

Per se limits – recommendations for defining cut-off values for psychoactive substance use in traffic

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Abstract

Background

Legislative regulations and enforcement practices for combating driving under influence (DUI) of alcohol are clearly defined. Per se limits are based on blood levels of alcohol correlating with increased accident risk. Research for defining risk of DUI of other psychoactive substances (DUID) is still partly insufficient. In order to facilitate legal practices, laws against DUID are currently based on zero tolerance. In fact, drivers are considered being “impaired” if any amount of a listed drug is detected in their blood. Due to technical improvements the detection of small traces of substances is meanwhile possible since a long time after actual drug consumption, although impairment is no longer to be expected due to metabolism and elimination.

Aims

The DRUID expert consensus established recommendations on how to define limits for psychoactive substance use in traffic.

Methods

The European DRUID project established a group of experts who are members of national working groups for defining analytical and/or risk thresholds. This group evaluated the results of DRUID, scientific literature and the experience of representatives of several EU Member States and Norway in determining cut-off levels.

Results

- Cut-offs should be defined for the most frequently used psychoactive substances
- In order to achieve compliance of the population towards cut-off regulations, they should be clear and comprehensible, pointing out the risks when used in traffic
- Thus, the definition of cut-offs should be based on current scientific knowledge
- The lowest substance concentration exerting an effect on driving should be preferred instead of the lowest limit of quantification/ detection
- For all psychoactive substances including alcohol, the same risk should be accepted

Discussion

When a country intends to determine per se cut-off levels, several considerations have to be taken into account. From a scientific point of view, the same risk should be anticipated for all psychoactive substances including alcohol. Nevertheless, every cut-off discussion should address the question if the DRUID approach, to determine risk thresholds equivalent to alcohol limits, is feasible for the respective case.

Introduction

The general conclusions of the Pompidou Group stated that “The law enforcement and judicial authorities should have clear legislative and regulatory provisions, in line with which they can prosecute and convict individuals driving a vehicle whilst under the influence of psychoactive substances” (Pompidou Group , 2004, p. 379).

In case of combating DUI of alcohol, legislative regulations and enforcement practices are clearly defined. So far, per se limits for alcohol are based on scientific research evaluating potential risks associated to alcohol consumption. A clear correlation between alcohol consumption, blood concentrations and the score of driving impairment has been proven since several years. However, up to now, defining exact limits for combating DUID still comprises a lot of challenges.

In the following, the recommendations of the DRUID expert group for the definition of per se limits for psychoactive substances (DRUID Deliverable D 1.4.2, 2011) are outlined and the DRUID risk research results are presented to exemplify the determination of a THC cut-off.

Determination of psychoactive substance cut-offs

Which drugs have to be chosen?

The list of psychoactive substances to be included in per se legislation shall embrace the substances most frequently found in the driving population and/or in drivers involved in an accident. Regulations for illegal drugs should be applied to the misuse of medicinal drugs as well.

How to deal with legal prescribed medicines?

For many legally prescribed drugs, an effect on driving ability has been proven. A clear distinction must be made with respect to chronic use and intermittent or even single use. In experimental studies, dosage effects were only investigated and observed with single users or new users. The reason for enrolling naive users in these experimental studies is the clear correlation between intake dose, systemic exposure and impairment in driving ability. It is not reasonable to define cut-off values for patients in long-term treatment due to adaptive metabolic changes often observed after chronic use. In this case, higher doses are prescribed due to decreasing efficacy. In parallel, patient are more and more used to compensate side effects like dizziness, headache and other side effects. In conclusion, the correlation between dosage and impairment can be best examined at an intra-individual level. Hence, an individual impairment check is an objective way to determine dose- response correlation and potential risks associated to drug use.

For legally prescribed drugs, the interaction with alcohol is also an important factor. Alcohol interacts with many medicines in an unfavourable way and thereby increases impairment. Hence, a careful evaluation of potential drug-alcohol interaction and respective recommendations should be part of the physician’s consultation.

