Risk estimations based on data from experimental studies, epidemiological studies and meta-analysis on driving under the influence

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Abstract

Background
Psychoactive substances are still a major reason for a large portion of heavy accidents. Nonetheless, large scale studies for assessing prevalence and risk particularly of illicit drugs and medicines in Europe are missing.

Aims
One important aim of DRUID was to gain new insights into the real degree of impairment caused by psychoactive drugs and to give recommendation of thresholds for psychoactive substances in traffic based on the different data pools within DRUID.

Methods
In DRUID, three different methodologies were applied in order to estimate traffic risk for driving under the influence of alcohol, drugs and medicines. (1) Meta-analyses of experimental studies on the impairing impact of alcohol, illicit drugs and medicines on driving-relevant performance indicators. (2) Experimental studies on the impairing potential of additional substances and of their combination with alcohol or sleep deprivation. (3) Epidemiological studies to quantify the prevalence and risk of different substances by roadside and hospital studies. Unfortunately, all three approaches lead to different parameters describing impairment or risk in an incomparable way. Within DRUID a method was developed to compare these different estimations, at least for alcohol, for which all three sources of information are available.

Results
It is shown that risk measures for different alcohol concentrations calculated from meta-analysis and experiments are in line with epidemiological risk for specific alcohol levels and comparable with former epidemiological risk studies for alcohol. Therefore it can be assumed that odds ratios calculated from meta-analysis and experiment are a fair estimation of epidemiological risk.

Impairing effects of stimulants could not be verified – neither in the experiments nor in meta-analysis. According to experiments and meta-analysis, a THC serum concentration of about 4 ng/ml shows similar impairment as 0.5 g/L alcohol. According to the meta-analysis the risk for medicines varies of course considerably for different substances even within one substance class and for different doses and concentrations.

Discussion and conclusions
The risk in traffic is inherently defined by a combination of the risk of a specific substance and its prevalence in traffic. Regarding this, alcohol is still by far the most risky substance in traffic in Europe.
Introduction

One major objective of DRUID was 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 paper.

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.

Different Methods for different data pools

Epidemiology

The most relevant information in order to determine thresholds is the information about the accident risk in traffic dependent on different substance concentrations. Direct information about the accident risk in traffic can only be gained by conducting epidemiological studies. Thus the most important data pool for estimating the risk of psychoactive substance use in traffic is based on roadside and hospital studies in DRUID. Risk calculations were done mainly as according to the usual practice by combining prevalence information (DRUID D 2.2.3 Part I & II) and accident information (DRUID D 2.2.5 and DRUID D 2.3.5). For the purpose of comparison with the other data pools, odds ratios were additionally calculated against the reference risk of BAC 0.05 g/L.

Experimental data

In order to make information from the experiments comparable to the risk measures of epidemiological data, two steps were necessary: First, the establishment of a reference risk which was set at a BAC of 0.05g/L. Consequently in every experimental setting a 0.05 g/L BAC condition was added to the other experimental conditions. Second, a pragmatic way of calculating odds ratios from experimental data was developed by treating drivers in the tested substance condition with a driving performance worse than the 0.05 g/L BAC reference as “accident” and drivers with a driving performance better than the 0.05 g/L BAC reference as “non-accident”. For methodological details see DRUID D 1.1.1.

Meta-analytical data

Because prevalence rates of most of the substances (especially by differentiating concentrations) are by far too low in free traffic to estimate epidemiological risk, a further data pool was used to provide additional information. Over the last decades a huge amount of studies was published looking at the effects of different medicines and drugs on performance measures. Thus a meta-analytical approach is used. First a reference function between concentration and impairment was established by a meta-analysis of alcohol (DRUID D 1.1.2a). Second a meta-analysis was done for medicines and illegal drugs and (DRUID D 1.1.2b). Again for the purpose of comparison, risk measures were calculated from these single findings in all of the published studies by treating significant results as “accidents” and non-significant results as “non-accidents”. Certainly most of the studies report effects at different dosages. As the same dosage leads to different effects on performance in the course
of time, the given dosage information was converted in a concentration information by establishing a time-dependent transfer-function.

**Results: The risk of substances**

**Alcohol**

In order to get an impression of the trustworthiness of the calculated risks, the alcohol related risk measures of all data pools were compared with the well-established risk functions from former epidemiological studies (Borkenstein, Crowther, Shumate, 1974; Blomberg, Peck, Moskowitz, Burns, & Fiorentino, 2005; Krüger, Kazenwadel & Vollrath, 1995), which were also related to the 0.05 g/L BAC level (see figure 1).

![Comparison of Different Risk Calculations](image)

**Figure 1: Comparison of different risk calculations (black/grey line: geometric mean of the risks (black: involvement; grey: responsibility) of Blomberg et al. (2005); Borkenstein et al. (1974) & Krüger et al. (1995); blue 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 1 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 established 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.

**Illicit Drugs (THC)**

When it comes to cannabis the prevalence rates in the general driving population vary between 0.1 % (DRUID D 2.2.2) and 3.3 % (estimation from the control group of a culpability study in France: DRUID D 2.2.4) with a mean European estimation of 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 mainly vary between 1 and 2, regardless of being injured, being killed or being culpable for a fatal accident. Even analyzing different THC concentrations the risk for an injury is between 1 and 3, even for concentrations above 5 ng/ml serum. Trusting the risks from the meta-analytical approach the risk is “only” 2-fold up to concentrations of 10 ng/ml serum 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.

**Medicines**

In experiments alprazolam (0.5 mg) was related to a significant decrease of driving performance. Epidemiology reveals a low risk for injury (1.5-3) and a higher risk for a fatality (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 (about 5). But 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 odds ratios are only a very crude estimation of the real risk and therefore have to be interpreted with care. The following substance concentrations show the highest risks with an odds ratio higher than 5 as compared to the 0.5 g/L alcohol reference: Promethazin > 6 ng/ml, alprazolam > 9 ng/ml, diazepam > 600 ng/ml, lorazepam > 10 ng/ml, meprobamate > 40000 ng/ml, triazolam > 7 ng/ml and flunitrazepam > 9 ng/ml.

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.

**Alcohol equivalents**

A further objective mainly of the meta-analytical approach was to determine substance concentrations which show comparable impairing effects as 0.05 g/L alcohol. Although from a legal point of view an impairment approach makes only limited sense for legal medicines, risk thresholds in traffic are often discussed for illegal drugs (especially for THC). Based on DRUID data 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.
Discussion and conclusion

Figure 2 illustrates the “position” of each substance with respect to prevalence and injury risk\(^1\). 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%.

![Combination of Prevalence and Risk](image)

**Figure 2: 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 risk at the same time - 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.
- 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.

\(^1\) For this illustration and further discussion injury risk is preferred instead of fatality risk because of more reliable data.
References


