Received: 7 August 2013

Revised: 16 October 2013

(www.drugtestinganalysis.com) DOI 10.1002/dta.1588

Cannabis use: a perspective in relation to the proposed UK drug-driving legislation

Kim Wolff^a* and Atholl Johnston^b

With regard to THC (Δ^9 -tetrahydrocannabinol), the main psychoactive constituent identified in the plant *Cannabis sativa L*, several facts are indisputable. Cannabis remains the most commonly used drug in the UK among those who reported driving under the influence of illegal drugs in the previous 12 months. There is a significant dose-related decrement in driving performance following cannabis use; raised blood THC concentrations are significantly associated with increased traffic crash and death risk. When cannabis and alcohol are detected together, there is a greater risk to road safety than when either drug is used alone. Patterns of use are important when interpreting blood concentration data: Smoking infrequently a single cannabis cigarette leads to peak plasma THC concentrations (21-267 µg/L) causing acute intoxication. In habitual, daily users, plasma THC concentrations range from 1.0 to 11.0 µg/L and are maintained by sequestration of the drug from the tissues. These facts undoubtedly make setting thresholds for drug-driving legislation difficult but there is clearly a case for cannabis. Determining minimum blood THC concentrations at which a driver becomes sufficiently impaired to be unable to safely drive a vehicle is of particular concern given the increasing medicinal use of the drug. Internationally legislation for driving under the influence of drugs (DUID) is based on either a proof of impairment or a *per se* approach. For the latter this can be either zero-tolerance or based on concentration limits such as those used for alcohol. The different approaches are considered against current scientific evidence. Copyright © 2013 John Wiley & Sons, Ltd.

Keywords: cannabis; drug-driving; road-traffic-collision; per se threshold; blood; THC

Introduction

Cannabis is the most common illicit drug detected in blood and oral fluid (OF) of night-time drivers.^[11] In the UK, in 2011, driving was recorded as a contributory factor in about 3% of fatal road traffic collisions (RTCs) with 54 deaths resulting from these incidents. This compares to 9% or 156 fatal road incidents, with 166 deaths, which have impairment by drink (alcohol–ethanol) reported as a contributory factor.^[2] Some evidence suggests drug driving is a much bigger road safety problem than reported and may be a factor in 200 road deaths per year.^[3]

Legislation is currently in place in the UK for driving whilst impaired under Section 4 of the Road Traffic Act 1988 (Driving, or being in charge, of a vehicle when under the influence of drink or drugs). In order to secure a conviction for driving while unfit through drugs it needs to be proven that: the suspect was driving, attempting to drive or in charge of a vehicle; was impaired so as to be unfit to drive; and the impairment was caused by the drugs.

Sir Peter North's^[3] review of drink and drug-driving law in Great Britain (2010) included the recommendation to create a new offence. The UK government accepted the recommendation and in the 2011 Department for Transport's (DfT) Strategic Framework for Road Safety, the government committed to explore the case for introducing an additional offence of driving with a specified controlled drug in the body, without the need to prove impairment. The proposed new offence would be a strict liability offence, in the same way as the offence of driving with more than the prescribed amount of alcohol in the body.

The introduction of the new offence reflects increasing evidence that the existing 'impairment' offence is insufficient to effectively deal with this problem, with a disproportionately small number of proceedings brought under it and a large proportion of those proceedings withdrawn or dismissed.

The Crime and Courts Bill, which was introduced into Parliament in May 2012 makes provision for a new offence of driving, attempting to drive, or being in charge of a motor vehicle with a specified Controlled Drug (i.e. drugs subject to the provisions of the Misuse of Drugs Act 1971) in the body above the concentration specified for that drug (Box 1).

Box 1. Controlled Drug - this is a legal definition referring to those drugs that are controlled under the British Misuse of Drugs Act 1971 - this regulates the import, export, possession, supply, and other aspects of activities relating to those drugs specified in the 1971 Act.

The medical defence

In order to safeguard those who take medication which may contain a Controlled Drug, which is specified for the purposes of the new offence, but who take it in line with the directions given to them by

- a Institute of Pharmaceutical Science, King's College London, 150 Stamford Street, London, SE1 9NH, UK
- b Barts and The London School of Medicine and Dentistry Queen Mary, University of London, Charterhouse Square, London, EC1M 6BQ, UK

^{*} Correspondence to: Kim Wolff, Reader in Addiction Science, Institute of Pharmaceutical Science, King's College London, 150 Stamford Street, London SE1 9NH, UK. E-mail: Kim.wolff@kcl.ac.uk

their doctor, pharmacist, or other recognized healthcare professional or the instructions contained in the Patient Information Leaflet (PIL), there is a medical defence. This allows a person to 'show that: (a) the specified controlled drug had been prescribed or supplied for medical or dental purposes; (b) the drug has been taken in accordance with any directions given by the prescriber, and with any accompanying instructions (so far as consistent with any such directions) given by the manufacturer or distributor of the drug.'

Therefore the new offence does not change the existing legal position whereby those who legitimately take their medication may be guilty of a road traffic offence if they are impaired or 'unfit' to drive due to the effects of that drug.

The case for cannabis

In Great Britain, cannabis is an illegal drug classified as a category B Controlled Drug under the Misuse of Drugs Act 1971 and therefore falls under the criteria listed for inclusion in the new offence and is discussed here in this regard. The prevalence of the drug in the population at large and hence the driving population will be considered as part of the rationale for inclusion in the new offence as this relates to the risk of use to road safety. Since the proposed new offence will be a strict liability offence, the amount of cannabis in the body above which it would be unsafe to drive is examined. The way in which cannabis is used will also be discussed and for the purposes of this review the following definitions will apply:

- Naïve user: an individual who uses the drug on a single oneoff occasion.
- Recreational user: an individual who uses cannabis infrequently but who is familiar with the effects of the drug.
- Habitual user: an individual who uses cannabis frequently on at least four days per week, who is tolerant to the physiological effects of the drug (dependent) and who is experienced in its use.
- Medicinal user: an individual prescribed a controlled drug containing THC for daily use.
- Passive exposure: an individual inhaling smoke from another person's cannabis cigarette.

Epidemiological prevalence

Several surveys demonstrate that cannabis is the most widely used illegal drug in Europe^[4] including the United Kingdom^[5] and the Crime Survey for England and Wales (CSEW),^[6] a house-hold survey of adults aged 16 and over, resident in England and Wales estimated that in 2011/2012 6.9% of adults aged 16 to 59 had used cannabis, which extrapolates to around 2.3 million people nationally.

Cannabis and driving

In terms of driver populations, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) found that between 0.3% and 7.4% of drivers tested positive for cannabis across seven roadside surveys conducted between 1997 and 2007 in Australia, Denmark, the Netherlands, Norway, and the United Kingdom.^[7] The negative impact of cannabis on driver performance has been widely accepted in Europe such that cannabis features in road traffic legislation in many European countries, as shown in Table 1.^[8–10] Many laws for DUID prescribe a zero tolerance for cannabis, which identifies drivers as being under

Table 1.	International thresholds and legislation in relation to blood		
THC concentration			

Country	Legislation	THC ^a threshold in blood	Reference
Sweden	Zero tolerance	0.3 μg/L	[8]
France	Zero tolerance	1.0 μg/L	[9]
Germany	Consensus limit ^b	0.5 μg/L	[9]
Switzerland	Threshold for	1.5 μg/L	[9]
	prosecution		
Portugal	Zero tolerance	3.0 μg/L	[9]
Norway	Impairment limit	1.3 μg/L	[10]
	Comparable to BAC	3.0 μg/L	
	50mg alcohol/100 mL		
	Comparable to BAC	9.0 μg/L	
	120mg alcohol/100 mL		

 $^{a}\Delta^{9}$ -tetrahydrocannabinol (THC) the main psychoactive constituent identified in the plant *Cannabis sativa L*.

^bUnder German federal law the laboratory limit of detection (LOD) for serum THC concentration is 1 ug/L (equivalent to 0.5 ug/L in whole blood) THC and has been the de facto legal limit since 1999.

the influence of cannabis if any amount of THC is detected in blood. This approach sets the legal level just above the laboratory limit of detection (LOD), making the legal limit (the limit of quantification, LOQ) a function of the ability of the laboratory to detect THC, rather than the impairment caused by it.

In 2010/2011, the CSEW carried a question relating to the prevalence of drug driving,^[11] and data show that for those who reported driving under the influence of illegal drugs at least once or twice in the previous 12 months, cannabis was the most commonly used drug during this time period (with 85% reporting use in the previous 12 months). In addition, a survey of 537 drivers in Scotland reported that 15% of respondents aged 17-39 years and 3% of over 40-year-olds admitted to driving a vehicle within 12 h of consuming cannabis.^[12] In young people with drivers' licences in the UK, self-reported rates of having ever driven under the influence of cannabis were 59% for clubbers and 40% for university students.^[13] In Australia, 88% injecting drug users reported ever driving under the influence of cannabis^[14] and 78% of known cannabis users drove within an hour of using the drug.^[15]

Laboratory analysis of blood samples (N = 3616) collected between January 2008 and October 2012 predominantly from England and Wales on behalf of the Centre for Applied Science and Technology (CAST) based at the Home Office taken in suspected cases of drug-driving which screened positive for one or more drugs confirmed the presence of cannabis in UK drivers. The data showed that cannabinoids were present in 58% of drug positive samples.^[16]

Impairment and cognitive studies

Cannabis exerts various physiological effects by interacting with specific cannabinoid receptors (CB receptors). In terms of driving performance, it is the CB₁ receptors in the brain that are particularly relevant, being concentrated in anatomical regions associated with cognition and motor coordination among others.^[17] Attentiveness, vigilance, and the perception of time and speed are all affected by cannabis.^[18] Indeed, a meta-analysis of 60 studies concluded that cannabis causes impairment in all areas of performance concerned with safe driving, including divided attention.^[19]

Early research assessing the effects of cannabis on driving performance is generally consistent and concludes that at higher doses cannabis impairs the psychomotor skills necessary for safe driving.^[20,21] Some experimental studies have shown however that experienced smokers of the drug who drive on a set course^[22] or in a simulated laboratory test show little functional impairment.^[23] A meta-analysis of over 120 studies has found frequent users of cannabis (unless used in conjunction with alcohol) show less impairment than infrequent users at the same dose, either because of physiological tolerance or learned compensatory driving behaviour but that the higher the estimated blood THC concentration, the greater the driving impairment.^[19] A review of both epidemiological and experimental research investigating the effects of cannabis on driving ability has been conducted by Rameakers *et al.*^[24]

The definition of the new legislation as a strict liability offence has necessitated a move away from the need to measure impairment and look more closely at road safety in relation to a prescribed amount of a drug in the body. To this end impairment will be discussed in relation to blood drug concentrations where this aids our understanding of driver safety.

