risk[41] of the different THC dosages remains below 3 in all concentrations.

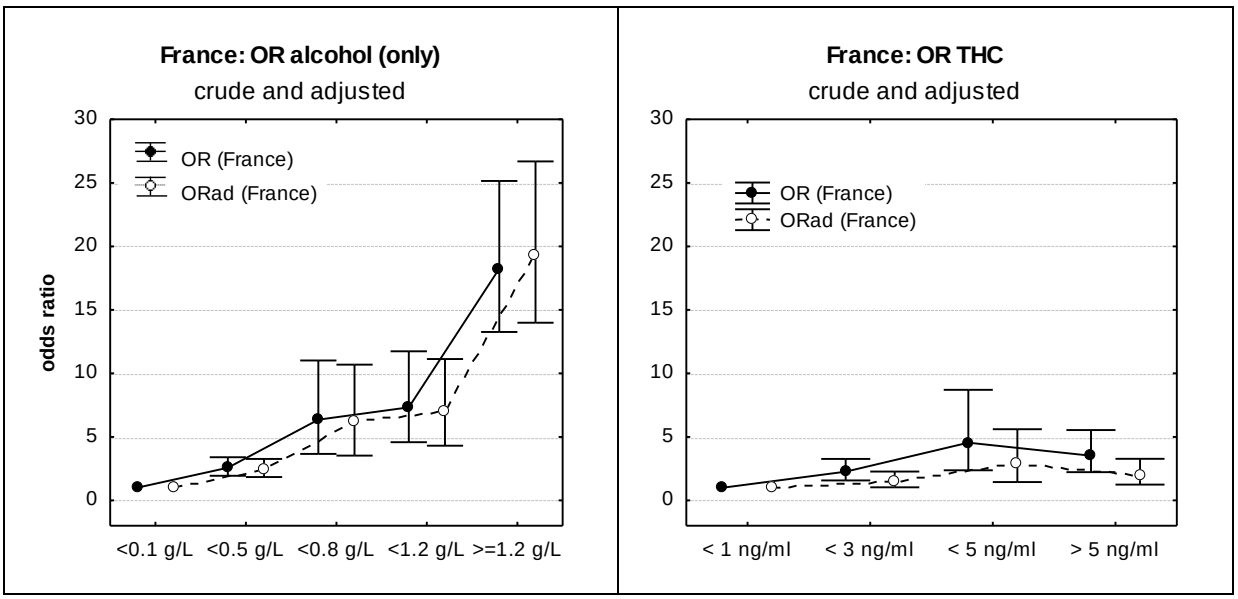


Figure 48: OR of different concentrations of alcohol and THC in France (unadjusted=filled dots and adjusted=circles).

Also interesting is the fact that when comparing the THC with the alcohol ORs, the alcohol risk does not change markedly when adjusting for THC dosages (and age and gender), whereas the risk for THC is decreased by approx. 30-40% when adjusting for alcohol (and age and gender). Like the risk of injury (chapter 8.4.1) the risk seems to decrease slightly with higher concentrations. Again different explanations are possible.

First a more pronounced habituation might be the reason assuming that mainly users with a high consumption dose are used to THC and therefore the impairing effect of THC diminishes. Second the time-lag between accident and blood sampling might play a role again, whereas the situation is somewhat different, because post-mortem the redistribution of a substance is dependent from the substance and very different to the elimination of a living body (see chapter 6.3.1). Additionally in the French fatality study not only immediately killed drivers are examined, but all drivers who were involved in a fatal accident. This implies some more uncertainties regarding the interpretation of the ORs for different cannabis concentrations:

"It was requested that the blood sample be taken as soon as possible after the crash. The elapsed time has no importance for immediately killed drivers (n=4933, 47% of subjects) because concentration of substance in the blood is unchanged after death. For surviving drivers, those who were negative to illicit drugs after a urinary test (n=3381, 32% of subjects) can really be considered as negative because these tests are very sensitive. In other words, they are built in such a way that there give very few false negatives. The elapsed time matters only for surviving drivers who get a blood dosage (n=2205, 21% of subjects). It is not excluded that, for some of these,

[41] adjusted for alcohol (in 5 dose categories), age, gender

the drug's measured concentration, and particularly the THC concentration, is significantly lower than the concentration at the time of the crash. Unfortunately, the time of the blood sampling is most often not reported (70% of missing values). For drivers where it is reported, the elapsed time is less than 10% within 1 hour, and about: one quarter between 1 and 2 hours, one quarter between 2 and 3 hours, 20% between 3 and 4 hours, and 20% after 4 hours. Consequently, doses and prevalences are probably somewhat under-estimated." (Gadegbeku et al., 2010).

The risks for amphetamines, cocaine and opiates are shown in Table 60. All of them are after adjustment not significantly different from one which means that there is no elevated risk for being involved in a fatal accident compared to being sober.

Table 60: ORs for the consumption of amphetamines, cocaine or opiates (yes vs no) of the risk of being responsible of a fatal crash for car drivers above 18 years old, France, 2001-2003, n=6932. (Gadegbeku et al., 2010)

substance	crude OR	95% CI	adjusted OR	95% CI
amphetamines	2.71	1.22-6.01	(1.54)	0.66-3.56
cocaine	(1.87)	0.78-4.53	(1.17)	(0.45-3.02)
opiates	(0.80)	0.48-1.33	(0.76)	(0.44-1.32)

adjusted = adjusted on alcohol (doses), cannabis (doses) age, gender

8.4.4 Experimental studies

8.4.4.1 THC

Within the experimental studies the medical substance dronabinol (a synthetic produced THC) was given orally in two dosages (10 and 20 mg) two different kinds of users (light and heavy) and compared to placebo and the alcohol reference of 0.5 g/L alcohol. As Figure 49 indicates no marked change in risk can be seen for all conditions. Nonetheless there is a trend that higher dosages are more impairing with respect to SDLP than lower, and that with the low dose of 10 mg light user are more impaired than heavy users.

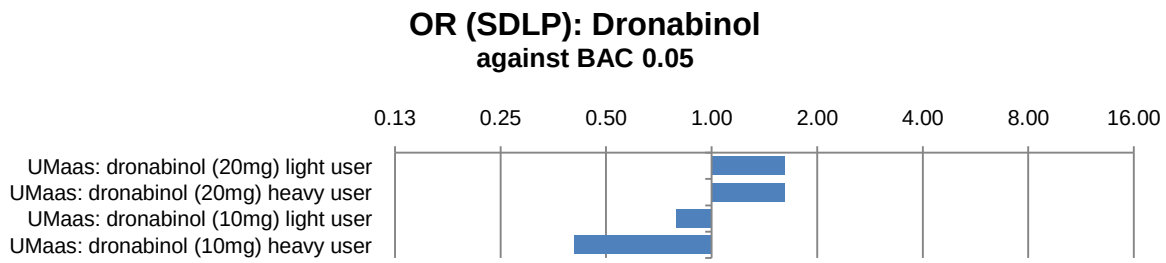


Figure 49: The risk (OR) of bad performance (SDLP) in the dronabinol experiment from UMaas compared to the reference of 0.5 g/L alcohol.

In the car-following task there were too many missing values so that the evaluation with respect to risk is omitted.

8.4.4.2 Stimulants

In DRUID stimulants were examined in four experiments:

(1) the combination of 0.5 g/L alcohol with doses of 75 and 100 mg MDMA (UMaas)

(2) the combination of 0.5 g/L alcohol with 100 mg MDMA (RugPsy)

(3) the combination of one night sleep deprivation[42] with doses of 25, 50 and 100 mg MDMA (UMaas) and

(4) the combination of 0.8 g/L alcohol with 10 mg dexamphetamine (TNO).

