Impairment due to alcohol, tetrahydrocannabinol, and benzodiazepines in impaired drivers compared to experimental studies

Gudrun Høiseth a,b, Grim Otto Berg-Hansen a, Åse Marit L. Øiestad a, Liliana Bachs a, and Jørg Mørland a,c

aNorwegian Institute of Public Health, Division of Forensic Sciences, Oslo, Norway; bCenter for Psychopharmacology, Diakonhjemmet Hospital, Oslo, Norway; cInstitute of Clinical Medicine, University of Oslo, Oslo, Norway

ABSTRACT

Objective: In some countries, per se laws for other drugs than alcohol are used to judge drunk and drugged drivers. These blood concentration limits are often derived from experimental studies on traffic relevant behavior of healthy volunteers. Knowledge about how results from experimental studies could be transferred to a real-life setting is missing. The aim of this study was to compare impairment seen in experimental studies to the impairment seen at apprehended concentrations in apprehended drunk and drugged drivers.

Methods: Results from previously performed meta-analyses of experimental studies regarding impairment from alcohol, tetrahydrocannabinol (THC), and benzodiazepines were compared to impairment in apprehended drunk and drugged drivers as judged by a clinical test of impairment. Both experimental studies and real-life cases were divided into 4 groups according to increasing blood drug concentration intervals. The percentage of impaired test results in experimental studies was compared to the percentage of impaired subjects among drivers within the same blood drug concentration window.

Results: For ethanol, the percentage of impaired drivers (n = 1,223) increased from 59% in the lowest drug concentration group to 95% in the highest drug concentration group, compared to 7 and 72% in the respective groups in experimental studies. For THC, the percentage of impaired drivers (n = 950) increased from 42 to 58%, the corresponding numbers being 11 and 42% for experimental studies. For benzodiazepines, the percentage of impaired drivers (n = 245) increased from 46 to 76%, the corresponding numbers being 16 and 60% for experimental studies. The increased odds ratio for impairment between 2 concentration groups was comparable for experimental studies and impaired drivers.

Conclusions: Fewer test results indicated impairment in experimental studies compared to impaired drivers in real life when influenced by similar blood concentrations of either ethanol, THC, or benzodiazepines. In addition, a comparable relationship between drug concentration and impairment was seen for both experimental studies and real-life cases.

We believe that the present study strengthens the background for using experimental studies to establish fixed concentration limits for drunk and drugged drivers, but experimental studies in an impaired driver population could further expand our knowledge.

Introduction

The relation between drug concentrations in blood and impairment has been studied widely and is especially interesting regarding traffic safety. An increasing number of countries are implementing per se laws for drugs other than alcohol, either zero tolerance limits or limits reflecting impairment (DuPont et al. 2012; Reisfield et al. 2012; Vindenes et al. 2012; Voas et al. 2013). With an epidemiological approach, the increased risk of traffic accidents after intake of certain drugs can be documented, but a causal relation cannot be concluded. For this purpose, experimental studies are necessary. For many years, such experimental studies regarding the psychomotor and cognitive effects of drugs have been performed. For ethanol, a vast literature exists on the subject, and a correlation between blood alcohol concentration and the degree of impairment is well established (Martin et al. 2013). For drugs like benzodiazepines and tetrahydrocannabinol (THC), the evidence for a dose–response relationship between blood concentrations of drugs and degree of impairment has also been documented (Berghaus and Grass 1997; Berghaus et al. 1998; Linnoila et al. 1990; Mattila et al. 1998; Ramaekers et al. 2000). The overall evidence from both epidemiological and experimental studies strongly indicates an increased hazard of traffic accidents after intake of these drugs of abuse (Drummer et al. 2004; Gjerde et al. 2015; Morland 2000; Ramaekers et al. 2000, 2004).

