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Review

Dose related risk of motor vehicle crashes after cannabis use

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Abstract

The role of Δ^9-tetrahydrocannabinol (THC) in driver impairment and motor vehicle crashes has traditionally been established in experimental and epidemiological studies. Experimental studies have repeatedly shown that THC impairs cognition, psychomotor function and actual driving performance in a dose related manner. The degree of performance impairment observed in experimental studies after doses up to 300 μg/kg THC were equivalent to the impairing effect of an alcohol dose producing a blood alcohol concentration (BAC) ≥0.05 g/dl, the legal limit for driving under the influence in most European countries. Higher doses of THC, i.e. >300 μg/kg THC have not been systematically studied but can be predicted to produce even larger impairment. Detrimental effects of THC were more prominent in certain driving tasks than others. Highly automated behaviors, such as road tracking control, were more affected by THC as compared to more complex driving tasks requiring conscious control. Epidemiological findings on the role of THC in vehicle crashes have sometimes contrasted findings from experimental research. Case-control studies generally confirmed experimental data, but culpability surveys showed little evidence that crashed drivers who only used cannabis are more likely to cause accidents than drug free drivers. However, most culpability surveys have established cannabis use among crashed drivers by determining the presence of an inactive metabolite of THC in blood or urine that can be detected for days after smoking and can only be taken as evidence for past use of cannabis. Surveys that established recent use of cannabis by directly measuring THC in blood showed that THC positives, particularly at higher doses, are about three to seven times more likely to be responsible for their crash as compared to drivers that had not used drugs or alcohol. Together these epidemiological data suggests that recent use of cannabis may increase crash risk, whereas past use of cannabis does not. Experimental and epidemiological research provided similar findings concerning the combined use of THC and alcohol in traffic. Combined use of THC and alcohol produced severe impairment of cognitive, psychomotor, and actual driving performance in experimental studies and sharply increased the crash risk in epidemiological analyses.

Keywords: Cannabis; Driving; Crash risk; Experimental; Epidemiology

1. Introduction

The effects of Δ^9-tetrahydrocannabinol (THC) on the ability of drivers to operate safely have traditionally been determined in epidemiological surveys of THC users' involvement in traffic accidents and in experimental studies to measure the drug's influence on skills related to driving (reviews: Robbe, 1994; Berghaus et al., 1998a,b; Bates and Blakely, 1999; Solowij, 1998; EMCDDA, 1999; O'Kane et al., 2002). The purpose of epidemiological studies is to determine both the severity of THC impairment and the prevalence of THC use among the driving population by measuring the frequency of cannabis use among drivers who do and do not become involved in crashes. Essentially they aim to determine if cannabis use is over represented among drivers who were involved in accidents. Experimental studies are designed to predict the effects of cannabis on driving ability by measuring their users' performances in laboratory tests of isolated psychological functions, driving simulators and on-the-road driving tests. In the context of well-designed experiments, drugs that produce large performance impairments in many different tests can be considered potentially hazardous to drivers whereas drugs that fail to produce any impairment can be considered safe. Experimental studies

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often provide the earliest evidence for a drug's hazard potential for driving.

Many excellent studies on the effects of cannabis on driving are available only as technical reports, proceedings or book chapters. That is unfortunate since reviews in general should not cover data that are not published in peer-reviewed sources. Yet, applying this rule invariably would seriously weaken any review in this field. We therefore decided to also include sources that did not appear in peer-reviewed formats, i.e. about 50% of the references, in order to fully summarize and integrate what is known about the effect of cannabis on performance and driving ability. In particular a summary of the literature relevant to the following research questions will be given:

- Does cannabis impair psychomotor, cognitive, and actual driving performance and increase the risk of becoming involved in traffic accidents?
- Is there a relation between performance impairment and cannabis dose or its concentration in plasma?
- Do combined effects of cannabis and alcohol on driving performance differ from those of either drug alone?
- Does cannabis affect all aspects of the driving task alike?