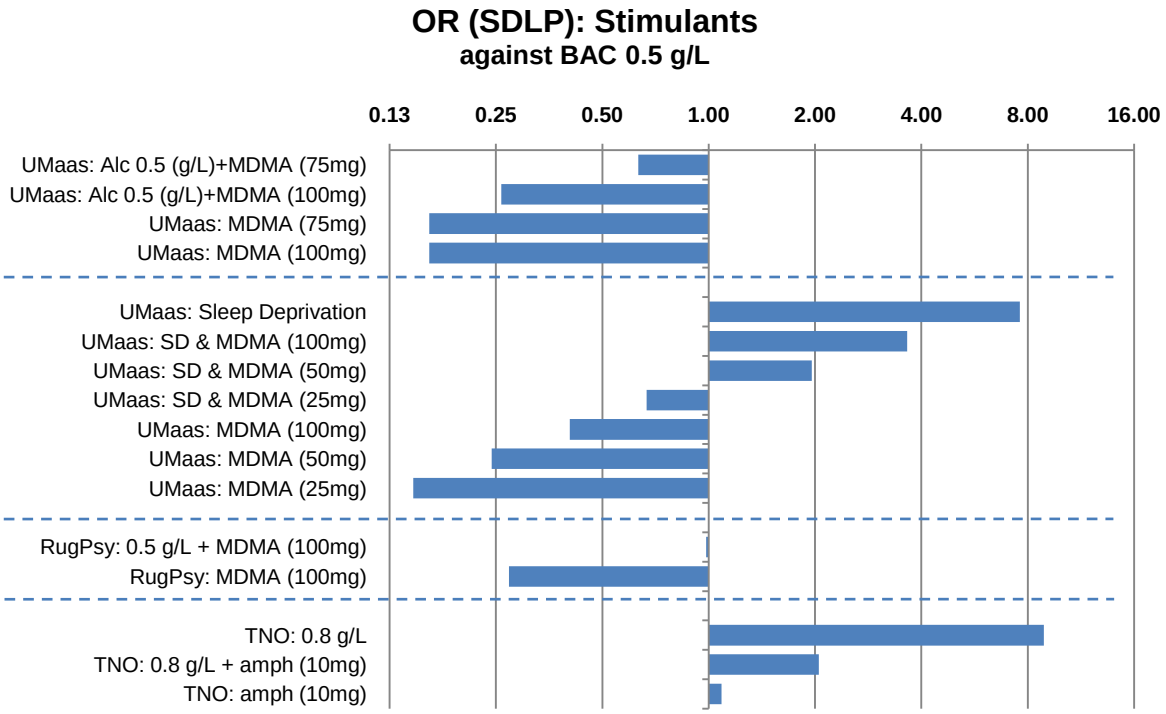


Figure 50: The risk (OR) of bad performance (SDLP) in the experimental studies from different studies (separated by dashed lines).

All conditions were compared to the respective alcohol calibration with 0.5 g/L. As Figure 50 indicates very obvious results can be drawn from these studies:

- one night of sleep deprivation alone shows a 8-fold risk compared to 0.5 g/L alcohol, as does 0.8 g/L alcohol in the study of TNO
- MDMA alone is improving driving performance notably in all experiments,
- MDMA in doses of 75 and 100 mg seem to compensate for the effect of 0.5 g/L alcohol (UMaas) but not for sleep deprivation (UMaas),
- Dexamphetamine alone is not more impairing than 0.5 g/L alcohol and is also only partly able to compensate for the effects of 0.8 g/L alcohol (TNO).

[42] One night of sleep deprivation means, that the subjects were awake from the morning until the next morning (24h) without sleeping prior to the experiment.

8.4.5 Meta-Analysis

8.4.5.1 Stimulants

As the results from Schulz, Vollrath, Klimesch, & Szegedi (1997) show (Table 61), hardly any impairing effects can be found for amphetamines[43] in experimental studies conducted until 1995.

Table 61: Summary of changes of performance due to amphetamine effects (Schulz et al. 1997).

	Significantly impaired effects		Not significantly changed		Significantly improved effects		All effects	
Performance area	**n**	**Line%**	**n**	**row %**	**n**	**row %**	**n**	**row %**
Tracking			13	87	2	13	15	100
Psychomotor function	1	1	61	84	11	15	73	100
Reaction	2	3	57	85	8	12	67	100
Visual function	1	1	69	76	21	23	91	100
Driving behaviour			1	100			1	100
Attention	5	2	264	83	51	16	320	100
Divided attention			27	90	3	10	30	100
Encoding/Decoding	8	5	137	89	9	6	154	100
Total	**17**	**2**	**629**	**84**	**105**	**14**	**751**	**100**

The same conclusion must be drawn from the report of Berghaus (1997). So from this perspective there is no proof for the impairing effect of amphetamines[44]. For DRUID more recent studies were inspected but *"…all in all the newer publication give no reason to a fundamental revalidation of the results summarized by the meta-analyses of 1997 concerning amphetamines.*

Even for ecstasy the experiments seemed to indicate similar results as for other amphetamines showing by far more improvements than impairments (especially (Lamers et al., 2003). Hence, concerning driver fitness as tested with "normal" doses (40 mg – 125 mg) in experimental studies, the risk potential of ecstasy comprised during the time of action primarily not the impairment of performance. (Berghaus et al., 2010).

In Schulz et al. (1997) the reported studies with cocaine comprise experiments with doses between 8 mg and 210 mg including test procedures 15 minutes up to 3 hours p.a. Again no marked impairing effects could be identified by a meta-analytical approach (see Table 62).

[43] d-amphetamine was the most frequent analyzed substance with doses applied between 1 and 34 mg and effects measured between 5 minutes and 34 hours p.a.
[44] For more detailed information see Berghaus et al. (2010).

Table 62: Summary of changes of performance due to cocaine effects (Schulz et al. 1997).

	Significantly impaired effects		Not significantly changed		Significantly improved effects		All effects	
Performance area	**n**	**row %**	**n**	**row %**	**n**	**row %**	**n**	**row %**
Reaction			7	88	1	12	8	100
Visual function			5	100			5	100
Attention			7	37	12	63	19	100
Encoding/Decoding			33	97	1	3	34	100
Total	**0**	**0**	**52**	**79**	**14**	**21**	**66**	**100**

8.4.5.2 Cannabis

The risk calculated from meta-analytical results for the oral administration of cannabis against the reference of 0.5 g/L alcohol is much lower for concentrations of < 2ng/ml (serum) and increases to 2-2.5 for concentrations <10 ng/ml. The same is true for smoking cannabis until concentrations of < 12 ng/ml.

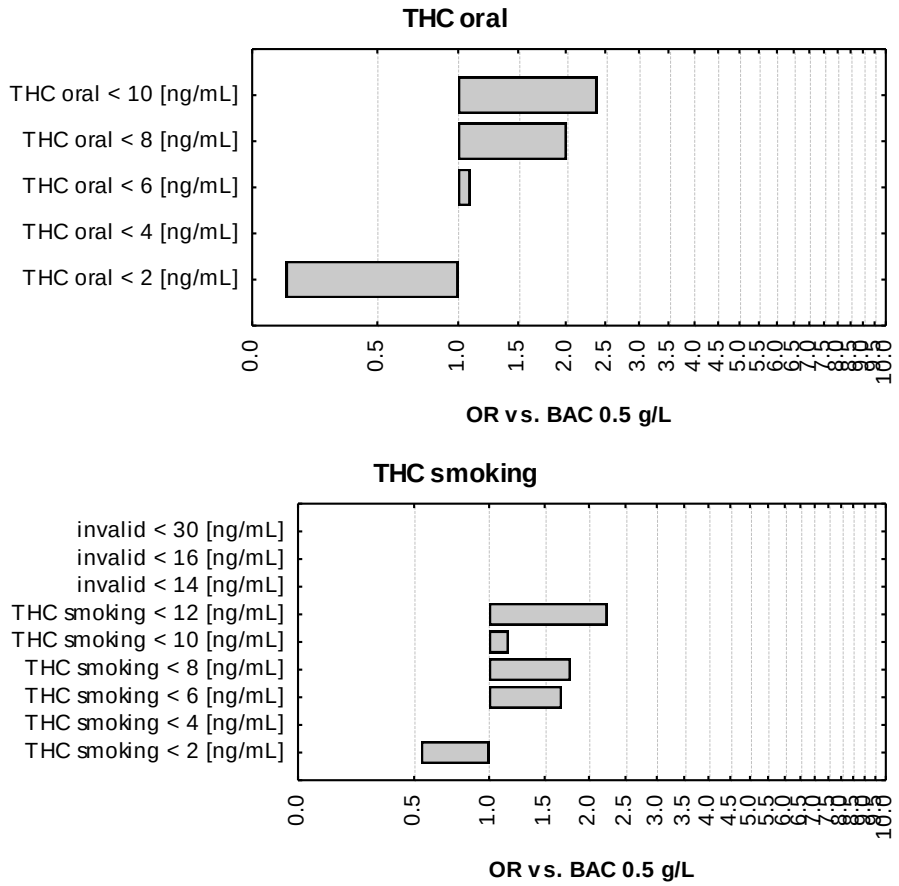


Figure 51: Risk of significantly impaired findings of different concentration classes of THC (oral application and smoked) compared to the reference of BAC 0.5 g/L.