Meta-analyses of driving related impairment from ethanol, benzodiazepines, and THC reported in experimental studies have been performed by Schnabel et al. (2010) and Berghaus and Grellner (2010). Based on these experimental studies of the effects on driving-related behavior, graphs describing the percentage of positive test results at each concentration level are presented. In most of these studies, young and healthy nonabusing subjects have been given one dose of a particular drug and then tested for impairment. Such evidence for drug impairment
from experimental studies is often transferred to the expected impairment seen after real-life drug use; for instance, in the establishment of per se laws for drugged driving. It would therefore be interesting to examine how results from experimental studies compare to a real-life population (e.g., a population of drug using drivers) because a comparison is missing in the literature. A lack of relation between impairment observed in experimental studies and in real life could be expected, because doses, degree of tolerance, drug use patterns, and factors other than drug use (e.g., sleep deprivation) are differing (DuPont et al. 2012).

In Norway, physicians perform a clinical test for impairment (CTI) shortly after the apprehension of offenders suspected of driving under the influence; in conjunction with the test, a blood sample for analysis of alcohol and drugs is drawn. This CTI is cruder than most of the tests used in experimental studies but nonetheless represents an objective measurement of the impairment observed in real life after ingestion of different drugs.

The aim of this study was to compare impairment in apprehended drunk and drugged drivers to the percentage of impaired test results seen in experimental studies when subjects were under the influence of the same blood concentrations of ethanol, THC, and benzodiazepines. We especially wanted to evaluate the concentration–response relationship between blood concentrations and impairment of alcohol, THC, and benzodiazepines in a real driving population compared to experimental studies.

Materials and methods

Study group real life cases (impaired drivers)

The present study used data from the existing database at the Norwegian Institute of Public Health (NIPH), Division of Forensic Sciences. The database contains the analytical results from blood samples collected among suspected drugged and drunk drivers. All cases were subject to a standard analytical program as described below. The database was searched for apprehended drivers in the time period between February 1, 2012, and April 30, 2015. Cases containing only ethanol or only THC and cases containing only one single benzodiazepine/z-drug (either alprazolam, clonazepam, diazepam, phenaazepam, flunitrazepam, lorazepam, nitrazepam, oxazepam, zolpidem, or zopiclone) with no other drugs being detected were selected as the study group. Zopiclone and zolpidem were also included in the benzodiazepine group because of their pharmacodynamic similarity with benzodiazepines and are further referred to in the benzodiazepine group.

Only cases containing a valid result on the CTI were included in the study. Cases were divided into categories according to concentration levels. This categorization was based on legislative blood concentration limits for driving under the influence of other drugs than alcohol, which was introduced in Norway in 2012 (Vindenes et al. 2012). The concentration windows used in the present study were based on these limits, but the highest limit for ethanol and THC was lowered to obtain also experimental data in all categories. The exact concentration intervals used to define each group are seen in Table 1. Blood benzodiazepine concentrations (other than diazepam) were transformed into diazepam-equivalent concentrations.

### Table 1. Concentration groups used for alcohol, THC, and diazepam-equivalent benzodiazepine concentrations (µM = µmol/L).

| Alcohol (%) | THC (µM)  | Diazepam equivalents (µM) |
|-------------|-----------|----------------------------|
| <0.02       | <0.004    | <0.200                     |
| 0.02–0.05   | 0.004–0.010 | 0.200–0.500               |
| 0.05–0.10   | 0.010–0.020 | 0.500–1.200               |
| >0.10       | >0.020    | >1.200                     |

Toxicological analytical methods and CTI (impaired drivers)

In Norway, when drunk or drugged driving is suspected by the police, a clinical examination is usually performed by a physician shortly after apprehension at the same time as a blood sample is collected for toxicological analyses. Most physicians are trained at medical school how to determine drug impairment by use of the CTI. In addition, some physicians are employed at the police and especially experienced in performing the CTI.

Toxicological analytical methods

All of the analytical methods applied were fully validated for routine use at the NIPH. Positive screening results were confirmed using 2 parallel analyses with a different analytical method. All blood samples were, according to the routine, initially screened for ethanol with a previously published enzymatic alcohol dehydrogenase method (Kristoffersen and Smith-Kielland 2005). Confirmation analysis was performed by a published method using headspace gas chromatography equipped with a flame ionisation detector (Kristoffersen et al. 2006). The analytical cutoff level (an administrative value just above the lower limit of quantification) used for ethanol in blood was 0.004%, and only values detected above this level were reported as positive.