2. Epidemiological studies

2.1. Prevalence of THC in crash involved drivers

Surveys conducted in widely separated localities have generally revealed the presence of THC in between 4 and 14% of drivers who sustained injury or death in traffic accidents (Cimbura et al., 1982; Terhune and Fell, 1982; Terhune et al., 1992; Chesher and Starmer, 1983; Mason and McBay, 1984; Donelson et al., 1985; Garriott et al., 1986; Daldrup et al., 1987; McLean et al., 1987; Cimbura et al., 1990; Soderstrom et al., 1995; Mercer and Jeffery, 1995; Logan and Schwilke, 1996; Drummer et al., 2003a). Occasionally higher values have been reported for groups of, predominantly, young males operating in one or another large American city (Williams et al., 1985; Soderstrom et al., 1988; Budd et al., 1989). These data however cannot be accepted as evidence showing that THC was responsible for the crashes, even though the prevalence of THC in the general driving populations is assumed to be lower. The reason is that alcohol was also found in 50–80% of the same drivers. It is highly likely that combination of THC and alcohol poses a bigger risk potential than those of either drug alone. Another limitation of these surveys is their lack of an appropriate control group. Prevalence studies indicate the extent to which substances such as THC and alcohol are present in the blood of (fatally) injured drivers. In the absence of comparable data from an appropriate control group selected from the general driving population, results of prevalence studies can never be taken to indicate the role of THC or other drugs in causing traffic crashes.

2.2. Culpability studies

Epidemiologists have tried to overcome the lack of normative data from the general driving population by analyzing the culpability index of drivers involved in traffic accidents. Basically, they distinguished between drivers that were responsible for their crash and those who were not. The former are taken as the cases and the latter as controls, for determining the odds ratio for responsibility for traffic accidents under the influence of cannabis. Classification of culpability should of course take place without knowledge of the drugs/alcohol status of drivers in order not to bias the classification process.

There have been several culpability studies that investigated the association between cannabis, alcohol, and traffic crashes. A summary of these studies and their measure of association is summarized in Table 1. Odd ratios (ORs) and 95% CIs presented in Table 1 are taken from the original study reports or adapted from Bates and Blakely's (1999) re-analyses of these data. It is important to note that in this type of analysis the crash culpability rates among drivers positive for THC are compared to crash culpability rates in drug (including alcohol) free drivers. The odds ratio of drug free drivers to become involved in a traffic crash is set to 1.0, and serves as the point of reference in order to determine the statistical significance of changes in odds ratios for drivers under the influence. If this reference value of 1.0 falls outside the 95% CI associated with odds ratios for a certain drug, we can safely conclude with 95% certainty that this drug significantly affected crash culpability. However, if the 95% CI includes the reference mean, the conclusion must be drawn that crash culpability rates of drugged drivers are comparable to crash culpability rates in drug free drivers.

All culpability studies have shown that alcohol and the combination of alcohol with cannabis significantly and strongly elevated crash culpability rates. In most studies the combined effects of cannabis and alcohol on crash culpability appeared additive, although a weak suggestion of a synergistic effect was also apparent in some. Yet, most culpability studies (Terhune and Fell, 1982; Terhune et al., 1992; Williams et al., 1985; Drummer, 1994; Hunter et al., 1998; Lowenstein and Koziol-Mclain, 2001) also seem to indicate that cannabis alone does not increase crash culpability. However, these culpability studies have identified cannabis use among drivers by solely measuring THC–COOH, an inactive carboxy metabolite of THC (Williams et al., 1985; Drummer, 1994; Hunter et al., 1998; Lowenstein and Koziol-Mclain, 2001), or by measuring either THC or THC–COOH (Terhune and Fell, 1982; Terhune et al., 1992) in blood or in urine. Following the use of cannabis, THC–COOH may be present in blood or urine for days. The presence of THC–COOH thus does not necessarily imply recent use of cannabis or impairment. Recent exposure to cannabis can only be safely assumed in the minority of culpability studies that determined cannabis use by the presence of THC in the blood.

Table 1
Summary of OR of becoming involved in fatal or injurious traffic accidents under the influence of cannabis, alcohol or their combination as reported in culpability studies