Cannabis use and risk of a road traffic collision (RTC)

The use of cannabis and the risk of an RTC have been systematically investigated. A meta-analysis of 9 epidemiological research studies summatively including 49 411 participants^[25] that examined observational studies of the effects of acute cannabis use on the risk of RTCs showed that the pooled risk of an RTC whilst driving under the influence of cannabis was almost twice the risk whilst not under the influence of this drug (OR: 1.92, CI 1.35 to 2.73; P = 0.0003). Chronic use is also problematic and in a population-based case control study of self-reported cannabis use and car crash risk, a strong significant association between habitual use and car crash injury (OR 9.5, 95% CI 2.8-32.3) after controlling for risky driving (travelling speed, sleepiness score, time of day etc.) was observed.^[26]

Risk estimates of an RTC whilst driving under the influence of cannabis vary and range from OR: 1.22 to OR: 9.50^[25–35] (Table 2). This may be because studies tend to use different criteria for calculating the risk estimate and in some cases lacked control of potentially confounding factors.^[36] For instance, study estimates of the collision risk have sometimes been confounded by the failure to separate out the effects of alcohol and other psychoactive substances.^[9] Consideration of the findings from meta-analysis has helped, by excluding poorly controlled research, to offset these methodological weaknesses. After taking age, and gender, and confounding factors into account and controlling for traffic conditions, the Integrated Project DRUID (Driving under the Influence of Drugs, Alcohol and Medicines) report (2011), estimated that the use of cannabis increased the risk of serious or fatal injury in an RTC by 1-3 times.^[33]

Summary estimates (Table 2) of risk for cannabis use show different odds for fatal (OR = 2.10 for fatal) compared to non-fatal accidents (OR = 1.74).^[25] This finding might be explained by differences in blood THC concentrations (either due to greater cannabis consumption or owing to a shorter time between consumption and measurement). In a study conducted in France, the mean time between roadside crash and blood sample

Table 2. An overview of the risks for involvement in, responsibility for or injury as the result of a traffic accident (as an odds ratio (OR)) when driving under the influence of cannabis and blood THC concentrations where available

Substance and blood levels	Odds Ratio (OR) ^a	References
Cannabinoids	OR: 1.22 (95% Cl: 0.55 - 2.73)	[27]
	OR: 2.79 (95% CI: 1.23 - 6.33; P <0.01) ~	[25]
	OR: 2.10 (95% Cl: 2.10 - 3.36; P <0.002) ~~	[25]
Cannabis detected	OR: 1.29 (99% Cl: 1.11 - 1.50)	[28]
-THC 1 μα/L blood	OR: 1.57 (95% Cl: 0.84 - 2.95)	[29]
-THC 1-2 µg/L blood	OR: 1.54 (95% CI: 1.09 - 2.18)	[29]
-THC 3-4 μg/L blood	OR: 2.13 (95% CI: 1.22 - 3.73)	[29]
-THC \geq 5 µg/L blood	OR: 2.12 (95% Cl: 1.32 - 3.38)	[29]
-THC 1 μg/L blood	OR: 2.50 (95% Cl: 1.50 - 4.20)	[30]
-THC \geq 5 µg/L blood	OR: 2.70 (95% Cl: 1.00 - 7.00)	[31]
	OR: 6.60 (95% Cl: 1.50 - 28.00)	[31]
	0R: 9.50 (95% Cl: 2.80 - 32.30)	[26,32]
Habitual cannabis use		
THC or THCCOOH + THC	OR: 1.38 (95% Cl: 0.88 - 2.17) *	[33]
	OR: 1.33 (95% Cl: 0.48 - 3.67) **	[33]
THC, or 11-OH-THC or		
THCCOOH > 0.5 μg/L	RR: 0.33 (99% CI: 0.12 - 0.92)	[34]
Used cannabis >50 times (18-21yrs)	OR: 1.60 (95% Cl: 1.20 - 2.00) ^	[35]

^aThe European study DRUID (Driving under the Influence of Drugs, Alcohol and Medicines) has classified ORs as "low risk" (OR <2.0), "medium risk" (OR >2.0 – 10.0) and "high risk" (OR >10.0), which is a useful guide. Although ORs that are less than 2 but greater than 1, where there is a narrow confidence interval that does not include 1, can also indicate that risk is significantly elevated.^[13]

~Road traffic collision, ~~Fatal collision,* Seriously injured based on aggregated data (a combination of study data),

** fatally injured based aggregated data, ^estimated rates of active accidents (moving vehicle).

collection was calculated to be 1.8 h \pm 0.9 h,^[30] in a Swiss study this timeline was 2.7 h,^[37] and in the UK has been tentatively estimated to be between 2 and 3 h.

In Sweden (where a zero-tolerance law operates), following a 10-year study of individuals apprehended for driving under the influence of cannabis (N = 8794), it was concluded that blood THC concentrations at the time of driving are probably much higher than at the time of sampling (30-90 min later).^[8] This is an important consideration when interpreting blood-drug concentration data in relation to driving performance. Sampling delays in excess of 2h may cause an underestimation of THC concentration in the blood of injured drivers who test positive for cannabis and may explain others' failure to find adverse effects.^[23] It is also important to note that when calculating the time of the last exposure from whole blood THC concentrations, a 0.5 whole-blood-toplasma (WB/P) ratio is usually employed.^[38]

THC blood concentrations between 1 µg/L and 2 µg/L have been shown to lead to an increased road traffic safety risk (OR: 1.57, 95% CI: 0.84-2.95) in a population-based case control study of 10 748 drivers, with known drug and alcohol concentrations, involved in fatal crashes in France between 2001 and 2003. The risk increased to OR 2.12 (CI 1.32–3.38) when THC blood concentrations were measured $\geq 5 \ \mu g/L^{[29]}$ and to OR: 6.60 (C1 1.5–28.0) in a case-control study of fatally injured drivers (N = 3398) in Australia undertaken to assess the effect of alcohol and drug use on the likelihood of drivers culpability.^[31]

THC blood concentrations

It is well established that the blood-concentration-time profile of THC^[39,40] shows a significant dose effect for driving performance. This has been observed in studies using normal healthy volunteers^[41]; in real-life situations (drivers with known THC concentrations, who were involved in fatal crashes^[29]; and in experimental studies to measure the drug's influence on skills related to driving in laboratory tests of isolated psychological functions, driving simulators and on-the-road driving tests.^[21,42]

Impairment

In a retrospective cross-sectional forensic database study (589 cases positive for THC only), blood THC concentration was related to conjunctival injection, pupil dilation, and to the overall risk of being judged impaired. The authors concluded that cannabis impairs driving ability in a concentration-related manner.^[43] There is also evidence of the detrimental effects of cannabis on complex motor tasks being subtle and much longer lasting.^[44]

In Norway, a police physician performs a clinical test for impairment (CTI) shortly after apprehension of drivers suspected of DUID. Khiabani *et al.* found that those who failed a CTI (N = 456) had higher blood THC concentrations than the drivers who were judged as not impaired (median; 2.5 µg/L (range; 0.3-45.3 µg/L) vs 1.9 µg/L (range; 0.32-24.8 µg/L), (p < 0.05). Furthermore, drivers with blood THC concentrations >3 µg/L had an increased risk of being judged impaired compared to drivers with lower concentration ranges.^[45]

International research in Norway (N = 589), Switzerland (N = 440), Sweden (N = 1276), and Finland (N = 2957) of drivers suspected of DUID with THC as the only psychoactive ingredient reported remarkably similar median blood THC concentrations: being 2.0 μ g/L (range 0.3–67 μ g/L); 2.2 μ g/L (range 0.3–45 μ g/L), 3.0 μ g/L and 3.8 μ g/L (range 1.0–60 μ g/L), respectively.^[8,37,46,47]

Ramaekers *et al.* determined that THC blood concentrations 1.0 to 2.5 μ g/L are appropriate for the lower and upper range of a THC limit for impairment above which drivers are at risk,^[24] whilst a Swiss study of DUID suspects (440 positive for THC only) found average blood THC concentrations of 5.0 μ g/L at the time of testing. It was suggested that a residual THC level of 5 μ g/L would appear to correlate with earlier observable driving impairment.^[23]

Crash risk

In experimental studies, researchers have highlighted a heightened crash risk for drivers who drive within 2 h of using cannabis,^[25] the risk being highly significant (Mantel-Haenszel rate ratio, relative risk = 7.0, 95% Cl, 3.1-16) when driving occurs within 60 min of use.^[48] A nationwide study (N = 17 484) of motorcycle and car non-fatal traffic injuries in Spain (2005) found cannabis use >4 days/week was significantly more likely to be associated with traffic injuries than those that had not used the drug.^[49] Similarly, regular use was significantly associated with crash risk after adjustment for confounders (OR: 9.5, 95% Cl 2.8-32.3).^[26,32]

Significant increased accident risk has been reported when the blood THC concentration is $\geq 5 \ \mu g/L$, whether or not ingestion had occurred recently and regardless of the origin of the drug (medicinal or illicit).^[29,31,41] Grotenhermen *et al.* suggest a range of 7.0 to 10 $\mu g/L$ THC in serum for an initial non-zero *per se* limit, equating to a range of 3.5 to 5.0 $\mu g/L$ of THC in whole blood as the most effective approach to separating drivers who are impaired by cannabis use from those who are no longer under the influence,^[50] although Blencowe *et al.* reported that *per se* thresholds in this range would exclude many from prosecution in Finland.^[47]

Equivalence to blood alcohol concentration (BAC)

Meta-analysis of 21 studies^[51,52] investigating acute cannabis ingestion and driving performance and meta-analysis of 78 studies investigating driving following cannabis smoked using a cigarette^[53] and meta-analyses of experimental studies on the impairment of driving-relevant skills by cannabis^[19] have all revealed remarkably similar blood THC concentration data 3.7 µg/L (range 3.1 µg/L to 4.5 µg/L and 3.8 µg/L THC (range for 3.3 µg/L to 4.5 µg/L) and serum THC concentrations of 7-10 µg/L impaired drivers to a level equivalent to a blood alcohol concentration (BAC) of 50 mg alcohol per 100 mL blood.

Controversies

Despite the overwhelming evidence concerning cannabis use and driver safety, there remain several areas of debate in the UK (and elsewhere) regarding its inclusion in road safety legislation. The key issues are discussed below.