All blood samples were also screened for a number of other drugs and medications relevant to impairment using a previously published ultra-high-performance liquid chromatography–tandem mass spectrometry (UHPLC-MS/MS) method (Oiestad et al. 2011). The drugs included in this method were opioids (buprenorphine, codeine, ethylmorphine, fentanyl, methadone, morphine, and oxycodone), stimulants (amphetamine, cocaine, methamphetamine, MDMA, methylphenidate), benzodiazepines (alprazolam, bromazepam, clonazepam, N-desmethylclonazepam, diazepam, phenaazepam, flunitrazepam, lorazepam, midazolam, nitrazepam, and oxazepam), nonbenzodiazepine hypnotics (zopiclone and zolpidem), LSD, ketamine, and THC. In addition, all cases were screened for gamma-hydroxybutyrate and pregabalin using another separate analytical method (Dahl et al. 2012). In addition, a small number of new psychoactive substances were analyzed in each case using a UHPLC-MS/MS method. These latter drugs changed throughout the study period; examples are methoxetamine, pyrazolam, and 5F-APINACA.

Positive toxicological results for THC or benzodiazepines were confirmed and quantified with a different toxicological testing method. All benzodiazepines were analyzed using a previously published UHPLC-MS/MS method (Sauve et al. 2012), with the cutoff values for benzodiazepines in the confirmation method (which were somewhat higher than in the screening method) being 0.20 µmol/L for diazepam, 0.20 µmol/L for N-desmethylclonazepam, 0.0040 µmol/L for clonazepam,
0.6 μmol/L for oxazepam, 0.005 μmol/L for phenazepam, 0.05 μmol/L for nitrazepam, 0.010 μmol/L for alprazolam, and 0.005 μmol/L for flunitrazepam. Zopiclone and zolpidem were analyzed using a previously published method (Eliassen and Kristoffersen 2014), with cutoff levels at 0.02 and 0.07 μmol/L, respectively.

Quantification of THC was performed using a gas chromatography–mass spectrometry (GC-MS) method, modified from a previously published method (Christophersen 1986). Whole blood (0.5 mL) was added 50 μL internal standard (THC-d3, 0.094 μmol/L) and extracted with 2 mL hexane. The hexane phase was evaporated to dryness before derivatization at 60°C for 40–50 min with 40 μL bis-(trimethylsilyl)trifluoroacetamide dissolved in acetonitrile in a ratio of 1:2. After evaporation, the residue was dissolved in 35 μL butyl acetate. Analysis were performed by GC-MS using a 0.20-mm I.D., film thickness of 0.33 mm, Agilent J&W capillary column VF-5ms, with a length of 12 m and a 5 m EZ guard-column, on an Agilent 7890A GC with an Agilent 7693 autosampler. Mass detection was performed in selected ion monitoring mode on an Agilent 5975C MSD. Instrument parameters were as follows: injection volume, 2 μL; injector temperature, 250°C; oven temperature programming: initial temperature 120°C held for 1 min, 30°C/min ramp to 320°C for 3 min; interface temperature, 280°C; carrier gas, helium; flow rate, 0.8 mL/min. The cutoff value for THC was 0.002 μmol/L. Only concentrations detected above the cutoff levels were reported as positive.

**CTI**

Drivers are usually apprehended by the police because of suspicious driving or due to involvement in traffic accidents. A physician draws a blood sample shortly after apprehension and at the same time also performs a CTI. The CTI consists of 25 tests and observations related to common signs of drug impairment. Examples of observations are the suspected driver’s motor coordination ability, cognitive performance, degree of alertness, and pupil diameter. The CTI has been described in detail elsewhere (Bramness et al. 2003). At the end the physician must conclude whether the driver is not impaired, mildly impaired, moderately impaired, or considerably impaired. In addition, a conclusion of “impairment impossible to determine” can be given. The latter group was excluded from the study. For some of the analyses performed in the present study, those subjects who were judged as mildly, moderately, and considerably impaired are merged into a single “impaired” group. The conclusion was the only variable of the CTI that was included in the present study.