8.4.6 Prevalence rate illicit drugs

When it comes to prevalence rates of illicit drugs (Table 63) the numbers are much lower than the prevalence of alcohol. Nonetheless there is a clear focus on southern and western countries compared to northern and eastern European countries.

Table 63: Prevalence rates illicit drugs.

	substance /country	Nothern				Eastern				Southern			Western		
		DK	FI	SE	NO	PO	HU	LT	CZ	IT	PT	ES	BE	NL	Europe
	negative	95.5	97.2		97.0	97.6	97.7	94.5	97.2	85.0	90.0	85.2	89.3	94.5	92.6
	drugs only	1.86	2.12		2.57	0.90	2.17	1.63	1.76	5.41	4.65	9.79	3.93	3.12	
	drugs-drugs	0.06	0.29	0.12	0.28	0.02	0.27		0.11	1.22	0.23	0.57	0.30	0.35	0.39
only	amphetamines	0.02	0.05	0.07	0.06	0.05	0.00	0.22	0.36	0.00	0.00	0.11	0.00	0.19	0.08
only	benzoylecgonine	0.00	0.03	0.00	0.06	0.00	0.00	0.00	0.00	0.31	0.00	0.18	0.17	0.12	
only	cocaine	0.00	0.00	0.00	0.01	0.00	0.04	0.00	0.00	0.93	0.03	1.31	0.03	0.18	0.42
only	THC	0.20	0.04	0.03	0.45	0.57	0.19	0.00	0.46	1.15	1.38	5.99	0.35	1.67	1.32
only	illicit opiates	0.00	0.00	0.00	0.00	0.09	0.00	0.00	0.00	0.30	0.15	0.05	0.09	0.01	0.07
combi	amphetamines	0.02	0.05	0.00	0.15	0.02	0.00	0.00	0.02	0.33	0.02	0.11	0.00	0.18	
combi	benzoylecgonine	0.00	0.00	0.01	0.01	0.00	0.00	0.00	0.00	0.04	0.00	0.08	0.05	0.08	
combi	cocaine	0.06	0.00	0.00	0.05	0.00	0.00	0.00	0.05	0.35	0.22	1.01	0.17	0.28	
combi	THC	0.11	0.00	0.00	0.16	0.02	0.02	0.00	0.11	0.96	0.41	0.90	0.14	0.43	
combi	illicit opiates	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.71	0.03	0.21	0.07	0.00	

The main statements from Houwing, Hagenzieker, Mathijssen, Bernhoft, Hels, & Kira (2011) were:

- *For illicit drugs THC is 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 in the weekend.*
- *As a tendency cocaine and amphetamines are often consumed with other substances in combination whereas THC is much more consumed alone.*

Concerning the combined use amphetamines and cocaine are used very often in combination with other substances. For example in NO 13.9 (71%) from 19.6 amphetamine positive drivers (weighted numbers) were positive for combined use[45]. Similar high percentages can be found for cocaine in NO, PT, BE, NL.

8.4.7 Summary illicit drugs

The risks of illicit drugs are quite different from country to country and from substance to substance. Making the situation more difficult the methodological approaches are different in the different epidemiological studies.

When it comes to **cannabis** the prevalence rates in the general driving population vary between 0.1 % (German Smartphone Survey, Walter et al., 2011b), chapter 7.2.1.1.3) and 3.3 % (estimation from the control group of a culpability study in France, Amoros et al., 2010), chapter 7.2.1.1.2) with a mean European estimation of

[45] again only countries are considered with more than 5 drivers positive for the respective substance.

1.3%. That is a higher prevalence than for most of the other tested substances but still much lower than the prevalence of alcohol.

The risk estimations vary between 1-2, regardless of being injured, being killed of being culpable for a fatal accident. Even analyzing different THC concentrations the risk for an injury the risk is between 1-3, even for concentrations above 5 ng/ml. Trusting the risks from the meta-analytical approach the risk is “only” 2-fold up to concentrations of 10 ng/ml compared to 0.5 g/L alcohol. In experiments 10 and 20 mg of dronabinol lead also to no distinct effects compared to 0.5 g/L alcohol.

8.5 The combined effects of alcohol and illicit drugs

8.5.1 Effects of simultaneous use of psychoactive drugs (Eva Schnabel & Günter Berghaus)

In the following, the consumption of different psychoactive substance within a time frame in which at least two substances act together is named combined or simultaneous use.

The analysis of epidemiological studies seemed to indicate that the simultaneous use of different psychoactive substances is the rule rather than the exception. Augsburger and colleagues, for example, examined drivers who were suspected of driving under the influence of psychoactive substances. During a two years period ranging from 2002 to 2003, they analyzed blood samples of 440 drivers in four Swiss cantons. In every second blood sample (50.7%), at least two psychoactive substances could be detected (Augsburger et al., 2005). During the years 2000 to 2002, Holmgren and colleagues analyzed alcohol, illicit drugs and pharmaceuticals in blood samples of fatally injured drivers (855 with a toxicological investigation) in Sweden. Within the investigation period, the percentage of cases with multiple drug intake increased from 10% to 26% (Holmgren, Holmgren, & Ahlner, 2005).

As far as we know, there are no systematic epidemiological studies up to now referring to the question of typical user groups of substance combinations. The following attempt of a grouping is therefore primarily based on the practical experience of an expert activity within the frame of criminal proceedings.

Table 64: User groups of substance combinations.

Users	Substance combinations
Unintentional combination	Alcohol + medicines
Intentionally combined use	
Young people	Alcohol, cannabis, amphetamines
Elderly and ill people	Medicines, opioids
Addicted people	Alcohol, illicit drugs, benzodiazepines

Regarding the group of elderly people, paying attention to the problem of simultaneous use is even more important. With increasing age, the simultaneous intake of different medicines becomes more common. From the age of 60, an average intake of three medicines per day can be assumed. By the expected

increasing aging of the population, the group of people that take different medicines simultaneously might become bigger and bigger.

Due to the importance of the simultaneous use of different psychoactive substances, one part of Task 1.1 is to evaluate prominent combinations of drugs, medicines, and alcohol for their impact on traffic safety.

By collecting empirical knowledge about the major psychoactive substances, studies were found in which not only the effect of single substances was tested but also the effect of substance combinations. The only substance for which more than just a few combination studies could be found was alcohol. However, a detailed analysis showed that even regarding alcohol there exist too few studies with the same second agent. (Berghaus et al., 2010) gathered 53 alcohol studies in which the combination with overall 35 different substances was tested. For most of these substances there are only one or two combination studies, with the exception of thioridazine (n=3), cocaine (n=3), MDMA (n=4), cannabis (n=10) and diazepam (n=13). Thus, the number of studies is too low for most combinations to evaluate their effects by means of a meta-analysis. Even if there are some combinations with more studies, like for example for alcohol and THC, the designs of the different studies and hence the influencing factors on the results of performance tests are too heterogeneous to combine them meaningfully in a meta-analytic approach as this was possible with the single agents. As an example, the effects of alcohol/cannabis combinations compared to placebo are summarized in the next table. The first digit shows the number of significantly impaired findings for the respective substance concentration and performance category, the second digit the number of all findings. Table 65 illustrates some of the difficulties when trying to summarize the results of the different studies.

Table 65: Number of significantly impaired findings of the alcohol/cannabis group versus the placebo group in comparison to the number of all findings concerning different substance concentrations and performance categories.