Different patterns of use

The method of consumption of cannabis (inhalation or ingestion) is known to play a role in the length and intensity of the psychoactive effect as does the quantity of cannabis used at any one time. Defining a typical THC dose is difficult since consumption varies and is confounded by the availability of different strains of the drug. For instance, 'non-skunk' strains of herbal cannabis are reported to contain 3% to 4% THC - unchanged from a decade ago.^[54] In 2004, the average THC content of Dutch homegrown cannabis (Nederwiet) was 20.4% THC and was significantly higher than that of imported cannabis (7.0% THC).^[55] Other strains are known to have different potency: Northern Lights has a THC content of 15-20% and Durban Poison, a South African strain, has a THC content of 8-15%.^[56] A recent study in Norway (N = 1747) found that between 2000 and 2010, the mean whole blood THC concentrations from drivers suspected of DUID had increased from 4.0 \pm 0.3 µg/L to 6.6 \pm 0.4 µg/L. The authors suggested that this was related to the increase in the potency of the drug during the study period.^[57]

Much has been made of the difference between naïve, recreational (infrequent, occasional) and habitual (frequent, dependent, tolerant) users as well as between acute and chronic effects in terms of driver performance. Some of the key areas are discussed below.

Recreational use of cannabis invariably involves smoking the drug (using a hookah, vaporizer, or cigarette), leading to the rapid passage of THC via inhalation into the blood stream. The plasma concentration time-course after inhalation resembles that after intravenous administration.^[58] After inhalation, absorption of THC is fast, causing maximal blood concentrations within minutes. Markedly bloodshot eyes (conjunctivae), heightened nervousness, greater alertness, and difficulty in paying attention are often recognized as evidence of acute cannabis intoxication.^[59] It has been reported that approximately 200 mg cannabis is typically smoked in an average rolled cigarette (about 5 mg to 30 mg active THC).^[60]

Cannabis is also widely ingested recreationally in foodstuffs (edibles) where quantities of THC can vary tremendously: brownies THC 35mg (25% extraction), pumpkin cake THC 64 mg, a single chocolate bar 45 mg to 60mg THC,^[61] although it is reported that one dose of an edible should contain about 20 mg of THC.^[44,62] A threshold for psychotropic effects of 0.2–0.3 mg THC per kg of body weight for a single oral dose in a lipophilic base, corresponding to 10–15 mg THC in an adult has been suggested.^[63]

Long-term use of cannabis over many years is not unusual and chronic, regular use of cannabis over 19-30 years has been described.^[64] Daily use is also common in habitual users and is almost always associated with dependence.^[65] Users may smoke five to ten cannabis cigarettes per day, thus tolerating daily doses of 100 mg THC or more.^[27] In those who use regularly, the maximal psychoactive effects of cannabis may persist for 4-6 h after use.^[66]

Consideration of the pharmacokinetics of cannabis, particularly the blood THC concentration may help clarify some of the issues raised as a difficulty in terms of formulating drug-driving regulations.

Pharmacokinetics

As with alcohol and other drugs, the influence of cannabis on driving behaviour depends on the dose taken in relation to the length of time between dosing and driving taking place.^[24] The pharmacokinetics of cannabis is complex and likely explained by a two- or three-compartment model. Unlike alcohol, and owing to its high lipid solubility and large volume of distribution, THC, regardless of the strain or the preparation consumed, is widely distributed in the body.

Smoking (inhalation) topology

Peak plasma THC concentrations typically occur within 3 to 15 min of inhalation but decline rapidly due to distribution into

body tissues and fat.^[17,36,52] Smoking cannabis produces significant acute effects despite variability in the bioavailability of THC from 10-14% in recreational (infrequent), to 23-56% in habitual users,^[67–69] and 18% in healthy volunteers.^[70] Bioavailability varies according to depth of inhalation, puff duration, and breath-hold. In a study of regular marijuana users, breath-hold (a common behaviour of cannabis smokers) duration (0, 10, and 20 s) and puff volume (30, 60, and 90 mL) were systematically varied. Post-smoking changes in CO exposure, plasma THC and subjective reports (especially acute intoxication) were significantly dose related to puff volume: 45 min post-smoking for 1.75% THC and for 3.55% THC cigarettes and puff volume 30, 60, and 90 mL plasma concentrations were 5.7 μg/L, 14.6 μg/L, and 22.9 μ g/L for the lower potency and were 12.8 μ g/L, 25.9 µg/L, and 30.5 µg/L for the higher potency cigarettes, respectively.^[71] Results suggest that puff volume rather than breathhold is important in determining blood THC concentrations and subjective effects.

Naïve and recreational use (infrequent user)

In those given doses (often experimentally) to duplicate a single cannabis cigarette (18 mg THC or less), a maximal psychotropic effect was found 20-40 min after smoking, but effects had largely disappeared 2.5 h later.^[19,40,51,52] Smoking a single, one-off, cannabis cigarette, leads to higher plasma THC concentrations in the body than that observed in habitual users. Smoking a single cannabis cigarette containing 16 mg, or 34 mg THC, saw average peak plasma THC concentrations of 84.3 µg/L (range: 50.0 to 129.0 µg/L), for the lower dose and 162.2 µg/L (range: 76.0 to 267.0 μg/L) for the higher dose, respectively^[69]; 3 h after smoking cigarettes containing 27 mg THC concentrations were 21.5 µg/L (range 3.2 to 53.3 μ g/L)^[72,73] and a blood THC concentration range of 33 to 77 µg/L for a 19 mg cigarette.^[74] THC concentrations rapidly decrease typically to between 1.0 and 4 ug/L within 3-4 h.^[73,75,76] Thus it would be reasonable to conclude that driving after smoking cannabis is not safe for those who use the drug infrequently. This is supported by a more recent meta-analysis and other studies of the concentration effect relationship of THC.[25,77]

The time-course of THC that has been ingested differs from inhaled THC as a result of the passage through the gut. Following ingestion absorption of THC is slow and unpredictable, with maximal concentrations occurring between 1 and 7 h post dose.^[51,78,79] Bioavailability is low with only 6% THC reaching the blood when orally administered^[69] and the onset of psychoactive effects occurs after a delay of 30-90 min, reaching their maximum after 2-3 h and lasting for about 4-12 h, depending on the dose.^[73] In addition, when THC is taken orally, concentrations of the equipotent metabolite 11-hydroxy-THC (11-0H-THC or THC-OH) THC are higher (due to greater amounts of THC entering the liver) bringing about a synergistic effect.^[70,71]

Maximal plasma THC concentrations after oral consumption of a 15 mg dose (2.7 to 6.3 μ g/L)^[80] and a chocolate cookie (20 mg dose) were lower (4.4 to 11.0 μ g/L) than that found after a single cannabis cigarette.^[63,81] However, a meta-analysis of 21 studies investigating cannabis ingestion and driving performance revealed that a blood THC concentration of 3.7 μ g/L (range 3.1 to 4.5 μ g/L) impaired drivers to a level equivalent to a BAC of 50 mg alcohol per 100 mL blood^[52] suggesting that ingestion of cannabis edibles is not recommended if intending to drive because of the prolonged and erratic duration of action of the drug.

In infrequent users, the difference in plasma THC concentration between peak and trough is usually greater than that observed in habitual users who if smoking daily (or near daily) will achieve a steady-state condition (rate of administration and rate of elimination reach an equilibrium): blood THC concentrations being maintained by the continual release of THC from the tissues into the general circulation. More recently, with the benefit of advanced analytical techniques, the steady state volume of distribution for THC was estimated to be 3.4 l/kg.^[82] In infrequent users plasma THC concentrations have been reported to fall below the laboratory limits of quantitation within 8-12 h,^[19] whereas in regular users, a mean blood THC concentration was found to be 0.7 μ g/L (SD 1.4 μ g/L) after 24 h abstinence and after 7 days abstinence on a closed research unit 0.3 µg/L (SD 0.7µg/L).^[83] Variable rates of release of THC from tissue stores have been reported and have led some to suggest that the detection of THC may not indicate recent use in daily cannabis users.^[81]

The plasma elimination half-life (the time taken for the blood drug concentration to reduce by half) is used to estimate how long a drug takes to leave the body and has been described as multiphasic for THC^[84]: the distribution phase $(t^{1/2}\alpha)$ is relatively short since THC is rapidly assimilated and distributed to adipose tissues. T¹/₂ α for regular users (about 2 h) is marginally different from recreational users (about 1.5 h) of cannabis.^[60,84] THC is slowly released back into the blood causing a relatively long terminal elimination ($t^{1/2}$ B) half-life.^[49] The $t^{1/2}$ B after oral or intravenous administration is reported to be between 19 h and 57 h,^[24,69,85,86] although a monitoring window of up to 72 h is considered too short leading to an underestimation of this parameter.^[82,87] When deuterium labelled THC was given to habitual users (using \geq 1 cigarette/day) and blood samples were collected for 10-15 days, t¹/₂ B was estimated to be 4.3 days.^[88] No significant pharmacokinetic differences between chronic and occasional users have been substantiated.[89]

Adipose tissue serves as a long-term storage site for THC. This particular pharmacokinetic attribute explains the non-correlation between blood THC concentration and pharmacodynamic effect.^[85] Unlike alcohol, there is no clear relationship between blood THC concentrations and impairment,^[50,73,90] with the time of maximum blood THC concentration proceeding the time of maximum impairment of driving-related abilities.^[51,52] This makes it much harder to generate blood concentration time date versus impairment curves for cannabis than it is for alcohol.^[23]

Metabolism

The major metabolite 11-hydroxy-THC (11-OH-THC or THC-OH) formed by hydroxylation after both inhalation and oral dosing is pharmacologically active (equipotent). It is further oxidised to generate the inactive 11-nor-9-carboxy-THC (THC-COOH), which is eliminated via the faeces and urine.^[82,85] 11-hydroxy-THC has a half-life of 120 h for frequent users and is eliminated more slowly (144 h) in infrequent users of the drug.^[91] Both 11-hydroxy-THC and the THC-COOH metabolite are detectable for a considerable time after a cannabis cigarette.^[91] THC-COOH is detectable in plasma for up-to 3 days (range 2-7 days)^[73,92] and in urine for longer.^[91,93]

Passive exposure

It has been reported in a small number of controlled studies in the 1980s that THC can be detected in blood after passive exposure to cannabis smoke. However, modern analytical methods suggest that due to the rapid distribution of THC in the body, which also occurs after passive exposure to low doses, serum THC concentration after exposure would be <1 µg/L within an hour, whilst similar and very low serum THC-COOH concentrations would also be observed (<2 µg/L). Higher blood concentrations were suggested as commensurate with the deliberate consumption of a psychoactive dose.^[94] Exposure of volunteers to cannabis smoke under real-life conditions failed to demonstrate blood THC concentrations at, or even near, those associated with impairment.^[95]

Medicinal cannabinoids

Various analogues of cannabis have been manufactured commercially for medical purposes. They act on the CB receptors and are assumed to produce the same psychoactive effects as illicit cannabis and can be detected in measureable quantities in blood, urine, hair, and saliva.