**Calculations of diazepam-equivalent concentrations**

All benzodiazepine and z-hypnotics concentrations were calculated into diazepam-equivalent concentrations, using the suggested equivalence factors in the proposal for the revised fixed limits for other drugs than alcohol in Norway (Vindenes et al. 2015). The factors for some of the most common benzodiazepines and z-hypnotics from this work are as follows: 48 for clonazepam, 0.33 for oxazepam, 20 for alprazolam, and 6.7 for zopiclone.

**Comparison with experimental studies**

Impairment seen in drugged and drunk drivers was compared to impaired test results seen in experimental studies for the same concentration intervals.

Percent impaired subjects in the concentration windows used to categorize impaired drivers (Table 1) were compared to the percentage impaired test results at the same concentration windows in experimental studies, based on the results summarized by Schnabel et al. (2010) and Berghaus and Grellner (2010). The experimental results by Schnabel et al. (2010) were based on 2,914 single effects on human performance and driving-related behavior for alcohol. The results from Berghaus and Grellner (2010) were based on 226 such effects (25 studies) for THC and 1,630 such effects (91 studies) for diazepam. From the published graphs showing blood concentration compared to impairment for THC and diazepam, the percentage of impaired test results within the corresponding concentration windows were manually assessed (p. 176 for THC, p. 71 for diazepam in Berghaus and Grellner [2010] and figure 35 in Schnabel et al. [2010]). The exact concentrations were inserted on the x-axis, and the mean of the corresponding percentage of impairment was read from the y-axis. For benzodiazepines, the results from studies concerning diazepam were used, because these represent the largest number of studies. It is specifically stated that results from drug-dependent subjects were excluded from the meta-analysis. For diazepam and THC, the concentrations were corrected for a serum/blood ratio of 1.8.

To compare the concentration–response relationship seen for experimental studies and impaired drivers, the odds ratio (OR) for impairment between different concentration groups was compared. For impaired drivers, this OR was calculated with a 95% confidence interval (CI), whereas for experimental studies, it was only possible to calculate the OR (lack of information on the number of subjects investigated). If the 95% CI for impaired drivers included the OR in experimental studies, the difference was considered not significant (P > .05).

**Ethics**

The study was conducted according to the data processing agreement with the Higher Prosecuting Authority, which stands as the owner of forensic materials in Norway. In accordance with this agreement, only anonymous data were used in the present study.

**Statistics**

IBM SPSS Software Ver. 22.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. Means and standard deviations are reported for the continuous variables and frequency distributions were used for the categorical variables. The number of impaired drivers in the different groups was compared using Pearson’s chi-square test (in the case of no cells with expected counts of less than 5). The concentrations of alcohol, benzo
diazepines, and THC in the impaired and nonimpaired drivers were compared using the Student’s t test. P values below .05 were considered statistically significant.
Results

Regarding real-life cases (impaired drivers), 17,871 blood samples from suspected drugged drivers were submitted for a full toxicological screening at the NIPH during the period February 1, 2012, to April 30, 2015. One thousand two hundred twenty-three of these contained alcohol only, 950 contained THC only, and 245 contained one single benzodiazepine only, in addition to a performed CTI with a valid conclusion. For each drug the cases were divided, based on the blood drug/alcohol concentrations determined, into 4 concentration window groups.

The percentage of impairment seen in each drug concentration group for impaired drivers compared to experimental studies is shown in Figure 1 and Table 2. After dividing real-life cases into not impaired and impaired (including mildly, moderately, and considerably impaired), the percentage of cases where drivers were judged as impaired was calculated for each drug and each concentration group. For ethanol \((n = 1,223)\), the proportion of impaired drivers increased from 59% in drug concentration group 1 (lowest concentrations) to 95% in drug concentration group 4 (highest concentrations; Figure 1a). For THC \((n = 950)\), the percentage of impaired drivers increased from 42% in drug concentration group 1 to 58% in drug concentration group 4 (Figure 1b), and for benzodiazepines \((n = 245)\), the fraction of impaired drivers increased from 46% in drug concentration group 2 (too few cases to calculate for group 1) to 76% in drug concentration group 4 (Figure 1c).