Substance	Authors	Odds ratio	95% CI
Drug free cases		1.0	
Alcohol	Terhune and Fell (1982);	5.4*	2.8–10.5
	Williams et al. (1985);	5.0*	2.1–12.2
	Terhune et al. (1992);	5.7*	5.1–10.7
	Drummer (1994);	5.5*	3.2–9.6
	Hunter et al. (1998);	6.8*	4.3–11.1
	Lowenstein and Koziol-Mclain (2001);	3.2*	1.1–9.4
	Drummer et al. (2003b)	6.0*	4.0–9.1
THC–COOH	Terhune and Fell (1982);	2.1	0.7–6.6
	Williams et al. (1985);	0.2	0.2–1.5
	Terhune et al. (1992);	0.7	0.2–0.8
	Drummer (1994);	0.7	0.4–1.5
	Hunter et al. (1998);	0.9	0.6–1.4
	Lowenstein and Koziol-Mclain (2001)	1.1	0.5–2.4
THC (range: ng/ml)			
<1.0	Hunter et al. (1998)	0.35	0.02–2.1
1.10–2.0		0.51	0.2–1.4
>2		1.74	0.6–5.7
1–100	Drummer et al. (2003a,b)	2.7*	1.02–7.0
5–100		6.6*	1.5–28.0
Alcohol/THC or THC-COOH	Williams et al. (1985);	8.6*	3.1–26.9
	Terhune et al. (1992);	8.4*	2.1–72.1
	Drummer (1994);	5.3*	1.9–20.3
	Hunter et al. (1998);	11.5*	4.6–36.7
	Lowenstein and Koziol-Mclain (2001)	3.5*	1.2–11.4

Significance of changes in OR is indicated as follows: *<0.05.

Only two culpability studies (Hunter et al., 1998; Drummer et al., 2003a,b) determined recent cannabis use by assessing THC in blood. While using identical methods for establishing culpability of the driver these studies generally showed that crash culpability for THC positive cases increased with rising concentrations of THC in blood (see Table 1). The study by Hunter et al. (also published in Longo et al., 2000) in 2500 injured drivers failed to establish a relation between relatively low concentrations of THC and driver culpability but did find that culpable drivers had a higher mean THC concentration, a difference that approached statistical significance ($P = 0.057$). Drummer et al. (2003b) also reported that increments in crash responsibility rates were most prominent at high concentrations of THC. They conducted a responsibility analysis in 3398 Australian fatally injured drivers recorded in their database between 1990 and 1999. THC was present in 58 cases in which no other psychoactive drug or alcohol was found. The median THC concentration was 10 ng/ml with a range from 1 to 100 ng/ml. THC positive cases showed an OR of 2.7 compared to drug free drivers, while taking into account interactions for age, gender, crash type, jurisdiction, and year of collection. The range of the confidence interval strongly suggested significance of the OR value as it did not include the reference value 1.0. Analyses on a subset of cases with THC concentrations of 5 ng/ml or higher revealed a culpability ratio of 6.6 in THC driver fatalities as compared to drug free cases. Since alcohol was a common factor found in cannabis positive cases, the effect of THC and alcohol combined was also evaluated relative to drivers who were only positive to alcohol (i.e. BAC > 0.05 g/dl). This analysis revealed a significant increment of crash risk (OR 2.9; 95% CI: 1.1–7.7) suggesting that THC does enhance alcohol-induced impairment, and that this impairment is at least additive to alcohol.

2.3. Case-control studies

Several epidemiological studies have attempted to include a representative control group to calculate risk ratio's for traffic related hospitalization after THC use. Hingson et al. (1982) conducted a anonymous random telephone survey of nearly 6000 16–19 years olds which indicated that frequency of driving after cannabis use was associated with greater accident involvement in the year prior to the interview. Compared to subjects who did not drive after cannabis use, subjects who drove after smoking marihuana on at least six occasions per month were 2.4 (95% CI: 1.4–14) times more likely to be involved in traffic accidents. Those who drove after marihuana use on at least 15 occasions per month were 2.9 (95% CI: 1.3–6.8) times more likely to have an accident.

Mura et al. (2003) conducted a case-control study to compare the prevalence of THC among injured drivers and control subjects that were recruited from emergency departments in six French hospitals. Total study population comprised of 900 drivers involved in a non-fatal accident and 900 control drivers who attended the same emergency units for non-traumatic reasons. Drivers and controls were matched for sex and age. THC (>1 ng/ml, no other drugs or alcohol present) was detected in 10% of the injured drivers and in 5% of the controls when averaged over all age groups. In cases and controls who were younger than 27 years, THC was detected in 15.3% of the cases and 6.7% of the controls, giving rise to an odds ratio of 2.5 and a 95% CI ranging from 1.5 to 4.2. In cases were both THC and alcohol (BAC $>$ 0.05 g/dl) were present the OR increased to 4.6 (95% CI: 2.0–10.7).

Gerberich Goodwin et al. (2003) conducted a retrospective study in a large prepaid Northern Californian health care program cohort ($N = 64,657$) to compare the incidence of traffic injury related hospitalization among THC users and non-drug users. All cohort members completed baseline questionnaires about health behaviors, including cannabis use between 1979 and 1985. Traffic injury related hospitalizations were identified from the date of baseline through December 1991. An increased risk ratio (OR = 2.3, 95% CI: 1.44–2.72) for motor vehicle injuries was demonstrated in male cannabis users relative to non-users.