Those on the market include dronabinol (Marinol[®]), a pure isomer of THC, which is licensed in the USA and Germany for cachexia (weight loss) in patients with AIDS patients and in chemotherapy patients who have not responded to traditional antiemetics.^[96] It is taken orally and is available in 2.5 mg, 5 mg and/or 10 mg dosages. Experimental studies found that dronabinol (10 mg to 20 mg) caused impairment in on-the-road driving tests in a dose dependent manner. In a single-dose (dronabinol 10 and 20 mg), double-blind, placebo–controlled study of recreational and chronic cannabis users, a dose-dependent effect was observed on driving performance when under the influence of THC regardless of the experience of the user.^[97] Impairments were deemed bigger than the effects caused by a BAC of 50 mg alcohol/100 mL blood, although effects were less pro-nounced in this regard after chronic dosing.^[98]

Nabilone (Cesamet®) a synthetic analogue of THC is licensed in the UK, Canada, and the USA for the nausea and vomiting associated with chemotherapy. Nabilone (usual dose 2-4 mg/day: 1 mg cesamet® capsule contains 1 mg of nabilone), is well absorbed and as with THC, there is a high first-pass effect and nabilone has a t½ α of about 2 h.^[99] Oral administration of a 2-mg dose of radio-labelled nabilone achieved peak plasma synthetic THC concentrations of approximately 2 µg/L within 2.0 h (1 µg/L whole blood).^[92] Clinical trials have found that nabilone produces less tachycardia and less euphoria than THC for a similar antiemetic response^[100] and following 2 mg/day dosing reaction time, working memory, divided attention, psychomotor speed and mental flexibility did not deteriorate during a 4-week treatment period.^[101]

Nabiximols (Sativex[®]), an oromucosal spray containing THC together with cannabidiol (CBD) is the first natural cannabis extract prescription medicine and is available in the UK and some European countries, Canada, and New Zealand. Nabiximols spray is delivered in a fixed dose of 2.7 mg THC and 2.5 mg CBD and is indicated in the treatment of moderate to severe spasticity in multiple sclerosis.^[96] Twelve subjects took part in a fed–fasted cross-over study and received a single dose of THC/CBD spray (4 sprays, 10.8 mg THC and 10 mg CBD) in the fasted then fed state (or vice versa) with a 3-day wash-out period between treatments. It took approximately 2 h to reach the mean peak THC plasma concentration, which in fed subjects ranged from 2.8 to 14.9 μ g/L compared with 0.97 to 9.34 μ g/L observed in the fasted state.^[102]

Although data is limited, it would seem that the use of orally administered, licensed medicinal cannabinoids, produces lower blood THC concentrations than observed in recreational and habitual users of the drug, providing medicinal cannabinoids are taken in accordance with directions given by the prescriber. Blood THC concentrations are higher in those given THC/CBD spray. However, in countries with a zero tolerance approach to cannabis use and driving those prescribed licensed medicinal cannabinoids may well achieve blood THC concentrations that would lead to a positive test (Table 1).

Synthetic cannabinoids

Over the last few years synthetic cannabinoid receptor agonists have been detected in samples of smoking mixes such as Spice, Aroma, K2 and Silver and are reported to have pharmacology similar to that of cannabis. These include AM-2201, JWH-018, JWH-019, JWH-122, JWH-210, JWH-307, AM-2201-pMe, MAM-2201 or JWH-122 5-fluoropentyl derivative, AM-1220, AM-1220-azepane, UR-144, XLR-11, JWH-122-pentenyl, AM-2232, and STS-135.^[103,104]

Usually sprayed onto dried herbal tobacco, they are marketed under a variety of names. 'Annihilation' was found to contain the synthetic cannabinoids AM-2201, MAM-2201 and UR144 in two seizures from Scotland.^[105] Many of the mixtures available under different brand names contain the same compounds, one of which (AM2201) has been identified in products traded as 'Black Mamba', 'Tai High Hawaiian Haze', and 'Bombay Blue Extreme'.^[106] In the UK (2011/2012), it was reported that 0.1% 16–59-year-olds used 'Spice' and other cannabinoids in the last year, with 0.4% 16–24-year-olds reporting use in 2010/2011.^[107]

We are only just beginning to learn about the relationship between synthetic cannabis use and driving performance. Very recent research suggests consumption of synthetic cannabinoids can lead to impairment similar to typical performance deficits caused by cannabis use which are not compatible with safe driving. These include centrally sedating effects and the impairment of the fine motor skills necessary for keeping the vehicle on track.^[103] The synthetic cannabinoid HU-210 (the (-)-1, 1dimethylheptyl analog of 11-hydroxy- Δ^8 - tetrahydrocannabinol) is reported to be 100 to 800 times more potent than natural THC and has an extended duration of action.^[108] It has been detected in three Spice products in the UK.^[109,110] Another, JWH-018 has been reported to have intoxicating effects, with serum JWH-018 concentrations generally in the 1–10 µg/L range during the first few hours after recreational usage.^[111] In North America, synthetic cannabinoid testing performed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) on those suspected of driving impaired reported JWH-018 (n=4), 0.1-1.1 μg/L; JWH-122 (n=3), 2.5 μg/L; JWH-210 (n=4), 0.1 μg/L; JWH-250 (n=1), 0.38 $\mu g/L$ and AM-2201 (n = 6), 0.43-4.0 $\mu g/L.^{[112]}$

Some argue that the toxicity of the synthetic cannabinoids are greater than that of natural cannabis, owing to the higher potency, the difficulties of proper dosing and also the possibility of the presence of several different cannabinoids in one smoking mix.^[113] There is a need to more fully assess the relationship between synthetic cannabinoid use and psychomotor and cognitive impairment^[112] and to give serious consideration to their inclusion in drug-driving legislation.

A problem, however, is that smoking mixes do not cause a positive drug test for cannabis or other illegal drugs using standard gas chromatography-mass spectrometry (GC-MS) drug-screening with library search or multi-target screening by LC-MS/MS, although bespoke methodology has enabled detection. Synthetic cannabinoids are not detected by older immunoassay drug screening methods employed for detecting metabolites of cannabis (THC, THCCOOH). However, JWH-018 usage is readily detected in urine using Spice screening immunoassays from several manufacturers focused on both the parent drug and its omega-hydroxy and carboxyl metabolites.^[114]

Driving and the combined use of cannabis and alcohol

The combined use of cannabis and alcohol produces severe impairment of cognitive, psychomotor, and actual driving performance in experimental studies and sharply increases the crash risk in epidemiological analyses.^[24,43] Experimental and epidemiological studies have demonstrated that consumption of even low to moderate doses of alcohol in combination with cannabis produces severe driver impairment and greatly increases the risk of an accident.^[22–24,45,115,116] The risk has been described as comparable to the sum of the effects of alcohol and THC when consumed separately.^[24] Although the results of culpability studies have been contradictory, all find the combination of alcohol and cannabis has worse consequences than cannabis use alone.^[19,117–119]

In a study in the UK of 126 fatalities in single-car crashes with cannabis use detected, three-quarters of drivers had BAC levels below the UK legal limit of BAC 80 mg alcohol/100 mL blood drivers.^[120] Some are concerned that cannabis use may be more prevalent than alcohol use as a road safety risk.^[121] Laumon *et al.*^[29] interpreting risk estimates as odds ratio's (ORs) for involvement in, or injury as the result of an RTC, when driving under the influence of cannabis and alcohol found significant increase in risk when alcohol and cannabis were consumed together (Figure 1, adapted from Laumon *et al.*^[29]).

The estimated odds ratio for cannabis and alcohol combined was higher than the sum of either cannabis or alcohol use alone. Many agree^[29,30,41,122-126] that the combination of alcohol and cannabis has a synergistic, multiplicative effect on driver performance. In a responsibility study, combined use of alcohol and cannabis multiplied the risk of causing a fatal accident OR: 8.39*1.89 = OR: 15.86.^[127]

However, legislating for the combined use of alcohol and cannabis as a road safety measure would appear complicated because of the operational difficulties of considering two separate compounds at the roadside that require two different testing procedures. One option that should be considered would be to set lower thresholds for both substances in the blood confirmation test.^[13] The technology for low breath-alcohol thresholds



Figure 1. The relationship between the odds ratio (OR) for the risk of a traffic accident when cannabis and alcohol are detected alone and when alcohol and cannabis use are detected concurrently (Data from Laumon *et al*⁽²⁹⁾). Positive detection of cannabis was defined as a blood \$9-tetrahydrocannabinol (THC, the main psychoactive constituent of cannabis) concentration of >1 +g/L and for alcohol (EtOH) as \geq 50 mg alcohol/100 mL blood.

K. Wolff and A. Johnston

(20 mg alcohol and 40 mg alcohol per 100 ml blood) already exists^[128] and could be used alongside roadside screening tests for THC.

Multiple drug-use and driving performance

The DRUID report^[9,126,127] and others^[124] found that in Europe, on average between 20% and 30% of cannabis use was in combination with other psychoactive substances and also noted that THC was most commonly detected when drugs were found in multi-drug combinations alongside cocaine, and (sometimes illicitly used) benzodiazepines. Legislating for the combined use of cannabis and other controlled drugs as a road safety measure is also complicated because of operational difficulties. Police officers may not recognize that those DUIDs are impaired as a result of the use of two or more substances and screening simultaneously at the roadside for several drugs may be technically difficult. In addition few drug-drug interactions have been fully characterised in the drug-driving context and the number of possible combinations is wide ranging. A solution to address the issue of multiple drug use and driving has yet to be formulated.

Collection of specimens for evidential analysis

Blood sampling is considered to be the most effective way to confirm the presence of THC in the body as it best relates to the scientific evidence in relation to driving performance. Whole blood is usually collected for this purpose but standardization of sample collection and transportation conditions are not well described. Robust guidelines in this regard are urgently needed. However, the choice of fluid for screening at the roadside is under discussion and several confounding factors have emerged.