The same concentration groups were used for experimental studies as for impaired drivers. From experimental studies, according to Schnabel et al. (2010), the percentage of impaired test results increased from 7% in drug concentration group 1 to 72% in drug concentration group 4 for alcohol (Figure 1a). According to Berghaus and Grellner (2010), the proportion of impaired test results increased from 11% in drug concentration group 1 to 42% in drug concentration group 4 for THC (Figure 1b) and from 16% in drug concentration group 2 to 60% in drug concentration group 4 for benzodiazepines (Figure 1c).

The increased OR for being impaired in group 4 compared to group 3 (the 2 groups with the highest number of impaired driving cases) was calculated for all drugs and compared to the corresponding OR in experimental studies. The impairment increased in group 4 relative to group 3 in a similar way for impaired drivers and the experimental studies. This is shown in Table 3. As seen in Table 3, the 95% CI for the OR in impaired drivers included the OR in experimental studies for alcohol, THC, and benzodiazepines, demonstrating no statistically significant differences. For both experimental studies and impaired drivers, there was no increase in impairment by THC in group 4 compared to group 3 (OR = 1.0 and 1.1, respectively). For alcohol and benzodiazepines, the impairment also increased in group 4, quite similar to that in drivers and experimental studies (Table 3). The increase in OR for being judged as impaired between groups 3 and 2 is also shown in Table 3.

In real-life cases, the concentrations of all drugs were higher in impaired compared to nonimpaired subjects (Table A1, see online supplement). This was statistically significant for alcohol \((P < .001)\), THC \((P < .001)\), and benzodiazepines \((P = .01)\). For ethanol, a significant increase in mean drug concentrations between the 2 highest impairment groups was seen \((P < .001)\), but for benzodiazepines, this increase was not statistically significant \((P = .24)\). No such increase was seen for THC (Figures A1a, A1b, and A1c, see online supplement).

Discussion

The main finding of this study was that fewer test results indicated impairment in experimental studies compared to impaired...
drivers in real life when influenced by similar blood concentrations of either ethanol, THC, or benzodiazepines. In addition, a comparable relationship between drug concentration and impairment was seen for both experimental studies and real-life cases.

The degree of concentration–response relationships was assessed by calculating ORs for impairment in one concentration group compared to the lower concentration group and then comparing the ORs between impaired drivers and experimental studies. The concentration–response relationship can also be visually compared in Figures 1a, 1b, and 1c. An overall assessment of the concentration–response for experimental studies and the concentration–response in impaired drivers indicates that these relationships are quite comparable for the 2 types of populations, showing increased impairment by increased concentrations for all drug groups. For THC, only a very small increase in impairment is seen between the 2 highest concentration groups.

The transfer of results regarding drug impairment from experimental studies to real-life cases is complicated, although an influence of the same concentrations of the same drugs is present. In experimental studies, single doses of drugs are most often ingested by healthy volunteers, and inclusion criteria and study design often make conditions quite similar to all participants. In real life, a population of drunk and drugged drivers can be assumed to represent considerable variation of drug dosing and tolerance. One could therefore expect that the pattern for impairment documented in experimental studies could not be retrieved in real life. The fact that we find quite similar concentration–response patterns for impaired drivers compared to experimental studies for alcohol, THC, and benzodiazepines is thus in favor of transferring results from experimental studies to a real-life drug use setting.