BAC	THC dose given[46]	Points in time of testing	Reaction time	Divided attention	Psycho-motor skills	Visual functions	Tracking	Driving	Total
0,03%	1,75%	10-20min			0/1			0/1	**0/2**
0,03%	3,33%	10-20min			1/1			0/1	**½**
0,04%	100µg/kg	25-30min						5/9	**5/9**
0,04%	200µg/kg	30min						7/8	**7/8**
0,05%	170µg/kg	---					1/1	3/8	**4/8**
0,06%	1,75%	10-20min			0/1			1/1	**1/2**
0,06%	3,33%	10-20min			1/1			1/1	**2/2**
0,07%	215µg/kg	100min	2/2		1/1		1/1		**4/4**
0,08%	320µg/kg	100min			1/1		1/1		**2/2**
0,09%	3,6%	75min				0/1			**0/1**
0,10%	40µg/kg	---		2/2					**2/2**
0,11%	100µg/kg	5min				2/2			**2/2**
Total			**2/2**	**2/2**	**4/6**	**2/3**	**3/3**	**17/29**	**30/45**

First of all, different concentrations of alcohol as well as different concentrations of THC were used in the studies. Second, there were different points in time when performance testing took place. Thus, testing started in the absorptive or in the eliminative phase of alcohol or of THC. Summarizing is also difficult as some studies tested effects of the substance combination versus placebo and some versus the

[46] Dose as % means the the concentration of THC in the smoked cigarette.

single substances (i.e. vs. alcohol or vs. cannabis). Thus, a meta-analysis of experimental studies on combined effects cannot be conducted in a meaningful way. Even a review of experimental studies would go beyond the scope of this report due to the variety of possible combinations – alone the some hundreds of agents of pharmaceuticals would imply an immense number of substance combinations. For more detailed information please see Berghaus et al. (2010) and Berghaus (2007).

8.5.2 THC and Alcohol

The combined effect of THC and alcohol could not be examined withing DRUID because of low prevalence rates. Former epidemiological research however indicates, that there is a marked increase of risk (either for injury of fatality) by combining THC and alcohol (Biecheler et al., 2007).

8.5.3 Stimulants and Alcohol

In DRUID the only conclusion which can be drawn for the combination of alcohol and stimulants are available from the experiments already outlined in chapter 8.4.4.2. There it seems that MDMA in doses of 75 and 100 mg seem to compensate for the effect of 0.5 g/L alcohol (UMaas) but not for sleep deprivation (UMaas). The TNO study indicates that Dexamphetamine (10 mg) does not compensate the effect of 0.8 g/L alcohol, but leads to a decrease of the OR from 8 to 2. In a more general sense that could mean that stimulants (as the name already implies) are in some cases capable to compensate for states or psychoactive substances which lead to any kind of sedation. Of course this depends on the kind of the stimulating substance and the dose/concentration. This topic is by far too complex to be discussed here sufficiently.

8.6 Consumption driving patterns (German Smartphone Survey)

In the German Smartphone Survey – Part II (Walter et al., 2011b, see also chapter 7.2.1.1.3) not only prevalence rates of different substances were estimated but also consumption and driving patters of controls and users were examined (Table 66).

Alcohol is consumed in higher doses and more frequently by males, in higher doses and more frequently by young age groups (18-24) and more frequently in urban and city areas[47]. Alcohol is mainly consumed in the evening and at night (especially at weekends) and alcohol DUI also mainly occurs in these time periods.

Cannabis is consumed in higher doses by males, in higher doses and more frequently by young and middle age groups (18-30) and more frequently and in higher doses in rural areas. Cannabis is consumed all day long and this accounts also for cannabis-DUI, which are (in concentrations > 4 ng/ml) mainly caused by young and middle age groups (18-29).

Stimulants are consumed more frequently by females, and in higher doses in rural and city compared to urban areas. Stimulants are mainly consumed late at night at

[47] With respect to alcohol dose there is an interaction between age and residence (rural/urban/city). For details see Walter et al. (2011b).

weekends (until early morning) and consequently stimulant DUID occur at the same time period. No age effects could be found.

Table 66: Overview of the main influences of gender, age, time and residence on the consumption of alcohol, cannabis and stimulants and connected drives under the influence.

		Alcohol	Cannabis	Stimulants
Who consumes?	gender	males > female (dose & DWC)	males > female (dose)	female > males (DWC)
	age	18-24 > 30-39 (CED) 18-24 > 25-39 (dose)	18-29 > 30-39 (CED)	
	residence	urban and city > rural (DWC) urban > rural and city (CED)	rural > urban (CED & dose)	rural/city > urban (dose)
When is consumed?		evening/at night (on weekends more until late at night/in the morning)	all day long	late at night/in the morning and especially on weekends
Who drives after consumption?		no gender/age/residence effects	18-29 > 30-39 (DUID with high intoxication; (THC>=4ng/ml) rural/city > urban (DUID) (THC>=1ng/ml, >=4ng/ml)	
When are DUI/DUID drives?		evening/at night (on weekends also quite often in the morning/afternoon)	any time of the day (on weekdays especially in the evening, on weekends also very often late at night)	weekends, mostly in the evening/at night, but also quite often in the morning/afternoon

DWC=Days with consumption within observation period
CED=Consumption events per day

Comparing this information from Germany with the prevalence information of whole Europe for the general (accident free) traffic (Houwing, Hagenzieker, Mathijssen, Bernhoft, Hels, & Kira, 2011) and injured/killed drivers (Isalberti et al., 2011) results in Table 67.

In the accident-free traffic **alcohol** is most prevalent among older male drivers during weekday nights and weekends, but with rather low BAC. In the accident involved drivers alcohol was mainly detected in high concentrations, also in male but more in younger drivers. The similar pattern applies for the combinations of alcohol with drugs and drugs with drugs: In both categories mainly young (< 35 years) males are present. Alcohol-drug combinations were mainly detected at nighttime but in FI, CZ and BE also at daytime.

Medicinal drugs (benzodiazepines, medicinal opiates and opioids) are more consumed by females aged over 50 years and were detected mainly during weekdays at daytime.

Within the illicit drugs **stimulants** differ in many aspects from the rest of the substances. Firstly they are very often detected with other substances in combination (in 30-80% of the cases). The time of consumption and also for detection in traffic is predominantly in the late night or even morning, especially on weekends. In the German Smartphone Survey (Walter et al., 2011b) stimulants was the only substance group which was more often consumed by females than by males. **THC** however is more consumed by males than by females and particularly by young persons (18-24 years). THC seems to be consumed all day long (German Smartphone Survey) but is interestingly detected mainly at weekend evenings.

Table 67: Overview of the main influences of gender, age, time and residence on the consumption of alcohol, cannabis and stimulants and connected drives under the influence.

		CHARACTERISTIC		
		WHO CONSUMES	**WHEN CONSUMPTION**	**WHEN DUI/DUID**
alcohol	**all conc.**	Controls[2]: male / >35 BAC ⇩ Injury[3]: male / <35 BAC ⇧	evening/nights weekends[1/2]	evening/at night [1/2] (weekends & morning/afternoon)
medicaments	**benzodiazepines**	female> male[2] > 50 years[2]		weekday daytime[6]
	z-drugs	-/-	-/-	-/-
	med. opiates and opioids	female> male[2] > 50 years[2]	-/-	-/-
stimulants	**stimulants**	female > males[1] 50-70% in combi.[2]	late night/morning & especially on weekends[1]	weekends (mostly evening/night & morning/afternoon)[1]
	cocain	30-80% in combi.[2]		
THC	**all concentrations**	18-24[2] males > female[1] 20-30% in combi.[2]	all day long[1]	weekend evening[2] any time of the day[1]
	illicit opiates	-/-	-/-	-/-
	alcohol-drugs	male>female[2] < 35 years[2]		night & FI,CZ,BE daytime[2]
	drugs-drugs	male>female[2] < 35 years[2]	South & NO: night-weekday[2]	

1 = result from D 222 (prevalence estimated by the German Smartphone Survey; (Walter et al., 2011b).
2 = result from D 223 (prevalence in general traffic; (Houwing, Hagenzieker, Mathijssen, Bernhoft, Hels, & Kira, 2011).
3 = result from D 225 (prevalence in injured and killed drivers; (Isalberti et al., 2011).

9 SYNOPSIS

9.1 General remarks

Table 68 summarizes all prevalence rates and risks estimated in DRUID for all substance groups with the three different methodological approaches. Some major facts should be kept in mind when comparing these numbers:

- The risk from meta-analysis (MA) is estimated from a huge amount of studies all dealing with single dose applications to healthy volunteers or regular dose applications of illicit drugs to occasional users. Moreover due to the method for the risk estimation from meta-analysis the risk is calculated vs. 0.5 g/L alcohol instead of 0.0 and no significance information is available.
- For experiments due to the method for the risk estimation the risk is also calculated vs. 0.5 g/L alcohol instead of 0.0 g/L and no significance information is available.
- The prevalence of substances in France was estimated from a control sample in a culpability study which might lead (in spite of careful definition of this group) to higher prevalences.
- The prevalence in Germany is estimated by the German Smartphone Survey with 200 regular drug consumers and extrapolated to the general population.