In general, immunoassays are used as a preliminary drugscreening test method in urine. Several urine-screening tests are available for cannabis with different cut-offs (the Amersham Cannabis RIA, 10 µg/L; the Roche Abuscreen® RIA, 100 µg/L 10 ug/L, Syva, Seimens®; and the Syva EMITR d.a.u.[™] Assay, 20 µg/L). However, false positive tests can occur when structurally related drugs are recognised by the antibodies or false negatives can arise when adulterants (Instant Clean Add-it-ive, or Clear Choice, www. detoxforless.com/pass-a-drug-test/) or diuretics are employed and affect the assay process. The window of detection for urinary cannabis is long ranging in both frequent users^[129,130] and in infrequent users.^[91] This finding is related to a cross reaction from the active metabolite 11-hydroxy-THC,^[60,73] and inactive metabolites^[131] with the antibody for THC-COOH.^[84]

Urine immunoassay screening tests that detect combinations of THC and metabolites, such as 11-hydroxy-THC and THC-COOH may detect the presence of cannabis for several days^[19,37,60] but not necessarily the presence of THC. It can take as long as 4 h for metabolites to appear in urine in concentrations sufficient to be detected by an immunoassay test.^[73] Positive urinalysis test results therefore only indicate previous use rather than time since last dose.^[41]

A further problem with urinalysis for the road driving context is that screening will only reveal whether a person has been exposed to cannabis, not whether they are impaired by it.^[132,133] In addition, Sewell *et al.* argues that a urine screening test that measures concentrations of the long-lasting metabolite THC-COOH but not THC is insufficient to classify a driver as intoxicated; as such a measure will include unimpaired drivers who have smoked only in the past.^[23] These issues preclude urinalysis as a suitable matrix for the road-side screening assessment or the confirmation of DUID.

The most accessible matrix for roadside detection of drugs is OF since it is easy to obtain. A debate is on-going with regard to whether OF THC concentration correlates well with blood THC concentration as an indirect indicator of driving impairment. The Integrated Project DRUID (2011) determined that there was not a reliable correlation between OF and blood THC (R^2 = 0.0003) using 162 positive cases. The mean OF/B ratio was 26.19 (95% CI 17.18 - 35.19), with a minimum OF/B ratio 0.09 and a maximum of 138.8. ^[134] OF measurements can be indicative of recent consumption.^[135] However, contamination of the buccal cavity is an issue for the detection of cannabis from use by oral, intra-nasal or smoking routes of administration (insufflations). 'Shallow depots' of cannabis may, following recent use, accumulate in the buccal cavity and produce elevated OF THC (contamination) concentrations after ingestion.^[85] Following controlled cannabis smoking (54 mg THC per cigarette) all participants tested THC positive, 6 h post-dose at the Substance Abuse and Mental Health Service (SAMHSA) cut-off (proposed 2 $\mu g/L)$ and the DRUID European cut-off (1 $\mu g/L).^{[136]}$

Cannabinoids do not pass readily from blood into OF although this does happen to some extent following consumption of high doses of the drug^[93] and THC may be released from depots in the buccal mucosa as has been shown for other drugs.^[137] Many researchers have demonstrated the same pattern of OF THC concentration-time data: namely initial very high (contamination) concentrations up to 1080 μ g/L^[138] and up to 2544 μ g/L^[139], with peak OF THC concentrations of 5800 μ g/L reported immediately after smoking,^[140] followed by rapid clearing, and a slower decline.

Initial work has suggested that OF THC concentrations can fluctuate over time making the prediction of blood THC concentrations, and the ratio from OF very difficult^[140]. However, OF THC concentrations have been used to predict positive blood tests in DUID suspects. Laloup *et al.*^[141] compared OF and plasma THC concentrations (Intercept® device) in those suspected of DUID. An OF THC concentration of 1.2 µg/L predicted a positive plasma test (sensitivity 94.7%, specificity 92.0%) for a zero tolerance plasma THC cut-off (0.5 µg/L), whilst an OF THC concentration of 5.2 µg/L reliably predicted a positive blood THC result (sensitivity 91.6%, specificity 88.6%) when a higher plasma cut-off was the target (2 µg/L). These values are below the manufacturer's cut-off for OF screening devices such as the Cozart RapiScan device (10 µg/L).

Whilst unproven as a confirmatory test, OF remains a viable matrix for roadside drug screening and has been used for random roadside testing including for cannabis in Queensland, Australia.^[142] OF has the added advantage of having almost no THC-COOH metabolite present^[136]: the window of detection will not therefore be overly extended as a result of cross-reaction on OF cannabis immunoassay tests.

Conclusion

Concern about the dangers of drug-driving has heightened in recent years and national survey estimates suggest that growing numbers of adults drive under the influence of illicit drugs, particularly cannabis. There is undoubtedly a need to include cannabis in UK drug-driving legislation since a definitive, significant, doserelated decrement in driving performance is observed for those who use the drug.

Crucially, raised blood THC concentrations are significantly associated with increased traffic crash and death risk regardless of the experience of the user. This evidence lends support to a *per se* threshold approach for cannabis. Those against such an approach have argued that this condones illicit drug use. When selecting a specific blood THC concentration, the risks of false positives and negatives must be balanced. A higher threshold will result in a high proportion of false negatives, especially if the time lag between roadside screening and confirmatory test is prolonged.

Several meta-analyses of different research studies^[9,51-53] provide consensus about the concentration of THC (3.7 µg/L) required to impair drivers to a level equivalent to a BAC of 50 mg alcohol per 100 mL blood. In addition, it is acknowledged that significant increased RTC risk has been reported when the blood THC concentration is $\geq 5 \mu g/L$, whether or not ingestion had occurred recently and regardless of the origin of the drug (medicinal or illicit).^[29,37,41,48,53] Blood THC concentration data are more varied (median 2.0 µg/L to 3.8 µg/L, range 0.3–67 µg/L) in international research of those apprehended for DUID,^[37,38,47,117] possibly due to time-related delays in sample collection. Legislators in the UK will also need to consider the variability in THC concentrations measured by different forensic laboratories in identical blood samples due to different methodological processes.

The scientific evidence is clear with regard to driving under the influence of cannabis (DUIC). Like alcohol, a strong relationship exists between increasing blood THC concentration and risk of a road traffic collision. However, interpretation of the evidence has been muddled by the conflation of two issues: that of fitness to drive (driver safety) under the influence of cannabis and that of criminality due to the illicit nature of the drug.

Using the approach currently used for alcohol which is based on road safety, a legal threshold would be agreed, i.e. if a driver exceeds this threshold they could be prosecuted without the requirement to prove impairment and that this impairment was caused by the drug in their body. This approach will help protect those legitimately prescribed the drug. The zero tolerance approach (no amount of THC is permissible in the body) is concerned with the criminality of the drug and relates to unlawful possession, although there is an anomaly here that in the UK at least it is not an offence to consume and have a controlled drug present in the body. Systematic study of cannabis use in British drivers may help to reassure those of the need for a *per se* approach.

References

- United Nations Office on Drug and Crime. UN World Drug Report. UN, 2011, Vienna, Italy, pp. 11–18.
- [2] Department for Transport. Reported Road Casualties in Great Britain, 2011 Annual Report, Transport Statistics publications, DfT, Gwent, Wales.
- [3] Department for Transport, Sir Peter North. Report of the Review of Drink and Drug Driving Law, 2010, Queen's Printer and Controller of Her Majesty's Stationery Office, dft publications. ISBN 9781 84864 0993.
- [4] M.F. Andreasen, J.B. Hasselstrom, I. Rosendal Prevalence of Licit and Illicit drugs in whole blood among Danish Drivers in Western Denmark. SOFT-TIAFT, San Francisco, 2011.
- [5] T. Assum, M.P. Mathijssen, S. Houwing, S.C. Buttress, R.J. Sexton, R.J. Tunbridge, R. Mathijssen, S. Houwing. The prevalence and relative risk of drink and drug driving in the Netherlands: a case control study in the Tilburg police district. Research of the European Research program IMMORTAL, 5th Framework Program. R-2005-9, 2nd Edition, Report No: D-R4, **2005**, SWOV, Institute for Road Safety Research, Leidschendam, The Netherlands.
- [6] Drug Misuse Declared: Findings from the 2011/12 Crime Survey for England and Wales, 2nd Edn. Available at: http://www.homeoffice.

gov.uk/publications/science-research-statistics/research-statistics/ crime-research/drugs-misuse-dec-1112/drugs-misuse-dec-1112-pdf. [July 2013].