We are not aware of previous studies comparing percentage of impairment seen at the same drug concentrations in experimental and real-life cases. Among previous experimental studies, some research was performed on subjects with drug experience (not included in the meta-analyses used in the present study). In these studies, a dose–response relationship between impairment and drug concentration has been documented for benzodiazepines (Evans et al. 1990; Mumford et al. 1995). In impaired drivers, although based on limited data, a concentration–response relationship for impairment judged by the CTI and drug concentrations has previously been indicated for benzodiazepines. In these studies, the concentration limits were much higher (Bramness et al. 2002; Gustavsen et al. 2009). This makes comparison with experimental studies difficult, because such high concentrations are not seen here. For THC, it has previously been shown, with use of an almost identical CTI, that no increase in impairment was seen at the highest concentrations (>0.020 µmol/L), a finding corresponding to our results regarding both populations (Khiabani et al. 2006). On the other hand, an increase in impairment for tracking performance and stop reaction time has been reported for the very highest concentrations (>0.1 µmol/L) in a previous study of recreational cannabis users (Ramaekers et al. 2006). For alcohol, a concentration–response relationship in impaired drivers was previously indicated (Bramness et al. 2002). The present study verified, when assessing impairment at the same blood drug concentrations, that the same pattern observed for a concentration–response relationship in experimental studies could be seen in real life for alcohol, THC, and benzodiazepines.

In recent years, some countries have started to use legislative limits based on experimental studies for conviction of drugged drivers (DuPont et al. 2012; Vindenes et al. 2012; Voas et al. 2013). In Norway, both impairment limits and graded sanction limits for 13 drugs other than alcohol have been established (Vindenes et al. 2012). This is based on the documented concentration–response relationship for these drugs from experimental studies. The application of such graded sanction limits is supported by the present study.

The fact that fewer subjects show impairment in an experimental setting compared to real life is an interesting finding. Although this is biased by the fact that drivers are often apprehended due to suspicion of impairment, it could to some degree be attributed to the different method for evaluating impairment between the 2 populations, and a previous experimental study of recreational cannabis users showed up to 100% impaired

Table 2. Percentage of drivers being judged as impaired and percentage of impaired test results from experimental studies after use of different drugs in each concentration window.

| Group 1 | Group 2 | Group 3 | Group 4 |
|---------|---------|---------|---------|
| Alcohol (%) | | | |
| Impaired drivers | Experimental | Impaired drivers | Experimental | Impaired drivers | Experimental | Impaired drivers | Experimental |
| 59 | 7 | 70 | 21 | 83 | 45 | 95 | 72 |
| THC (%) | | | |
| Impaired drivers | Experimental | Impaired drivers | Experimental | Impaired drivers | Experimental | Impaired drivers | Experimental |
| 42 | 11 | 43 | 29 | 57 | 42 | 58 | 42 |
| Benzodiazepines (%) | | | |
| Impaired drivers | Experimental | Impaired drivers | Experimental | Impaired drivers | Experimental | Impaired drivers | Experimental |
| 2% | 5 | 46 | 16 | 55 | 40 | 76 | 60 |

a Not calculated due to only 3 cases of benzodiazepines in group 1.

Table 3. Increase in OR for being judged as impaired between different concentration groups.a

| Increase in OR between group 4 and 3 for being judged as impaired | Increase in OR between group 3 and 2 for being judged as impaired |
|---------------------------------------------------------------|---------------------------------------------------------------|
| Impaired drivers, OR (95% CI) | Experimental studies, OR | P* | Impaired drivers, OR (95% CI) | Experimental studies, OR | P* |
| Alcohol | 4.2 (2.5–7.0) | 3.1 | ns | 2.1 (1.1–3.8) | 3.1 | ns |
| THC | 1.1 (0.8–1.6) | 1.0 | ns | 1.8 (1.2–2.5) | 1.8 | ns |
| Benzodiazepines | 2.6 (1.3–5.2) | 2.3 | ns | 1.4 (0.4–3.8) | 3.5 | ns |

a Ninety-five percent confidence intervals are reported in addition to ORs for impaired drivers. This could not be calculated for experimental studies.