Data from these studies clearly suggests that cannabis increases a driver's risk to become involved in a road crash. Yet, it has been argued that such associations may be confounded by life style factors typical for cannabis users. Fergusson and Horwood (2001) for example established a statistically significant relation between self-reported frequency of cannabis use and self-reported accidents rate (OR 1.6, 95% CI: 1.2–2.0) in a birth cohort of 907 young New Zealanders (aged 18–21). Adjusting for risky driver behaviors and unsafe driver attitudes characteristic for cannabis users however eliminated the association between cannabis use and crash risk. The latter analysis suggests that traffic accident risk among cannabis users is related to their life style rather than to cannabis use per se. However, these results may also be taken to support an alternative explanation: i.e. cannabis stimulates risky driving behaviors and/or attitudes that are linked to accident risk.

Two studies (Dussault et al., 2002; Movig et al., 2003) have employed a prospective case-control study design that has historically been the design of choice for epidemiological studies of the role of alcohol in motor vehicle crashes (Borkenstein et al., 1974). Crash risk was evaluated by calculating the odds of an individual in a crash sample testing positive for cannabis to the odds of an individual testing positive for cannabis in the exposure sample, that is, in a roadside survey sample of non-crash-involved drivers using the same roads in the same time frame. In the study by Movig et al. (2003), cases ($N = 110$) were car drivers involved in road crashes in the Tilburg area of The Netherlands, whereas controls ($N = 816$) were recruited at random from the general driving population on public roads in the same Tilburg region between May 2000 and August 2001. Controls were tested for the presence of cannabis by means of urine sample screening. If no urine sample could be collected a blood sample was requested. In total, 79.3% of the control group was willing to participate in the study. Cases were tested for cannabis use by means of blood or urine samples taken directly in the emergency room. Among cases, 13 (12%) tested positive for cannabis as compared to 49 (6%) among controls. A non-significant increase in risk ratio was reported for cannabis (OR = 1.22, 95% CI: 0.55–2.73) indicating no association between exposure to cannabis and road accidents. A possible explanation for the latter finding may be the lack of statistical power given the relatively low number of (cannabis) cases and controls that were included in this survey. The power available for comparison of proportions depends on the prevalence rates of drugs in the samples under study. If the prevalence rates are low as with most drugs the sample under study should be relative high. It was one of the major arguments for the authors' decision in 2001 to continue their case-control study for another 3-year-period in order to multiply the number of cases and controls by about a factor 4. Results of the complete study should become available in 2005.

Dussault et al. (2002) presented preliminary results of a large case-control study comparing the presence of cannabis in crash involved drivers ($N = 354$) to presence of cannabis in drivers participating in a roadside survey ($N = 11574$) between 1999 and 2001 in Quebec, Canada. The survey sample was distributed proportionally to the number of crashes per time of day (eight 3-h periods) and day of the week (7 days). Cannabis was detected in urine of 19% of all cases whereas the same drug was detected in urine or saliva of 6.2% of the controls. Actual participation rate among controls as defined by how many controls were willing to provide a saliva or urine sample was 84.6%. Case-control analysis suggested that cannabis is associated with twice the risk of being fatally injured in traffic (OR 2.2; CI: 1.5–3.4). Sharp elevations in crash risk were found for combined use of cannabis with alcohol (BAC $>$ 0.08 g/dl; OR 80.5; 95% CI 28.2–230.2), cocaine (OR 8.0; 95% CI: 3.1–20.7), and benzodiazepines (OR 21.3; 95% CI: 5.3–86.0). Remarkably, a culpability analysis of all cases did not reveal a significant rise in crash risk in cannabis users, indicating that this type of analyses may be less conclusive.