Table 68: Prevalence rates and risks calculated with different methodological approaches for all substance groups. Bold numbers in the risk part are indicating statistically significant OR.

		PREVALENCE [%]				OR = RISK [x-fold]					
		DRUID	FRANCE	GERMANY	HOT-SPOT[48]	EXPERI. vs. 0.5 g/L	MA vs. 0.5 g/L	injury (ALL)	fatality (ALL)	CuI (FR)	CuI (GE)
alcohol	**all conc.**	3.48	5-7	18-24: 1.57[2] 25-39: 3.3[2]				**7.5**	**12-92**	**8.4**	**4.6**
	0.1-0.5 g/L	1.96	NA	NA	South & BE		0.4 - 1.0	1.1	**3-9**	**2.5**	1.6
	0.5-0.8 g/L	0.68				1.3 - 4.8[3]	1.0 - 2.5	**3.8**	**20-46**	**6.1**	NA
	0.8-1.2 g/L	0.42			South & East		2.5 - 12.6	**13.9**	**8-278**	**6.9**	1.2
	>1.2 g/L	0.39						**55.3**	**144-500**	**19.3**	**20.8**
medicaments	**benzodiazepines**	0.90	NA	NA	PT, BE	5-16[4]	depends on substance & concen-tration	**2-3**	**5-7**	NA	1.7
	z-drugs	0.12			North not: East	< 1					NA
	med. opiates and opioids	0.35			not: East	< 1		**5-8**	**5**		
stimulants	**amphetamines**	0.08	0.3-0.4	0.02		< 1	< 1	**8-9**[1]	**24-28**	1.54	NA
	cocaine	0.42	0.30		South (ES, IT) not: North&East		< 1	**3**	**22**[1]	1.17	
THC	**THC all conc.**	1.32	2.8-3.3	0.14	South & NL	0.5-1.8	1-2	1.4-**2.4**	1.3-**1.8**[1]	**1.89**	0.3
	THC 1-3 ng/ml	NA				NA	< 1	2.7	NA	**1.53**	NA
	THC 3-5 ng/ml						1	1.8		**2.84**	
	THC > 5 ng/ml						2	0.67		**2.01**	
	illicit opiates	0.07	0.9-1.2					2-4	**10***	0.76	
	alcohol-drugs	0.37		0.02	South	NA	NA	**28-37**			
	drugs-drugs	0.39			South & West			**4-35**			

(1) = probable bias due to low cell counts, (2) combinations included, (3) = vs. placebo, (4) = alprazolam (0.5 mg)

In general the major shortcoming of the DRUID studies, which aims particularly to assess risks for different psychoactive substances is, that quite few people drive with psychoactive substances (besides alcohol), which is – in the first place – a good message for traffic safety. But for risk assessment that means, that in most of the cases

(1) no concentration based information is possible;
(2) information could be biased by randomly finding one intoxicated person more or less in cases or controls;
(3) confidence intervals are huge.

Considering the estimations of substance prevalence rates (besides alcohol) of former studies this outcome was partly foreseeable as already stated in Krüger et al. (2008): *"Here it becomes clear that for other substances than for THC or benzodiazepines a reliable answer to the question of accident risk will be difficult to give. The problem is not the prevalence of the substances in cases but in controls, where the exposure rate is usually low."*

However some important messages from DRUID risk studies can be summarized.

[48] The "Hot-Spots" concerning prevalence rates refer to the countries covered in the DRUID roadside study. So other countries cannot be labeled as "Hot-Spots" in this context.

9.2 Alcohol

Alcohol is a psychoactive substance which is not only widely accepted but often even an essential component of social life, in part of business as well. Therefore it is not surprising that the alcohol prevalence in general is the highest of all examined substances (3.48%). Nonetheless the way of dealing with alcohol is different in different European countries and thus differences in prevalence rates of different alcohol concentrations in the European countries are not surprising.

But as a matter of fact the epidemiological risk of being injured or killed in a traffic accident due to alcohol consumption starts to increase dramatically from 0.8 g/L on. The same accounts for the experimental studies, in which different concentrations of alcohol (0.3, 0.5 and 0.8 g/L) were tested. The alcohol related risk calculated from meta-analysis increases nearly linearly up to concentrations of 1.1 g/L indicating, that the risk estimation by means of meta-analysis seems to be less sensitive to alcohol impairment than epidemiology.

Thus alcohol in higher concentrations combines a high risk with a relatively high prevalence in the general driving population and therefore alcohol should remain the focus of traffic safety measures.

9.3 Medicines

Prevalence rates for medicines are discussed in detail in chapter 8.3.5 indicating European rates lower than 1% with prevalence rates higher than 1% for benzodiazepines in HU, LT, PT, ES and BE.

Epidemiological risks could only be estimated for very rough substance categories like benzodiazepines, z-drugs and medicinal opioids and opiates. The risk for benzodiazepines and z-drugs seems to be between 2-3 for an injury and 5-7 for a fatality. For medicinal opioids and opiates the European risk estimation is 5-8 for injury and around 5 for a fatality. Experiments in DRUID showed a comparable or even lower risk for the examined user groups of patients taking different hypnotics or opiods than 0.5 g/L alcohol. Also zopiclone was less impairing than the alcohol reference. Only 0.5 mg alprazolam proofed to be highly impairing showing an 5-fold risk of already treated anxiety patients compared to 0.5 g/L alcohol and a 16-fold risk of healthy volunteers. This result indicates that the development of tolerance and habituation plays a major additional role for resulting impairment.

Nonetheless the inspection of experimental studies (meta-analysis) reveals, that impairment strongly depends on the kind of substance and their concentration. But these studies have been conducted on healthy volunteers with single medicine applications. Therefore the results deliver necessary information regarding the driver´s fitness after single medication intake or the beginning of a persisting medical treatment.

Medicines usually are prescribed to sick people in order to decrease impairment from illness and the effect of a medicine differs from patients to healthy subjects. Thus it was shown that patients in long term treatments perform better than without treatment or in comparison to healthy consumers. For this topic a DRUID expert group conducted a workshop with the following results.

- A properly prescribed medicine includes right information of the patient by the practitioner. Patients in long-term treatment with psychoactive medicines should not be stigmatized by the need to carry a special “medication passport”. Other than with drug users, the responsibility and compliance of patients under long-term treatment usually is high.
- 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 were only investigated and observed with single users or new users. Hence, an impairment check is an objective way to judge recreational use.
- 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.

Therefore the use of legal prescribed medicines should not be controlled by legal countermeasures. In this situation it seems much more expedient to implement a comprehensive information system for medical doctors and patients in order to inform them about the potential risk of the different substances, the maximum impairment, the duration of intake after which habituation has taken place, etc. instead of defining thresholds. (For details see Berghaus et al., 2010; Gómez-Talegón, Fierro, Del Río, & Álvarez, 2011).

9.4 Illicit drugs

When it comes to illicit drugs the situation is completely different for THC and stimulants. THC shows a prevalence of 1.37% in Europe which is about 1/3 of the alcohol prevalence rate and about the same prevalence rate as all screened medicines together. The risk of impairment caused by different THC concentrations is difficult to assess. Nonetheless the epidemiological, the experimental and the meta-analytical approach result in rather low risk estimations of 2.4-fold risk at maximum for an injury. So THC seems to be much less impairing and risky than most of the other examined substances. Although the relationship between concentration and injury risk was difficult to proof in epidemiology it is pharmacologically evident and obvious in the meta-analysis. In Meta-analysis a serum concentration of 3.8 ng/ml THC proofs as equivalently impairing as 0.5 g/L alcohol. This value might be the bases for a threshold discussion. When transferring this value of equivalence into a threshold, information about measurement reliability and confidence intervals should be kept in mind (for details see Verstraete et al., 2011). So from the scientific point of view a zero-tolerance for cannabis cannot be justified by the related traffic risk if the legislative countermeasures for psychoactive drugs including alcohol are to be based on the same risk assessment. This is a strong argument for achieving the compliance of the population (Krismann & Schöch, 2010).

As we know from (Walter, Hargutt, & Krueger, 2011a):

“Many users say they would appreciate a threshold for driving under the influence of cannabis. Controls as well – although to a lower degree – support a threshold for cannabis. The most frequently specified reasons were the long traceability of the

substance in body fluids and a feeling of injustice compared to persons who drink and drive. Pfeifer and Hautzinger (2001; cited by Gelau & Pfafferott, 2009) suggest that the severity of sanctions should reflect the severity of the offence. If users do not think it is more severe to drive under the influence of cannabis than under the influence of alcohol, a higher penalty for drug offences will not be accepted and the willingness to obey the law will be restricted."