b Difference between impaired drivers and experimental studies.
test results at very high concentrations of THC (>0.1 µmol/L; Ramaekers et al. 2006). In that study, concentrations of THC corresponding to concentration group 2 in the present study showed about 60% impairment (tracking performance and stop reaction time) compared to 22% in the meta-analysis by Berghaus and Grellner (2010). This probably shows the importance of the type of experimental test used to demonstrate drug impairment. To some degree, it is probable that the population of impaired drivers shows some baseline impairment compared to healthy volunteers, because quite a large proportion of subjects is impaired also at very low drug concentrations. This situation, which was also indicated in previous studies (Bosker et al. 2012; D’Souza et al. 2008), could be caused by changes in brain function and behavior that could be caused by drug use but are not related to the acute intoxication (Bosker et al. 2013). If this were true, an increase in traffic risk would be expected in this population, even when very low blood drug levels are present. It could also be argued that the impairment seen at very low drug concentrations could be caused by the stress associated with being apprehended by the police and tested by a doctor. In such cases, the impairment seen at low drug concentrations is not necessarily accompanied by increased crash risk. However, because drivers completely negative at toxicological analyses show little impairment in the CTI (Bachs et al. 2006), the latter explanation is less likely.

We studied the concentrations of drugs at different impairment levels especially for impaired drivers, who showed more impairment than those in experimental studies. Very limited data for this method of studying the concentration–response relationship has previously been published and then only from older data materials (Brannness et al. 2002). When we compared the mean blood concentration of drivers judged as not impaired, mildly impaired, and moderately/considerably impaired, increased concentrations were seen in all impairment levels for alcohol and to some degree for benzodiazepines. For THC, the highest impairment level did not show higher drug concentrations than those mildly impaired, in conjunction with an apparent threshold limit for impairment from THC.

In our study there were fewer drivers judged as impaired due to THC and benzodiazepines compared to ethanol, and this was also to some degree the case in experimental studies. This could imply that THC and benzodiazepines do not have as detrimental an effect as ethanol or that the CTI and partly other impairment tests used have a lower sensitivity to THC- and benzodiazepine-induced impairment. For THC, there was also a smaller proportion of drivers in the highest THC blood concentration group, corresponding to BAC above 0.10%, compared to benzodiazepines and ethanol. This can perhaps be explained by the kinetic properties of THC: the blood concentration of THC drops rapidly during the first hour or so after intake, and the blood sample is drawn too late to catch many of the originally high concentrations.

The present study has some limitations. A weakness of the present study is the use of different methods to measure impairment in experimental studies and in real-life drivers. In experimental studies, a battery of psychomotor and cognitive tests relevant for traffic safety is used. These are often more sophisticated, sensitive methods. Impairment in drivers is assessed by CTI, which was originally developed for alcohol and later modified to better identify other drugs as well. There is also a possible bias in assessment of impairment of ethanol, because the consumption of alcohol produces a characteristic breath odor. Benzodiazepines have no such obvious sign of drug use but, shortly after intake, the smell of smoke and other signs could be apparent after use of THC. It has earlier been shown that the modified version of CTI has good internal validity for benzodiazepines (Brannness et al. 2002) and THC (Khiabani et al. 2006). The CTI is suspected to be less sensitive to drug impairment, although the present data actually indicate high sensitivity with a large number of impaired subjects. External validity—that is, the ability of the test to predicate increased crash risk—is more difficult to examine. In addition, for experimental studies, the percentage of all single positive test results was reported, whereas percentages of impaired subjects (overall impression based on single test results) were reported from real life. In addition, the extraction of data from the previous meta-analysis of experimental studies (Berghaus and Grellner 2010; Schnabel et al. 2010) was based on reading figures, not original data. Information on spread of the data was therefore not available. The 2 populations were compared for the same concentration intervals, but the distribution within the intervals could differ. This is probably most relevant for the highest concentration group, where very high concentrations were found in some impaired drivers.

The strength of the present study is the comparison of experimental and real-life cases at the same drug concentration levels. For impaired drivers, the use of the same CTI is a methodological strength, as well as use of identical and accurate analytical methods and standards during the total study period.

In conclusion, this study showed that a similar drug/alcohol concentration–response relationship is observed for clinical impairment in real life as for behavioral impairment in experimental studies. Although generally less impairment was seen in experimental studies, we believe that the study strengthens the background for using per se limits based on experimental studies in real-life traffic cases.

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