3. Experimental studies of cannabis and performance

Determination of the effect of THC on performance has mostly been based on information provided by the field of psychopharmacology. Psychopharmacologists have devised a large number of "psychomotor" tests, characterized by contingent motor responding to an imposed discrete or continuous signal (e.g. reaction time, attention, tracking, and

critical flicker/fusion frequency tests), and "cognitive" tests for measuring various mnemonic functions but also deductive reasoning. Finally, tests were developed to measure some aspects of "real life" performance such as driving in a simulator, through staged maneuvers on a course closed to other traffic or on public roads in actual traffic. Experimental studies have followed both parallel group and crossover designs, most with both placebo- and alcohol controls. The great advantage of experimental studies that have been conducted is their ability to determine the intrinsic pharmacological effects of THC on performance without the confounding factors that always obscure or exaggerate the effect in the natural environment. However, until now the experimental approach has been mostly limited to studies assessing the acute effects of THC on performance, i.e. the effects of THC on performance after a single dose. Experimental data on performance effects after repeated doses of THC is generally lacking. As a consequence, it is currently not known whether THC users adapt to acute effects of this drug as a result of tolerance. Neither have the effects of THC been systematically studied in novel users versus experienced users to establish differences in sensitivity between subgroups of users. These issues will certainly gain importance with the possible introduction of cannabis as a medicinal drug for the (sub)chronic treatment of pain or inflammation. It is for this reason that the Institute of Medicine, Washington DC, advises to assess the cognitive and psychomotor functioning before and regularly during the course of a chronic regimen of cannabis treatment to determine the extent to which tolerance to the impairing effects of cannabis develops and whether new problems develop (Watson et al., 2000).

3.1. Psychomotor performance and cognition

Numerous experimental studies have been conducted to investigate the effects of THC on isolated cognitive functions and psychomotor skills related to driving performance. These have generally shown that THC in doses between 40 and 300 μg/kg causes a dose dependant reduction in performance at laboratory tasks measuring memory function, divided and sustained attention, reaction time, tracking or motor control (reviews: Moskowitz, 1985; Chesher, 1986; Chait and Pierri, 1992; Robbe, 1994; Berghaus et al., 1998a; Solowij, 1998; EMCDDA, 1999). One of the most consistently reported behavioral effects of THC is a disruption in the free recall of previously learned information. Recall of items learned before cannabis use is generally not affected, suggesting that THC impairs learning and the acquisition of information but not its retrieval from memory. Short-term or working memory is generally impaired in complex tasks, but at high doses also in simple tasks.

The magnitude of the THC effects on performance furthermore varied with the application form, i.e. smoking or oral intake, and time post THC use. Berghaus et al. (1998a,b) conducted a meta-analysis in 87 studies on the effects of THC on psychomotor function, including tracking, reaction time performance, perception, eye-hand coordination, body sway, signal detection, divided or sustained attention tasks. Their analysis demonstrated that the percentage of psychomotor tasks showing significant performance impairment after THC was highest during the first hour after smoking or between 1 and 2 h after oral intake. Peak impairment after THC was comparable to alcohol induced performance impairment seen at blood alcohol concentrations >0.05 g/dl. The number of significant performance effects sharply declined to about zero over 3–4 h after THC use. Only higher doses of THC produced prolonged performance impairment. The authors also established a concentration–effect curve, which indicated that, at least for low concentrations, plasma concentrations of THC are approximately linearly related to the magnitude of performance impairment. This relation was almost identical in experiments with smoking compared to experiments with oral intake of cannabis. In general, performance declined in about 35% of all tests applied at plasma concentrations of about 5 ng/ml THC, when compared to placebo. Impairment increased with higher plasma levels of THC. Maximal performance decrement, i.e. impairment in 70–80% of all psychomotor tests, was seen at concentrations between 14 and 60 ng/ml THC. The THC concentration effect curve was based on all experimental tests included in the meta-analysis. The majority of these experimental tests were conducted between 15 min and 4 h after drug intake. THC concentrations were estimated from dose and time of testing by means of pharmacokinetic modeling (Sticht and Käferstein, 1998). A summary of the major findings from Berghaus et al.'s meta-analysis is given in Table 2 and Fig. 1.

3.2. Driving simulators and on-the-road driving tests

A potential disadvantage of experimental laboratory studies is that it is often unknown whether tests of skills related to driving serve as a good model for the driving task as a whole. Many tests are short and relatively simple and do not necessarily reflect performance in the real world. Driving is probably one of the most complex psychomotor tasks. It is difficult to conceive, much less simulate, every situation that confronts drivers. Tests for measuring effects of drugs in driving simulators, over closed-course driving terrain or on real roads in normal traffic are most likely to approach reality. Yet, also these tests can often measure only parts of the total driving behavior. However, it is generally accepted that the closer a test approaches reality, the better the chance of measuring effects that cause crashes.