The prevalence of stimulants is estimated in DRUID to approximately 0.5% in Europe (amphetamines 0.08%, cocaine 0.42%) – much lower than the prevalence of most other substances. The situation concerning risk is perhaps the most difficult one for stimulants. On the one hand there exists the European estimation of an 8-fold risk for injury and a 25-fold risk for a fatality. Especially the risk for injury is based on a very low number of cases and controls and therefore prone to biases, so that 2 out of 3 merging methods did not come to a common estimation. On the other hand culpability studies show only a minor elevated risk for amphetamines (1.54, French culpability study). To make the situation even more complicated absolutely no impairing effects of stimulants could be proofed in the DRUID experiments or by evaluating former studies by means of meta-analysis. Stimulants even seem to compensate for the impairing effects of low alcohol concentrations to a minor degree in real driving studies (Ramaekers et al., 2010).

Consequently there can be no doubt, that in experimental settings stimulants are not under suspicion of decreasing driving relevant performance. Trusting the epidemiological risk one must assume other factors are mediating the risk of being injured or killed in real traffic. Different explanations are possible:

First the **doses** and therefore concentrations examined in the DRUID experiments were rather low (due to ethical reasons). Unfortunately case numbers were too small to perform a concentration based analysis with epidemiological data. But it might be the case that concentrations in traffic are much higher than the concentrations realized in experiments, explaining a higher injury risk in real traffic. The doses of 25 to 100mg MDMA in the two respective DRUID experiments (J. Ramaekers et al., 2010) results in plasma concentrations of about 100-250 ng/ml. In the control sample of the epidemiological studies blood samples were only available for BE, IT and NL. From there 12 controls were positive for MDMA, 7 of them in combination with other substances (2 with cocaine, 1 with THC, 1 with cocaine and THC, 1 with cannabis and illicit opiates, 1 with medicinal opioids, 1 with alcohol and cannabis). The blood concentration range was for 10 of the 12 (combinations included) also from 30 to 250 ng/ml and one with 327 ng/ml and one with 745 ng/ml. So the concentrations of MDMA examined in the experimental studies do not differ too much from the concentrations in controls. In the injured and killed cases only 4 were positive for MDMA (from all countries) respectively, making reliable statements difficult. Thus the hypothesis of very different dosages in experiments and in controls on the road seems not to be the whole truth.

Second there might be some kind of **interaction between the substance and the situations** which are actively looked for by users under the influence of stimulants. Stimulants are stimulating, probably increasing the affinity to action, fun, speed, risky behavior etc. In a highly controlled experimental setting these substance effects are hard to quantify because the subjects must have some degrees of freedom concerning their behavior, which is not really compatible with most experimental designs, especially in real driving. In DRUID a gap acceptance test was implemented

to measure these effects but for some reasons it was not very sensitive. So it remains speculation if these factors are responsible for a probable risk in real traffic.

Third the probably increased risk in traffic is due to sleep deprivation after long waking periods. In DRUID experiments it could be shown

"…that sleep deprivation produced severe impairment in actual driving performance as expressed by a significant rise in SDLP and a large number prematurely terminated driving tests during early morning sessions. In general, MDMA did not affect actual driving performance and did not interact with the effects of sleep deprivation" (Ramaekers et al., 2010).

Looking at the respective risks (see chapter 8.4.4.2) combinations of MDMA and sleep deprivation is still worse than the reference of 0.5 g/L alcohol whereas MDMA alone is always much better than the reference. So driving after one night of sleep loss and 6-8 hours after MDMA consumption seems to be very critical. Consequently the question arises, how many stimulant users drive after the stimulating effects of MDMA has fade away (approx. 6 hours after MDMA intake) but without sleeping in between. To answer this question the data of the German Smartphone Survey (Walter et al., 2011b) could be used, in which daily protocols of substance users exist. For the category stimulants the following half life periods were set: amphetamine: 16 hours, MDMA: 20 hours, cocaine: 2 hours (Schulz & Schmoldt, 2003). Using these thresholds for substance positive drives the time-lag between substance consumption and driving was inspected, separated for subjects who slept between consumption and driving and those who did not (Figure 52).

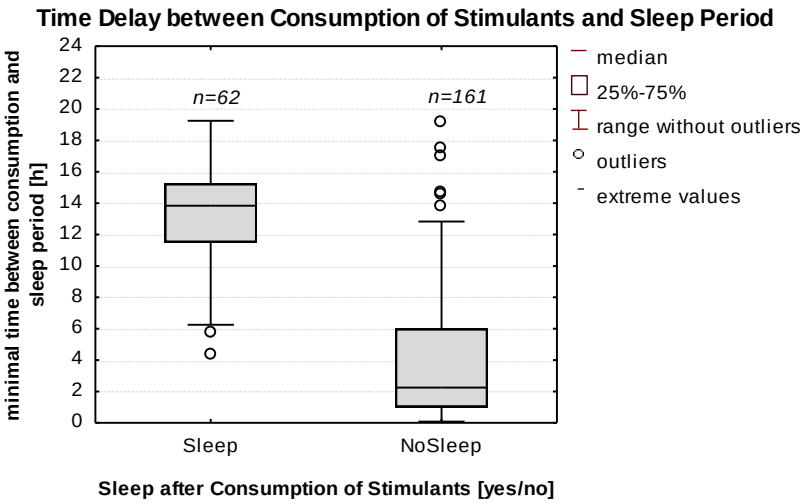


Figure 52: Distribution of the time-lag between substance intake and driving separated for subjects who slept in between and those who did not.

	N	%	Mean	KI-95	KI+95	Median	Perz25	Perz75
NoSleep	161	72,2%	3,96	3,34	4,58	2,25	1	6
Sleep	62	27,8%	13,35	12,58	14,11	13,83	11,5	15,25

Obviously about 30% of the substance positive drives within the German sample drive after sleeping and are not as problematic as the rest. Approximately 72% of the stimulant positive drives occur without sleep between substance intake and the drive, but with a mean time-lag of about 4 hours. 50% of these drives were done within 2 hours after consumption, 75% within 6 hours. So most of these drives happen rather

short after substance intake and therefore while the stimulating effect is still present. Thus the most dangerous situation in this context – that a person is awake the whole night, suffers from sleep deprivation and takes part in traffic a long period after consumption (i.e. after the stimulating effects of stimulants had fade away) – seems not to be the rule, at least on German roads.

9.5 Combinations

The topic of combinations of different substances could also only be answered very crudely due to the low number of cases and/or controls. Nonetheless epidemiology comes to fairly trustworthy estimations for Europe with prevalence rates of about 0.4% for alcohol-drug and also for drug-drug combinations. The risks are figured with 4-35 for drug-drug combinations and 28-32 for alcohol-drug combinations. So both kinds of combinations seem to lead to much higher risks than any substance alone, except high alcohol dosages.

9.6 Summary

Figure 53 illustrates the “position” of each substance with respect to prevalence and injury risk[49]. The three substance categories, which are connected with extreme high risks (OR>10), are the two high alcohol concentrations (0.8-1.2 and > 1.2 g/L) and the combination of alcohol and drugs, all of them presenting with moderate prevalence rates of about 0.4%. In the risk range from a 5- to 10-fold injury alcohol including all concentrations is dominant with a prevalence rate of 3.5%. Moreover the epidemiological doubtful risk of amphetamines, medicinal opioids/opiates and drug-drug combinations are also in this range, but showing much lower prevalence rates (for amphetamines 0.08%) and therefore less demand for action. The group of illicit opiates, z-drugs and cocaine shows risks between 2-3 and prevalence rates lower than 0.5%.

Alcohol with concentrations between 0.5-0.8 g/L, benzodiazepines and THC show all prevalence rates higher than 0.5% which would call for action from this point of view. However, epidemiological risks of benzodiazepines (OR=3) and THC (OR=2) are smaller than the risk for alcohol concentrations, which are comparable to the legal limit in most of the European countries. Additionally it is important to remember that the group of benzodiazepines consists of a huge amount of substances which result in very different impairment levels depending on the actual concentration. For THC the relationship between concentration and injury risk might be biased by methodological artifacts. Last but not least no elevated risk could be proofed for low alcohol concentrations (0.1-0.5 g/L) and amphetamines as shown in the experimental studies and the meta-analysis.