- [7] European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Drug use impaired driving and traffic accidents. EMCDDA Insights Series No 8. Office for Official Publications of the European Communities, Luxembourg, 2008.
- [8] A.W. Jones, A. Holmgren, F.C. Kugelberg. Driving under the influence of cannabis: a 10-year study of age and gender differences in the concentrations of tetra hydrocannabinol in blood. *Addiction* **2008**, *103*, 452.
- [9] Driving under the Influence of Drugs, Alcohol and Medicines (DRUID). DRUID deliverable D3.2.2, Summary of main DRUID results: Driving under the influence of drugs, alcohol, and medicines, TRB 91ST Annual meeting, USA Dutch Forensic Institute Report, 2012.
- [10] V. Vindenes, D. Jordbru, A.B. Knapskog, E. Kvan, G. Mathisrud, L. Slørdal, J. Mørland. Impairment based legislative limits for driving under the influence of non-alcohol drugs in Norway. *Forensic Sci. Int.* **2012**, *219*, 1.
- [11] RRCGB. 2011 Annual Report. Self-reported drink and drug driving: Findings from the Crime Survey for England and Wales. Available at: https://www.gov.uk/government/uploads/system/uploads/ attachment_data/file/9278/rrcgb2011-05.pdf [July 2013].
- [12] J. Neale, N. McKeganey, G. Hay, J. Oliver. Recreational drug use and driving: A qualitative study. The Scottish Executive Central Research Unit, The Stationery Office, Edinburgh, 2000
- [13] P. Terry, K. Wright. Self-reported driving behaviour and attitudes towards driving under the influence of cannabis among three different user groups in England. *Addict. Behav.* 2005, *30*, 619.
- [14] S. Darke, E. Kelly, J. Ross. Drug driving among injecting drug users in Sydney, Australia: Prevalence, risk factors and risk perceptions. *Addiction* 2004, 99, 175.
- [15] C. Jones, N. Donnelly, W. Swift, D. Weatherburn. Driving under the influence of cannabis: The problem and potential countermeasures. *Crime Justice Bull.* 2004, 87, 1.
- [16] Driving under the influence of drugs. The report of the Department for Transport Expert Panel. Available at: https://www.gov.uk/government/publications/ driving-under-the-influence-of-drugs--2. [July 2013].
- [17] P. Sharma, P. Murthy, M.M. Bharath. Chemistry, metabolism, and toxicology of cannabis: Clinical implications. *Iran J. Psychiat.* **2012**, *7*, 149.
- [18] I. Kurzthaler, M. Hummer, C. Miller, B. Sperner-Unterweger, V. Günther, H. Wechdorn, H.J. Battista, W.W. Fleischhacker. Effect of cannabis use on cognitive functions and driving ability. *J. Clin. Psychiatry* **1999**, *60*, 395.
- [19] G. Berghaus, B. Guo. Medicines and driver fitness--findings from a meta-analysis of experimental studies as basic information to patients, physicians and experts. in Alcohol, Drugs, and Traffic Safety--T95: Proceedings of the 13th International Conference on Alcohol, Drugs and Traffics Safety (Eds: C. Kloeden, A. McLean) Adelaide, Australia, **1995**, NHMRC Road Accident Research Unit. ISBN 090820413 pp. 295–300.
- [20] M.N. Bates, T.A. Blakely. Role of cannabis in motor vehicle crashes. *Epidemiol. Rev.* **1999**, *21*, 222.
- [21] G. O'Kane, D.C. Tutt, L.A. Bauer. Cannabis and driving: A new perspective. *Emerg. Med.* 2002, 14, 296.
- [22] L.R. Sutton. The effects of alcohol, marihuana and their combination on driving ability. J. Stud. Alcohol **1983**, 44, 438.
- [23] R.A. Sewell, J. Poling, M. Sofuoglu. The effect of cannabis compared with alcohol on driving. Am. J. Addict. 2009, 18, 185.
- [24] J.G. Ramaekers, G. Berghaus, M. van Laar, O.H. Drummer. Dose related risk of motor vehicle crashes after cannabis use. *Drug Alcohol Depend.* 2004, 73, 109.
- [25] M. Asbridge, C. Poulin, A. Donato. Motor vehicle collision risk and driving under the influence of cannabis: Evidence from adolescents in Atlantic Canada. *Accident Anal. Prev.* **2005**, *37*, 1025.
- [26] S. Blows, R. Ivers, M. Woodward, J. Connor, S. Ameratunga, R. Norton. Vehicle year and the risk of car crash injury. *Inj. Prev.* 2003, *9*, 353.
- [27] K.L. Movig, M.P. Mathijssen, P.H. Nagel, T. van Egmond, J.J. de Gier, H.G. Leufkens, A.C. Egberts, Psychoactive substance use and the risk of motor vehicle accidents. *Accident Anal. Prev.* 2004, *36*, 631.
- [28] M. Bédard, S. Dubois, B. Weaver. The Impact of Cannabis on Driving. *Revue Canadienne De Sante Publique* 2007, 98, 6.
- [29] B. Laumon, B. Gadegbeku, J.L. Martin, M.B. Biecheler. Cannabis intoxication and fatal road crashes in France: Population based case-control study. *Brit. Med. J.* 2005, 331, 1371.

- [30] P. Mura, P. Kintz, B. Ludes, J.M. Gaulier, P. Marquet, S. Martin-Dupont, F. Vincent, A. Kaddour, J.P. Goulle, J. Nouveau, M. Moulsma, S. Tilhet-Coartet, O. Pourrat. Comparison of the prevalence of alcohol, cannabis and other drugs between 900 injured drivers and 900 control subjects: Results of a French collaborative study. *Forensic Sci. Int.* **2003**, *133*, 79.
- [31] O.H. Drummer, J. Gerostamoulos, H. Batziris, M. Chu, J. Caplehorn, M.D. Robertson, P. Swann. The involvement of drugs in drivers of motor vehicles killed in Australian road traffic crashes. *Accidnte Anal. Prev.* 2004, 36, 239.
- [32] S. Blows, R.Q. Ivers, J. Connor, S. Ameratunga, M. Woodward, R. Norton. Marijuana use and car crash injury. *Addiction* 2005, 100, 605.
- [33] Driving under the Influence of Drugs, Alcohol and Medicines (DRUID). Main results to be communicated to different target groups. Available at: http://www.druid-project.eu/cln_031/ nn_107548/Druid/EN/ deliverables-list/downloads/Deliverable __7_3_2, templateId=raw, property=publicationFile. pdf/ Deliverable_7_3_2.pdf. [July 2013].
- [34] G. Gmel, H.A. Kuendig, J.A. Rehm, N. Schreyer, J.B. Daeppen. Alcohol and cannabis use as risk factors for injury – a case-crossover analysis in a Swiss hospital emergency department. *BMC Public Health* **2009**, *9*, 40.
- [35] F.M. Fergusson, L.J. Horwood. Cannabis use and traffic accidents in a birth cohort of young adults. *Accident Anal. Prev.* 2001, 33, 703.
- [36] M.R.J. Baldock. Review of the literature on cannabis and crash risk (CASR010), Centre for Automotive Safety Research, Department for Transport, Energy and Infrastructure (SA), Adelaide, 2007.
- [37] M. Augsburger, N. Donzé, A. Ménétrey, C. Brossard, F. Sporkert, C. Giroud, P. Mangin. Concentration of drugs in blood of suspected impaired drivers. *Forensic Sci. Int.* 2005, 153, 11.
- [38] C. Giroud, A. Menetrey, M. Augsburger. Delta(9)-THC, 11-OHDelta(9)-THC and Delta(9)-THCCOOH plasma or serum to whole blood concentrations distribution ratios in blood samples taken from living and dead people. *Forensic Sci. Int.* **2001**, *123*, 159.
- [39] G. Jager. Cannabis. in Drug Abuse and Addiction in Medical Illness, (Eds: J.C. Vester, K. Brady, M. Galanter, P. Conrod), Springer, New York, 2012, pp. 151–162.
- [40] F.Grotenhermen. Harm reduction associated with inhalation and oral administration of cannabis and THC. J. Cannabis Ther. 2001, 1, 133.
- [41] S.R. Watchel, M.A. ELSohly, S.A. Ross, J. Ambre, H. de Wit. Comparison of the subjective effects of delta-(9) tetrahydrocannabinol and marijuana in humans. *Psychopharmacology (Berl)* 2012, 161, 331.
- [42] European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Literature Review on the Relation between Drug Use, Impaired Driving and Traffic Accidents. CT.97.EP.14 EMCDDA, Lisbon, **1999**.
- [43] J.G. Bramness, H.Z. Khiabani, J. Mørland. Impairment due to cannabis and ethanol: clinical signs and additive effects. *Addiction* 2010, 105, 1080.
- [44] V.O. Von Leirer, J.A. Yesavage, D.G. Morrow. Marijuana carry-over effects on aircraft pilot performance. *Aviat. Space Envir. Md.* **1991**, 62, 221.
- [45] H.Z. Khiabani, J.G. Bramness, A. Bjørneboe, J. Mørland. Relationship between THC concentration in blood and impairment in apprehended drivers. *Traffic Inj. Prev.* 2006, 7, 111.
- [46] R. Kronstrand, A.W. Jones. Drugs of abuse analysis. in Encyclopedia of Forensic Sciences, (Eds: J.A. Siegel, P.J. Saukko, G.C. Knuffer), Academic Press, San Diego, CA, 2000, pp. 598–610.
- [47] T. Blencowe, A. Pehrsson, S. Mykka nen, T. Gunnar, P. Lillsunde. Cannabis findings in drivers suspected of driving under the influence of drugs in Finland from 2006 to 2008. *Forensic Sci. Int.* 2012, 217, 107.
- [48] J. Pulido, G. Barrio, P. Lardelli, M.J. Bravo, T.M. Brugal, A. Espelt, L. de la Fuente. Cannabis use and traffic injuries. *Epidemiology* 2011, *22*, 609.
- [49] J. Pulido, G. Barrio, P. Lardelli, M.J. Bravo, E. Regidor, L. de la Fuente. Association between cannabis and cocaine use, traffic injuries and use of protective devices. *Eur. J. Public Health* **2011**, *21*, 753.
- [50] F. Grotenhermen, G. Leson, G. Berghaus, O.H. Drummer, H.P. Krüger, M. Longo, H. Moskowitz, B. Perrine, J.G. Ramaekers, A. Smiley, R. Tunbridge. Developing limits for driving under cannabis. *Addiction* **2007**, *102*, 1910.
- [51] G. Berghaus, E. Schulz, A. Szegedi. Cannabis und fahrtüchtigkeit. Ergebnisse der experimentellen forschung [Cannabis and driving

skills: Results of experimental research]. in Cannabis im Straßenverkehr [Cannabis and Driving], *(Eds*: G. Berghaus, H.P. Krüger). Gustav Fisher Verlag, Stuttgart, **1998**, pp. 73–97.