Should metabolites be included?

In most cases, per se legislation will be limited to the parent drugs and/or active metabolites. In this case, a clear correlation of dose intake, systemic exposure, and driving impairment needs to be the basis for determination of cut-offs. However, in some cases, it is necessary to take into account metabolites, e.g. when the parent drug is unstable and is metabolised very rapidly. The inclusion or exclusion of metabolites will depend on the choice of matrix, storage conditions and preservatives added in the sampling tubes. Further on, it may also be useful to detect metabolites, not because they are included in the per se legislation, but because they increase the level of certainty of the toxicological determination.

Which cut offs are applicable to be implemented in legal regulations?

So far three different classes of substance cut-offs have been established. To determine which cut-off level shall be applied when implementing into the legislation, the scientific rationale should be clear.

- “Risk thresholds”: Concentrations in blood that indicate impairment or a certain accident risk (e.g. 0.5 g/L BAC).
- “Lower effect limits”: The lowest concentration with an effect on driving (e.g. 0.2 g/L BAC).
- “Limit of detection” (LOD) and “Limit of quantification” (LOQ): Concentration that guarantees a valid and reliable analytical result due to technical limitations of measurements.

At the moment European countries which implemented zero tolerance regulation use usually the LOQ as cut-off. However, it is difficult to achieve the compliance of the driving population to legal regulations if cut-offs are implemented that do not indicate the point where driving impairment starts. Especially if, substance intake was too long ago that it affects driving. Thus, for combating DUID, the implementation of “risk thresholds” and “lower effect limits” are adequate.

Which empirical data should be used for defining cut-offs?

Cut-off values for psychoactive substances can only be established by considering risk assessment based on empirical science. The most relevant information for the determination of cut-offs is the increased accident risk related to a quantified substance concentration in blood. Therefore, epidemiological studies have to be conducted, but representative studies comparing prevalence in accident-free and accident-involved populations are difficult and expensive. Especially for substances with low exposure rates in the population, a huge sample needs to be examined in order to get reliable estimations. Thus, for most of the substances, either legal or illegal, epidemiological data necessary for calculating risk indices are incomplete or even missing. This leads to substantial problems for the estimation of risks. In these cases experimental data should fill the knowledge gaps.

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

- use epidemiological data on the accident risk of different single substance concentrations. If this data is not sufficient,
- use experimental data. If this data is not sufficient,

- let national expert rounds determine cut-offs by using additional information (e.g. pharmacokinetic drug profiles, consumption behaviour). If this information is not sufficient,
- use the LOQ (the advantage is that new drugs may easily be implemented into the list of impairing substances).

For the comparison and integration of study outcomes, resulting from different methodologies (case-control or responsibility studies, experiments in simulator or on-road), a reference curve is helpful. As stated in the “Guidelines for Drugged Driving Research” (Walsh et al. 2008, p.1263), in DRUID, alcohol data delivered through these different study methodologies have been used as the gold standard (DRUID Deliverable D1.3.1, 2011). Thus, to determine risk thresholds for illicit drugs, DRUID partners intended to find a concentration in blood at which the accident risk or, in experimental studies, the impairment of driving or performing abilities are equivalent to that associated with 0.5g/L BAC. This approach starts from the premise that alcohol impaired driving is tolerated up to a BAC of 0.5g/L in most European countries. This accepted risk should be applied to define drug cut-offs as well. Hence, for the cut-off definition it is recommended:

- to use alcohol data as reference (Guidelines for Drugged Driving Research, recommendation B2)
- to use blood as specimen (Guidelines for Drugged Driving Research, recommendation B21)

How to deal with combined drug consumption?

The epidemiological studies performed by DRUID have shown that people often use more than one psychoactive substance and that the combination of alcohol and drugs, or the combination of more than one drug, increases the accident-risk exponentially. If one applies the cut-offs defined for a single drug to a combined use as well, one would anticipate an increased accident risk. In these cases of uncertainty, it is recommended to use the LOQ instead of the per se limits “risk threshold” or “lower limit of effect”.