[49] For this illustration and further discussion injury risk is preferred instead of fatality risk because of more reliable data.

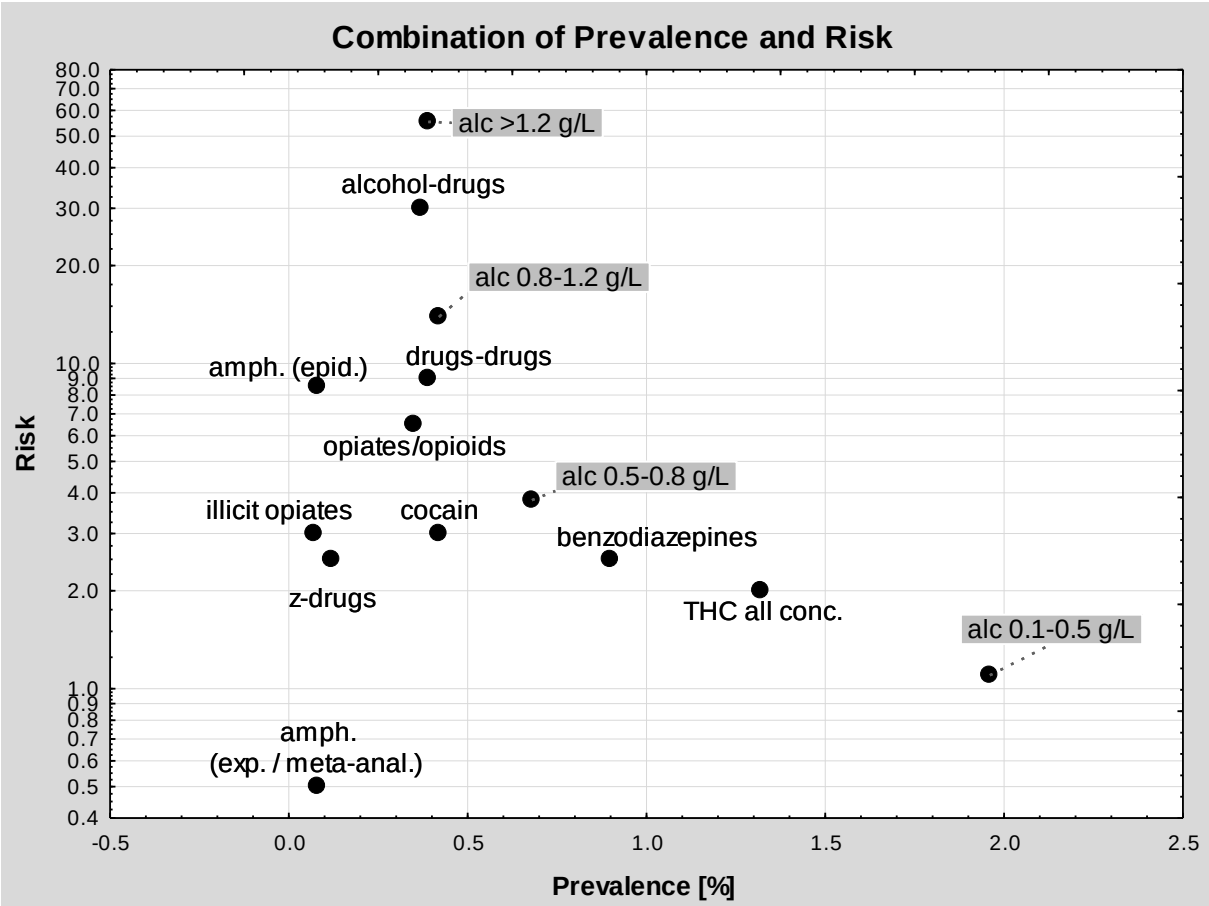


Figure 53: Illustration of prevalence and risk (logarithmic scaling) for the DRUID substance categories.

So from the perspective of traffic safety – especially looking at prevalence rates and risks - the following statements can be done:

- Alcohol, especially in high concentrations must remain focus number one.
- The combination of alcohol and drugs or medicines seems to be a topic, which should be addressed more intensively because it leads to very high risks in traffic.
- The problems of medicines in traffic should be addressed by information of doctors and patients, not by defining thresholds (see Gómez-Talegón et al., 2011).
- THC and amphetamines are a minor risk factor from a scientific point of view.
- More research is needed to investigate probable risks of amphetamines in real traffic and the mediating factors.
- From the perspective of risk, sleep deprivation should also be addressed as a high accident risk factor.

10 REFERENCES

Amoros, E., Gadegbeku, B., & Laumon, B. (2010). Prevalence study: Main illicit psychoactive substances among all drivers involved in fatal road crashes in France. EU Project DRUID, WP 2, Deliverable 2.2.4.

Augsburger, M., Donzè, N., Mènètrey, A., Brossard, C., Sporkert, F., Giroud, C. (2005). Concentration of drugs in blood of suspected impaired drivers. *Forensic Science International, 153*, 11-15.

Berghaus, G. (1997). *Arzneimittel und Fahrtüchtigkeit. Metaanalyse experimenteller Studien*. unpublished report. Bundesanstalt für Straßenwesen.

Berghaus, G. (2007). Kombinierte Einnahme von (psychotropen) Substanzen und Fahrsicherheit. In B. Madea, F. Mußhoff & G. Berghaus (Eds.), *Verkehrs-medizin* (pp. 562-578). Köln: Deutscher Ärzteverlag.

Berghaus, G., Schulz, E., & Szegedi, A. (1998). Cannabis und Fahrtüchtigkeit. Ergebnisse der experimentellen Forschung. In G. Berghaus & H.-P. Krüger (Eds.), *Cannabis im Straßenverkehr* (pp. 73-98). Stuttgart: Fischer.

Berghaus, G., Sticht, G., Grellner, W., Lenz, D., Naumann, T., & Wiesenmüller, S. (2010). Meta-analysis of empirical studies concerning the effects of medicines and illegal drugs including pharmacokinetics on safe driving. EU Project DRUID, WP 1, Deliverable 1.1.2b.

Bernhoft, I. M., Assum, T., Frison, G., Hels, T., Houwing, S., & Mathijssen, M. (2007). Working paper “Uniform design and protocols for carrying out case-control studies” EU Project DRUID, WP 2, Deliverable 2.1.2.

Biecheler, M.-B., Gadegbeku, B., & Amoros, E. (2007). Working paper: Cannabis, driving and road safety: a review of the scientific literature. EU Project DRUID, WP 2, Deliverable 2.1.3.

Blomberg, R. D., Peck, R. C., Moskowitz, H., Burns, M., & Fiorentino, D. (2005). *Crash Risk of Alcohol Induced Driving*. Dunlap and Associates Inc.

Borkenstein, R. F., Crowther, R. F., Shumate, R. P., W.B., Z., & Zylman, R. (1974). The role of the drinking driver in traffic accidents (The Grand Rapids Study). *Blutalkohol, 11* (Supplement 1).

Brookhuis, K. A., & de Waard, D. (1993). The use of psychophysiology to assess driver status. *Ergonomics, 36*(9), 1099-1110.

Drummer, O. H. (1994). Drugs in Drivers Killed in Australian Road Traffic Accidents. The Use of Responsibility Analysis to Investigate the Contribution of Drugs to Fatal Accidents. 0594.

Drummer, O. H. (2004). Postmortem toxicology of drugs of abuse. *Forensic Science International, 142*(2-3), 101-113.

Federal-Motor-Transport-Authority. (2004). Jahresbericht 2004.

Federal-Motor-Transport-Authority. (2009). Jahresbericht 2009.

Follmer, R., Gruschwitz, D., Jesske, B., Quandt, S., Lenz, B., Nobis, C. (2008). MID 2008 - Mobilität in Deutschland - Ergebnisbericht: Struktur – Aufkommen – Emissionen – Trends. FE-Nr. 70.801/2006.

Gadegbeku, B., Amoros, E., & Laumon, B. (2010). Responsibility study: Main illicit psychoactive substances among car drivers involved in fatal road crashes in France. EU Project DRUID, WP 2, Deliverable 2.3.2.

Gelau, C., & Pfafferott, I. (2009). Verhaltensbeeinflussung durch Sicherheitskommunikation und Verkehrsüberwachung. In H.-P. Krüger (Ed.), *Enzyklopädie der Psychologie - Verkehrspsychologie* (Vol. 2, pp. 81-126). Göttingen: Hogrefe.