- [52] G. Berghaus, G. Sticht, W. Grellner, D. Lenz, T. Naumann, S. Wiesenmüller. Driving under the Influence of Drugs, Alcohol and Medicines (DRUID). 6th Framework programme, Deliverable 1.1.2b, Meta-analysis of empirical studies concerning the effects of medicines and illegal drugs including pharmacokinetics on safe driving. **2010**, Transport RTD Program, University Wursburg, UWURZ, Germany.
- [53] Driving under the Influence of Drugs, Alcohol and Medicines (DRUID). Summary of main DRUID results, TRB 91ST Annual meeting, USA Dutch Forensic Science. Available at: http://www. drugscope.org.uk/Resources/Drugscope/Documents/PDF/Good% 20Practice/cannabis_submission.pdf. [May 2013].
- [54] European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Annual report on the state of the drugs problem in Europe. EMCDDA, Lisbon, November. Available at: www.emcdda. europa.eu/publications/annual-report/2010. [May 2013].
- [55] F.T. Pijlman, S.M. Rigter, J. Hoek, H.M. Goldschmidt, R.J. Niesink. Strong increase in total delta-THC in cannabis preparations sold in Dutch coffee shops. *Addict. Biol.* **2005**, *10*, 171.
- [56] Marijuana Growers Headquarters. How best to use medical marijuana. Available at: http://www.marijuanagrowershq.com/how-best-to-usemedical-marijuana-smoking-vs-edibles-and-tinctures/ [July 2013].
- [57] V. Vindenes, D.H. Strand, L. Kristoffersen, F. Boix, J. Mørland. Has the intake of THC by cannabis users changed over the last decade? Evidence of increased exposure by analysis of blood THC concentrations in impaired drivers. *Forensic Sci. Int.* **2013**, *226*, 197.
- [58] M. Perez-Reyes, S. Di Guiseppi, K.H. Davis, V.H. Schindler, C.E. Cook. Comparison of effects of marihuana cigarettes to three different potencies. *Clin. Pharmacol. Ther.* **1982**, *31*,617.
- [59] S. MacDonald, R. Mann, M. Chipman, B. Pakula, P. Erickson, A. Hathaway, P. MacIntyre. Driving behaviour under the influence of cannabis or cocaine. *Traffic Inj. Prev.* **2008**, *9*, 190.
- [60] A.C. Moffat, M.D. Osselton, B. Widdop. in Clarke's Analysis of Drugs and Poisons, 3rd edn, Pharmaceutical Press, Bath, UK, 2004.
- [61] mg of THC in edibles. Bluelight >Focus Forums > Cannabis > Discussions >. http://www.bluelight.ru/vb/ archive/index.php/t-549317. html . v. Bulletin Version 4.1.12. [June 2013].
- [62] How best to use medicinal marijuana: Smoking vs Edibles and Tinctures. http://www.marijuanagrowershq.com/how-best-to-use-medical-marijuana-smoking-vs-edibles-and-tinctures/ [July 2013].
- [63] F. Grotenhermen, G. Leson. Reassessing the Drug Potential of Industrial Hemp. 2002, pp. 0–48. nova-Institut, Hürth, Germany.
- [64] S.E. Rooke, M.M. Norberg, J. Copeland, W. Swift W. Health outcomes associated with long-term regular cannabis and tobacco smoking. *Addict. Behav.* 2013, 38, 2207.
- [65] D. Reilly, R. Didcott, W. Swift, W. Hall. Long-term cannabis use: characteristics of users in Australian rural areas. Addiction **1998**, 93, 837.
- [66] M. Kochanowski, M. Kała. Tetrahydrocannabinols in clinical and forensic toxicology(English Abstract). *Przegl. Lek.* 2005, 62, 576.
- [67] F. Musshoff, B. Madea. Review of biologic matrices (urine, blood, hair), as indicators of recent or On-going cannabis use. *Ther. Drug Monit.* 2006, 28, 155.
- [68] S. Agurell, M. Halldin. Pharmacokinetics and metabolism of 9 tetrahydrocannabinol and other cannabinoids with emphasis on man. *Pharm. Rev.* **1986**, *38*, 21.
- [69] A. Ohlsson, J.E. Lindgren, A. Wahlen, S. Agurell, L.E. Hollister, H.K. Gillespie. Single dose kinetics of deuterium labelled delta-1-tetrahydrocannabinol in heavy and light cannabis users. *Biomed. Mass Spect.* **1982**, *9*, 6.
- [70] A. Ohlsson, J.E. Lindgren, A. Wahlen, S. Agurell, L.E. Hollister, H.K. Gillespie. Plasma delta-9-tetrahydro- cannabinol concentrations and clinical effects after oral and intravenous administration and smoking. *Clin. Pharmacol. Ther.* **1980**, *28*, 409.
- [71] J.L. Azorlosa, M.K. Greenwald, M.L. Stitzer. Marijuana smoking: Effects of varying puff volume and breathhold duration. *J. Pharmacol. Exp. Ther.* **1995**, *272*, 560.
- [72] S.J. Gross, T.E. Worthy, L. Nerder, E.G. Zimmermann, J.R. Soares, P. Lomax. Detection of recent cannabis use by saliva delta 9-THC radioimmunoassay. J. Anal. Toxicol. **1985**, 9, 1.
- [73] F. Grotenhermen. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin. Pharmacokinet.* **2003**, *42*, 327.
- [74] L.E. Hollister, H.K. Gillespie, A. Ohlsson, J.E. Lindgren, A. Wahlen, S. Agurell. Do plasma concentrations of delta 9-tetrahydrocannabinol reflect the degree of intoxication? J. Clin. Pharmacol. **1981**, *21*, 1715.

- [75] J.E. Manno, B.R. Manno, P.M. Kemp, D.D. Alford, I.K. Abukhalaf, M.E. McWilliams, F.N. Hagaman, M.J. Fitzgerald. Temporal indication of marijuana use can be estimated from plasma and urine concentrations of delta-9-tetrahydrocannabinol, 11-hydroxy-delta-9-tetrahydro cannabinol, and 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid. J. Anal. Toxicol. 2001, 25, 538.
- [76] M.A. Huestis, J.E. Henningfield, E.J. Cone. Blood cannabinoids: I. Absorption of THC and formation of 11-OH-THC and THC-COOH during and after marijuana smoking. J. Anal. Toxicol. **1992**, *16*, 276.
- [77] S. Harder, S. Rietbrock. Concentration-effect relationship of delta-9tetrahydrocannabiol and prediction of psychotropic effects after smoking marijuana. *Int. J. Clin. Pharm. Th.* **1997**, *35*, 155.
- [78] S. Agurell, M. Halldin, J.E. Lindgren. Cannabis and cannabinoids in the treatment of cancer. *Addiction* **1996**, *91*, 1585.
- [79] B. Law, P.A. Mason, A.C. Moffat, R.I. Gleadle, L.J. King. Forensic aspects of the metabolism and excretion of cannabinoids following oral ingestion of cannabis resin. J. Pharm. Pharmacol. **1984**, 36, 289.
- [80] S. Frytak, C.G. Moertel, J. Rubin. Metabolic studies of delta-9tetrahydro cannabinol in cancer patients. *Cancer Treat. Rep.* 1984, 68, 1427.
- [81] E.L. Karschner, E.W. Schwilke, R.H. Lowe, W.D. Darwin H.G. Pope, R. Herning, J.L. Cadet, M.A. Huestis. Do Δ^9 -Tetrahydrocannabinol concentrations indicate recent use in chronic cannabis users? *Addiction* **2009**, *104*, 2041.
- [82] M.A. Huestis. Human cannabinoid Pharmacokinetics. Chem. Biodivers. 2007, 4, 1770.
- [83] E.L. Karschner, E.W. Schwilke, R.H. Lowe, W.D. Darwin, R.I. Herning, J.L. Cadet, M.A. Huestis. Implications of plasma Delta9tetrahydrocannabinol, 11-hydroxy-THC, and 11-nor-9-carboxy-THC concentrations in chronic cannabis smokers. J. Anal. Toxicol. 2009, 33, 469.
- [84] A.C. Moffat, M.D. Osselton, B. Widdop, Clarke's Analysis of Drugs and Poisons, 4th edn, London, 2011.
- [85] J.P. Goullé, E. Saussereau, C. Lacroix. Delta-9-tetra hydrocannabinol pharmacokinetics (English abstract). Ann. Pharm. Fr. 2008, 66, 232, DOI: 10.1016/j.pharma.2008.07.006. Epub 2008 Aug 29. Review.
- [86] M.E. Wall, B.M. Sadler. Metabolism, disposition, and kinetics of delta-9-tetrahydro cannabinol in men and women. *Clin. Pharmacol. Ther.* **1983**, *34*, 352.
- [87] E. Johansson, S. Agurell, L.E. Hollister, M.M. Halldin. Prolonged apparent half-life of delta 1-tetrahydro- cannabinol in plasma of chronic marijuana users. J. Pharm. Pharmacol. 1988, 40, 374.
- [88] E. Johansson, M.M. Halldin, S. Agurell, L.E. Hollister, H.K. Gillespie. Terminal elimination plasma half-life of Δ^1 -tetrahydrocannabinol (Δ^1 -THC) in heavy users of marijuana. *Eur. J. Clin. Pharm.* **1989**, *37*, 273.
- [89] M.A. Peat. in Advances in Analytical Toxicology II (Ed: R.C. Baselt), Year Book Medical Publishers, Chicago, 1989, pp. 186.
- [90] H. Kalant. Adverse effects of cannabis on health: an update of the literature since 1996. Prog. Neuro-psychoph. 2004, 28, 849.
- [91] P. Kelly, R.T. Jones. Metabolism of tetrahydrocannabinol in frequent and infrequent marijuana users. J. Anal. Toxicol. **1992**, *16*, 228.
- [92] A. Reiter, J. Hake, C. Meissner, J. Rohwer, H.J. Friedrich, M. Oehmichen. Time of drug elimination in chronic drug abusers. Case study of 52 patients in a "low-step" detoxification ward. *Forensic Sci. Int.* 2001, 119, 248.
- [93] G. Milman, D.M. Schwope, D.A. Gorelick, M.A. Huestis. Cannabinoids and metabolites in expectorated oral fluid following controlled smoked cannabis. *Clin. Chim. Acta* **2012**, *413*, 765.
- [94] S.W. Toennes, J. Röhrich, C. Wunder. Interpretation of blood analysis data found after passive exposure to cannabis. Arch. Fur. Kriminologie. 2010, 225, 90.
- [95] J. Röhrich, I. Schimmel, S. Zörntlein, J. Becker, S. Drobnik, T. Kaufmann, V. Kuntz, R. Urban. Concentrations of delta9-tetrahydrocannabinol and 11-nor-9-carboxytetrahydro cannabinol in blood and urine after passive exposure to Cannabis smoke in a coffee shop. J. Anal. Toxicol. 2010, 34, 196.
- [96] K. Green, K. de Vries. Issues for pharmacists when patients use cannabis therapeutically at home. *Pharm. J.* 2012, 289, 531.
- [97] W.M. Bosker, K.P.C. Kuypers, E.L. Theunissen, A. Surinx, R.J. BlanKespoor, G. Skopp, W.K. Jeffery, H.C. Walls, C.J. van Leeuwen, J.G. Ramaekers. Medicinal ⁹tetrahydro cannabinol (dronabinol) impairs on-theroad driving performance of occasional and heavy users but is not detected in standard field sobriety tests. *Addiction* **2012**, *107*, 1837.