Legal regulations

The cut-offs of psychoactive substances should go in line with the alcohol cut-offs and their legal regulations. The list of drugs in per se legislation can even be limited to a few substances, if per se law is combined with an impairment law that covers all other impairing substances. Moreover, with regard to new drugs, it might take some time before different cut-offs have been established.

Driving ability after acute drug effects

“Post acute effects” are impairing effects not caused by the drug itself, but caused by the symptoms of “hang over”. These will be excluded for the determination of cut-offs. This is similar with the procedure of determining the alcohol limit. If impairment would be measured the next morning after having consumed large quantities of alcohol, impaired performance could be detected below a BAC of 0.5 g/L. For alcohol, its presence in blood or breath is required for sanctioning. This may be the same for all illegal drugs, despite the fact that many substances afterwards cause deterioration as well (post-acute phase).

DRUID results for cut-off determination of THC

In the following these general recommendations for the establishment of cut offs will be used for the definition of a THC cut-off based on the DRUID results

In the DRUID project the relative risk for a driver being seriously injured in an accident due to substance use was calculated by comparing the number of accident free drivers (with and without substance use) with drivers being seriously injured (with and without substance use). The relative risk of a driver being killed in an accident was calculated in the same way. However, although more than 50.000 drivers participated, the prevalence of drivers' drug consumption was too small to calculate the accident risk for different drug concentrations other than alcohol. In case of THC consumption, independent of its concentration in the drivers' blood, the relative risk estimates, varied between countries to a high degree. However, based on data from all countries, the relative risk of getting seriously injured or being killed while positive for cannabis were not significantly above 1 with a risk of getting seriously injured of 1.38 (CI: 0.88-2.17) and the risk of being killed of 1.33 (CI: 0.48-3.67).

Only for the DRUID responsibility study which included 7.455 drivers, it was possible to split the results in three THC concentration levels. The highest "level" of a nearly 3-fold culpable accident involvement (OR: 2.84, CI 1.44-5.60) was found with a THC value between 3-5 ng/ml in whole blood. This goes in line with findings of other responsibility studies as well as with the literature findings for case control studies (DRUID Deliverable D2.1.3, 2011).

As no quantifiable relationship between THC concentration and accident risk was found in the epidemiological studies, it was only possible to set an exact THC cut-off by a meta-analysis of experimental studies. It was found that the serum concentration of 3.8ng/mL THC (\approx 2ng/mL in whole blood) causes the same impairment as 0.5mg/mL alcohol. For this risk threshold, a measurement error was calculated and added. The meta-analysis may also be used to define limits comparable to lower or higher BAC levels.

Conclusion and Discussion

Any cut-off discussion should address the question if the DRUID approach to determine risk threshold equivalent to 0.5g/L alcohol is feasible. From a scientific point of view, it can only be justified to accept the same risk for all psychoactive substances including alcohol. From a political point of view the determination of risk thresholds equivalent to 0.5g/L alcohol might be questionable, because a BAC of 0.5g/L is not a legal limit in all European countries. Some Member States have lower alcohol limits and therefore, risk threshold calculations for THC would have to be adapted accordingly. Further on, to determine a risk threshold equivalent to a determined BAC from experimental studies, it has to be assured that the study parameters are sensitive for the specific substance effects. This affects the definition of stimulant cut-offs. Epidemiological data are too rare to deliver concentration based risk results and up to now the experimental settings are not applicable for testing impairing stimulant effects. As long as no sensible parameters to measure a stimulant effect are established, a pragmatic approach to define cut-offs should be chosen. That means in general, if not enough scientific studies – whether epidemiological nor experimental - are available, pharmacokinetic data and the knowledge about the consumption behaviour and habits should support the determination of cut-offs.

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