Gjerde, H., & Verstraete, A. (2010). Can the prevalence of high blood drug concentrations in a population be estimated by analysing oral fluid? A study of tetrahydrocannabinol and amphetamine. *Forensic Science International, 195*(1-3), 153-159.

Gómez-Talegón, T., Fierro, I., Del Río, M. C., & Álvarez, J. F. (2011). Establishment of framework for classification/categorisation and labelling of medicinal drugs and driving. EU Project DRUID, WP 1, Deliverable 4.3.1.

Grotenhermen, F., Leson, G., Berghaus, G., Drummer, O. H., Krüger, H.-P., Longo, M. (2005). Developing Science-Based Per Se Limits for Driving under the Influence of Cannabis (DUIC) - Findings and Recommendations by an Expert Panel.

Hels, T., Bernhoft, I. M., Lyckegaard, A., Houwing, S., Houtenbos, M., Mathijssen, R. (2011). Risk of injury by driving with alcohol and other drugs. EU Project DRUID, WP 2, Deliverable 2.3.5.

Holmgren, P., Holmgren, A., & Ahlner, J. (2005). Alcohol and drugs in drivers fatally injured in traffic accidents in Sweden during the years 2000-2002. *Forensic Science International, 151*, 11-17.

Houwing, S., Hagenzieker, M., Mathijssen, R., Bernhoft, I. M., Hels, T., Janstrup, K. (2011). Prevalence of alcohol and other psychoactive substances in drivers in general traffic Part II: Country reports. EU Project DRUID, WP 2, Deliverable 2.2.3.

Houwing, S., Hagenzieker, M., Mathijssen, R., Bernhoft, I. M., Hels, T., & Kira, J. (2011). Prevalence of alcohol and other psychoactive substances in drivers in general traffic Part I: General results. EU Project DRUID, WP 2, Deliverable 2.2.3.

Isalberti, C., Van der Linden, T., Legrand, S.-A., Verstraete, A., Bernhoft, I. M., Hels, T. (2011). Prevalence of alcohol and other psychoactive substances in injured and killed drivers EU Project DRUID, WP 2, Deliverable 2.2.5.

Kauert, G. F., Ramaekers, J. G., Schneider, E., Moeller, M. R., & Toennes, S. W. (2007). Pharmacokinetic properties of delta9-tetrahydrocannabinol in serum and oral fluid. *Journal of Analytical Toxicology, 31*(5), 288-293.

Kraus, L., Pfeiffer-Gerschel, T., & Pabst, A. (2006). Cannabis und andere iIllegale Drogen: Prävalenz, Konsummuster und Trends. Ergebnisse des Epidemiologischen Suchtsurveys 2006. *Sucht, 54*(S1), 16-25.

Krismann, M., & Schöch, K.-H. (2010). Evaluation of Legal Measures to Combat DUI/DUID. Del. 1.4.1.

Krüger, H.-P., Hargutt, V., & Brookhuis, K. (2008). Theoretical Framework for Substance Effects on Safe Driving. EU Project DRUID, WP 1, Deliverable 1.1.1.

Krüger, H.-P., Schulz, E., & Magerl, H. (1996). Medikamenten- und Drogennachweis bei verkehrsunauffälligen Fahrern - Roadside Survey. Berichte der Bundesanstalt für Straßenwesen (27/96).

Krüger, H. P., Kazenwadel, J., & Vollrath, M. (1995). Accident risk in driving under the influence under special consideration of risk-increasing factors. In H.-P. Krüger (Ed.), *Das Unfallrisiko unter Alkohol. Analyse, Konsequenzen, Massnahmen* (pp. 1-113). Suttgart: Gustav Fischer Verlag.

Laapotti, S., & Keskinen, E. (2009). Relative risk of impaired drivers who were killed in motor vehicle accidents in Finland. EU Project DRUID, WP 2, Deliverable 2.3.3.

Lamers, C. T. J., Ramaekers, J. G., Muntjewerff, N. D., Sikkema, K. L., Samyn, N., Read, N. L. (2003). Dissociable effects of a single dose ecstasy (MDMA) on psychomotor skills and attentional performance. *Journal of Psychopharmacology, 17*(4), 379-387.

Madea, B., & Dettmeyer, R. (2007). *Basiswissen Rechtsmedizin*. Heidelberg: Springer.

Morland, J., & Strand, M. (2010). Psychomotor relevant performance: 1. After single dose administration of opioids, narcoanalgesics and hallucinogens to drug naïve subjects 2. In patients treated chronically with morphine or methadone / buprenorphine. EU Project DRUID, WP 1, Deliverable 1.1.2c.

O'Hanlon, J. F., Haak, T. W., Blaauw, G. J., & Riemersma, J. B. (1982). Diazepam impairs lateral position control in highway driving. *Science, 217*, 79-81.

Passie, T., Seifert, J., Schneider, U., & Emrich, H. M. (2002). The pharmacology of psilocybin. *Addiction Biology, 7*(4), 357-364.

Prisinzano, T. E. (2005). Psychopharmacology of the hallucinogenic sage Salvia divinorum. *Life Sciences, 78*(5), 527-531.

Ramaekers, J. (2011). Driving performance of medicated and unmedicated patients with sleep/anxiety disorders. EU Project DRUID, WP 1, Deliverable 1.2.2.

Ramaekers, J., Bosker, W., Kuypers, K., Simons, R., Martens, M., Hjälmdahl, M. (2010). Effects of stimulant drugs on actual and simulated driving. EU Project DRUID, WP 1, Deliverable 1.2.1.

Ramaekers, J. G., & O'Hanlon, J. F. (1994). Acrivastine, terfenadine and diphenhydramine effects on driving performance as a function of dose and time after dosing. *European Journal of Pharmacology, 47*, 261-266.

Ravera, S., & de Gier, J. J. (2010). Relative accident risk of patients using psychotropic medicines in the Netherlands: A pharmacoepidemiological study. EU Project DRUID, WP 2, Deliverable 2.3.1.

Schnabel, E., Hargutt, V., & Krueger, H. P. (2010). Meta-analysis of empirical studies concerning the effects of alcohol on safe driving EU Project DRUID, WP 1, Deliverable 1.1.2a.

Schulz, E., Vollrath, M., Klimesch, C., & Szegedi, A. (1997). Fahruntüchtigkeit durch Cannabis, Amphetamine und Cocain. Berichte der Bundesanstalt für Straßenwesen: Mensch und Sicherheit (81). Wirtschaftsverlag.

Schulz, M., & Schmoldt, A. (2003). Therapeutic and toxic blood concentrations of more than 800 drugs and other xenobiotics. *Pharmazie, 58*(7), 447-474.

Thorsteinsdóttir, K., Mühlhäußer, J., Paul, L., Lottner, S., Schick, S., & Hell, W. (2011). Responsibility study: Psychoactive substances among killed drivers in Germany, Lithuania, Hungary and Slovakia. EU Project DRUID, WP 2, Deliverable 2.3.4.

Verstraete, A., Knoche, A., Jantos, R., Skopp, G., Gjerde, H., Vindenes, V. (2011). *Per se limits - Methods of defining cut-off values for zero tolerance*. EU Project DRUID, WP 1, Deliverable 1.4.2.

Vorndran, I. (2009). Unfallentwicklung auf deutschen Straßen 2008. Statistisches Bundesamt Deutschland. *Wirtschaft und Statistik 7/2009*. Wiesbaden

Walter, M., Hargutt, V., & Krueger, H. P. (2011a). German Smartphone Survey - Part II: Person-related characteristics of drug users and drug drivers compared to controls. EU Project DRUID, WP 2, Deliverable 2.2.2b.

Walter, M., Hargutt, V., & Krueger, H. P. (2011b). German Smartphone Survey - Part I: Prevalence of psychoactive substances and consumption patterns in traffic, based on a smartphone survey in Germany. EU Project DRUID, WP 2, Deliverable 2.2.2.

Widmark, E. M. (1932). *Die theoretischen Grundlagen und die praktische Verwendbarkeit der gerichtlich-medizinischen Alkoholbestimmung*. Berlin: Urban & Schwarzenberg.

Wille, S. M. R., Raes, E., Lillsunde, P., Gunnar, T., Laloup, M., Samyn, N. (2009). Relationship between oral fluid and blood concentrations of drugs of abuse in drivers suspected of driving under the influence of drugs. *Therapeutic Drug Monitoring, 31*(4), 511-519.