- [98] Driving under the Influence of Drugs, Alcohol and Medicines (DRUID). Prevalence of alcohol and other psychoactive substances in injured and killed drivers, Deliverable D1.1.2b. Available at: http://www.west-info.eu/files/Druid-report-08-2011.pdf [May 2013].
- [99] E.L. Karschner, W.D. Darwin, R.S. Goodwin, S. Wright, M.A. Huestis. Plasma cannabinoid pharmacokinetics following controlled oral Δ9-Tetrahydrocannabinol and oromucosal cannabis extract administration. *Clin. Chem.* **2011**, *57*, 66.
- [100] I.J. McGilveray. Pharmacokinetics of cannabinoids. Pain Res. Manag. 2005, 10, 15A.
- [101] T. Kurzthaler, C. Bodner, G. Kemmler, T. Entner, J. Wissel, T. Berger, W.W. Fleischhacker. The effect of nabilone on neuropsychological functions related to driving ability: an extended case series. *Hum. Psychopharmacol.* 2005, 20, 291.
- [102] C.G. Stott, L. White, S. Wright, D. Wilbraham, G.W. Guy. A phase I study to assess the single and multiple dose pharmacokinetics of THC/CBD oromucosal spray. *Eur. J. Clin. Pharmacol.* **2013**, *69*, 1135.
- [103] F. Musshoff, B. Madea, G. Kernbach-Wighton, W. Bicker, S. Kneisel, M. Hutter, V. Auwärter. Driving under the influence of synthetic cannabinoids ("Spice"): A case series. *Int. J. Legal Med.* **2013**, May 1, Epub ahead of print.
- [104] N. Langer, R. Lindigkeit, H.M. Schiebel, L. Ernst, T. Beuerle. Identification and quantification of synthetic cannabinoids in 'spice-like' herbal mixtures: A snapshot of the German situation in the autumn of 2012. *Drug Test. Anal.* 2013, DOI: 10.1002/dta.1499
- [105] Association of Chief Police Officers (ACPO). Written evidence presented to the Advisory Council on the Misuse of Drugs. Available at: https://www.gov.uk/.../advisory-council-on-the-misuseof-drugs [May 2013].
- [106] Talk-to-Frank. Advisory Council on the Misuse of Drugs. *Available at*: www.talktofrank.com/drug/cannabis. [June 2013].
- [107] K. Smith, J. Flatley. Drug Misuse Declared: Findings from the 2010/ 11 British Crime Survey England and Wales, 2011, Home Office Statistical Bulletin (HOSB). ISBN 1759 7005. London, UK.
- [108] W.A. Devane, A. Breuer, T. Sheskin, T.U. Järbe, M.S. Eisen, R. Mechoulam. A novel probe for the cannabinoid receptor. J. Med. Chem. 1992, 35, 2065.
- [109] European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). EMCDDA Insights Series No 8, Drug use impaired driving and traffic accidents. Office for Official Publications of the European Communities, Lisbon, **2008**.
- [110] European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Action on new drugs briefing paper: Understanding the 'Spice' phenomenon. EMCDDA, Lisbon, **2009**.
- [111] A.A. Westin, W.R. Brede, K.A. Espnes. Synthetic cannabis, English abstract. *Tidsskr. Nor. Laegeforen.* 2012, 132, 2289.
- [112] J.Y. Yeakel, B.K. Logan. Blood synthetic cannabinoid concentrations in cases of suspected impaired driving. J. Anal. Toxicol. 2013, 37, 547.
- [113] R. Kronstrand, M. Roman, M. Andersson, A. Eklund. Toxicological findings of synthetic cannabinoids in recreational users. J. Anal. Toxicol. 2013, 37, 534.
- [114] W.C. Rodrigues, P. Catbagan, S. Rana, G. Wang, C. Moore. Detection of synthetic cannabinoids in oral fluid using ELISA and LC-MS-MS. J. Anal. Toxicol. 2013, 37, 526.
- [115] D. Giovanardi, C.N. Castellana, S. Pisa, B. Poppi, D. Pinetti, A. Bertolini, A. Ferrari. Prevalence of abuse of alcohol and other drugs among injured drivers presenting to the emergency department of the University Hospital of Modena, Italy. *Drug Alcohol Depend.* 2005, 80, 135.
- [116] E. Romano, R.B. Voas, Drug and alcohol involvement in four types of fatal crashes. J. Stud. Alcohol Drugs 2011, 72, 567.
- [117] K. Terhune, C. Ippolito, D. Hendricks, Y.G. Michalovic, S.C. Bogema, P. Santinga, R. Blomber, D.F. Preusser. The incidence and role of drugs in fatally injured drivers. National Highway Traffic Safety Administration, Department of Transportation, Washington, DC, USA, **1992**.
- [118] A.F. Williams, M.A. Peat, D.J. Crouch, J.K. Wells, B.S. Finkle. Drugs in fatally injured young male drivers. *Public Health Rep.* **1985**, 100, 19.
- [119] C.E. Hunter, R.J. Lokan, M. Longo, J. White, M. White. The prevalence and role of alcohol, cannabinoids, benzodiazepines and stimulants in non-fatal crashes. Forensic Science, Department for Administrative and Information Services, Adelaide, Australia, **1998**.

- [120] A. Crancer Jr, A. Crancer. The Involvement of Cannabis in California Fatal Motor Vehicle Crashes, 1998–2008. Available at: http:// druggeddriving.org/pdfs/CAMJStudyJune2010.pdf [May 2013]
- [121] D.M. Fergusson, L. Horwood, J.M. Boden. Is driving under the influence of cannabis becoming a greater risk to driver safety than drink driving? Findings from a longitudinal study. *Accident Anal. Prev.* 2008, 40, 1345.
- [122] O.H. Drummer. A review of the contribution of drugs in drivers to road accidents. in Inquiry into the effects of drugs (other than alcohol) on road safety in Victoria, incorporating collected papers. LV North, Government Printer, Australia, **1995**, pp. 1–28.
- [123] M.C. Longo, C.E. Hunter, R.J. Lokan, J.M. White, M.A. White. The prevalence of alcohol, cannabinoids, benzodiazepines and stimulants amongst injured drivers and their role in driver culpability. *Accident Anal. Prev.* **2000**, *32*, 623.
- [124] M.C. Longo, C.E. Hunter, R.J. Lokan, J.M. White, M.A. White. The prevalence of alcohol, cannabinoids, benzodiazepines and stimulants amongst injured drivers and their role in driver culpability: Part ii: The relationship between drug prevalence and drug concentration, and driver culpability. *Accident Anal. Prev.* 2000, *32*, 623.
- [125] G.B. Chesher. The effects of alcohol and marijuana in combination: a review. *Alcohol* **1986**, *2*, 105.
- [126] Driving under the Influence of Drugs, Alcohol and Medicines (DRUID). Prevalence of alcohol and other psychoactive substances in injured and killed drivers. Available at: http://www.west-info. eu/files/Druid-report-08-2011.pdf [June 2013].
- [127] B. Gadegbeku, E. Amoros, and the SAM group. 6th Framework programme. Deliverable 2.3.2., Relative risk estimates for alcohol and other psychoactive substances impaired drivers in fatal accidents, based on the DRUID 6th Framework Programme - D 7.3.2 Main DRUID results to be communicated to different target groups 130 responsibility approach in France. Driving under the Influence of Drugs, Alcohol and Medicines (DRUID), **2010**. [June 2013].
- [128] K.M. Dubowski, N.A. Essary. Measurement of low breath-alcohol concentrations: Laboratory studies and field experience. J. Anal. Toxicol. **1999**, 23, 386.
- [129] K. Wolff. Biological markers of drug use. in Addiction Psychiatry, Psychiatry, (Eds: E.J. Marshall, M. Farrell). The Medicine Pub Co Ltd, London, 2007.
- [130] P. Lafolie, O. Beck, G. Blennow, L. Boréus, S. Borg, C.E. Elwin, L. Karlsson, G. Odelius, P. Hjemdahl. Importance of creatinine

analyses of urine when screening for abused drugs. *Clin. Chem.* **1991**, *37*, 1927.

- [131] M.-B. Biecheler. Cannabis, driving and road safety: A review of the scientific literature, Driving under the Influence of Drugs, Alcohol and Medicines (DRUID) Deliverable 2.1.3. www.druid-project.eu. [June 2013].
- [132] M.N. Bates, T.A. Blakely. Role of cannabis in motor vehicle crashes. *Epidemiol. Rev.* **1999**, *21*, 222.
- [133] Ögden E.J., Moskowitz H.. Effects of alcohol and other drugs on driver performance. *Traffic Inj. Prev.* **2004** *5*, 185.
- [134] A. Verstraete, A. Knoche, R. Jantos, G. Skopp, H. Gjerde, V. Vindenes, J. Mørland, K. Langel, P. Lillsunde. Per se limits - Methods of defining cut-off values for zero tolerance. Driving under the Influence of Drugs, Alcohol and Medicines (DRUID). 6th Framework Program, Deliverable 1.4.2. BASt. 2011.
- [135] O.H. Drummer. Drug testing in oral fluid. Clin. Biochem. Rev. 2006, 27, 147.
- [136] D. Lee, R. Vandrey, D.R. Mendu, S. Anizan, G. Milman, J.A. Murray, A.J. Barnes, M.A. Huestis. Oral fluid cannabinoids in chronic cannabis smokers during rral △9-Tetrahydro cannabinol therapy and smoked cannabis challenge. *Clin. Chem.* **2013**, Epub ahead of print.
- [137] J.A. Henry, K. Ohashi, J. Wadsworth, P. Turner. Drug recovery following buccal absorption of propranolol. *Brit. J. Clin. Pharmacol.* 1980, 10, 61.
- [138] Niedbala R.S., Kardos K.W., Fritch D.F., Kunsman K.P., Blum K.A., Newland G.A., Waga J., Kurtz L., Bronsgeest M., Cone E.J.. Passive cannabis smoke exposure and oral fluid testing. II. Two studies of extreme cannabis smoke exposure in a motor vehicle. J. Anal. Toxicol. 2005, 29, 607.
- [139] G.F. Kauert, J.G. Ramaekers, E. Schneider, M.R. Moeller, S.W. Toennes. Pharmacokinetic properties of delta9-tetrahydro cannabinol in serum and oral fluid. J. Anal. Toxicol. 2007, 31, 288.
- [140] M.A. Huestis, E.J. Cone. Relationship of Delta 9-tetrahydrocannabinol concentrations in oral fluid and plasma after controlled administration of smoked cannabis. J. Anal. Toxicol. **2004**, 28, 394.
- [141] M. Laloup, M. Del Mar Ramirez Fernandez, M. Wood, G. De Boeck, V. Maes, N. Samyn. Correlation of Delta9-tetrahydro cannabinol concentrations determined by LC-MS-MS in oral fluid and plasma from impaired drivers and evaluation of the on-site Dräger Drug Test. Forensic Sci. Int. 2006, 161, 175.
- [142] J. Davey, J. Freeman. Screening for drugs in oral fluid: drug driving and illicit drug use in a sample of Queensland motorists. *Traff Inj. Prev.* 2009, 10, 231.