Studies in interactive driving simulators (Smiley et al., 1981; Stein et al., 1983; Smiley, 1986; Sexton et al., 2000) showed that THC doses up to 200 μg/kg increased lateral position variability, headway variability, and caused subjects to ignore navigational information. The highest dose increased speed variability and caused the subjects to hit roadway

Table 2
Frequency of performance impairments (%) observed in the total number of psychomotor tests applied in 87 experimental studies as a function of dose, time after dosing and route of administration of THC

THC-dose (mg)	Time after smoking (h)									
	<1		1–2		2–3		3–4		4–5	
	Impaired (%)	# Tests	Impaired (%)	# Tests	Impaired (%)	# Tests	Impaired (%)	# Tests	Impaired (%)	# Tests
Route of THC administration: smoking										
<9	61	271	36	33	(30)	10	(0)	10	(0)	11
9–18	53	193	38	48	(38)	8	(0)	6	(0)	2
≥18	64	64	36	28	(40)	10	(53)	15	(67)	3
Overall	58	528	37	109	36	28	26	31	(13)	16
Route of THC administration: oral										
<9	(33)	3	14	49	27	37	(8)	13	–	–
9–18	(0)	3	39	41	42	45	(18)	17	–	–
≥18	(0)	3	60	45	(40)	15	(33)	15	(45)	11
Overall	(11)	9	37	135	36	97	20	45	(45)	11

Performance decrements associated with less than 20 psychomotor assessments are put in brackets because of their limited predictive validity (adapted from: Berghaus et al., 1998a (2)).

obstacles more often and to react more slowly to subsidiary task demands. Yet, THC also caused subjects to drive in a more conservative manner. They maintained a longer headway, refused more opportunities to pass, and when they did, began this maneuver at greater distance from the approaching vehicle. However, this compensatory behavior was never sufficient to fully overcome the overall impairing effect of cannabis. Studies designed to test the effects of THC on vehicle handling performance during staged maneuvers on terrain closed to traffic generally failed to show any dramatic changes in performance (Attwood et al., 1981; Casswell, 1979; Peck et al., 1986). However, THC doses and number of subjects in these studies were generally too low to achieve sufficient statistical power to detect any drug effect on performance.

Klonoff (1974) was the first to conduct a driving test in actual traffic. A total of 38 subjects were divided over separate groups to receive placebo, THC 4.9 or 8.4 mg. After smoking subjects drove for 45 min on city streets of Vancouver while aspects of their performance were rated by a professional examiner from the State Department of Motor Vehicles. No evidence was given of the reliability of these subjective judgments, and this may have been the source of the large variability found in performance after cannabis. Out of 11 scales of subjective judgments that were used in this study only three seemed to be significantly affected following the highest dose: concentration, care while driving and judgment.

The most comprehensive series of driving tests in actual traffic were conducted by a group of researchers at

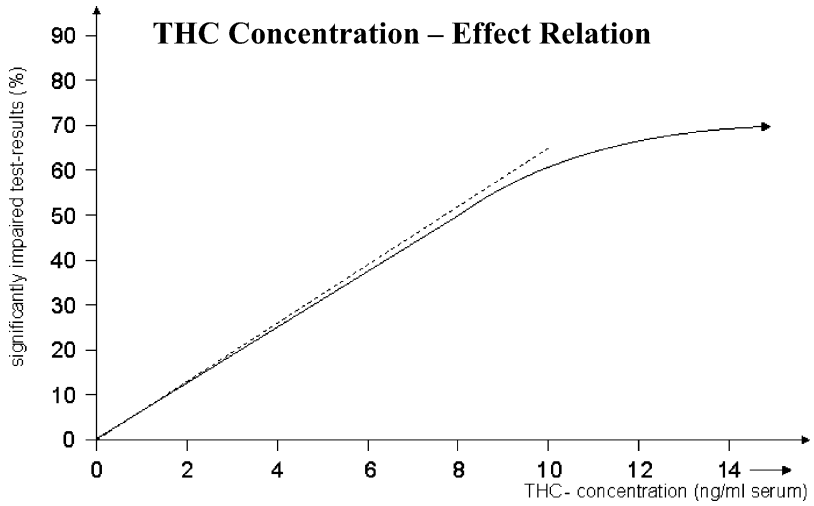

Fig. 1. Frequency of performance decrements (%) observed in the total number of psychomotor tests applied in 87 experimental studies as a function of THC concentration in plasma after eating (---) and smoking (—) cannabis (adapted from Berghaus et al., 1998a (2)).

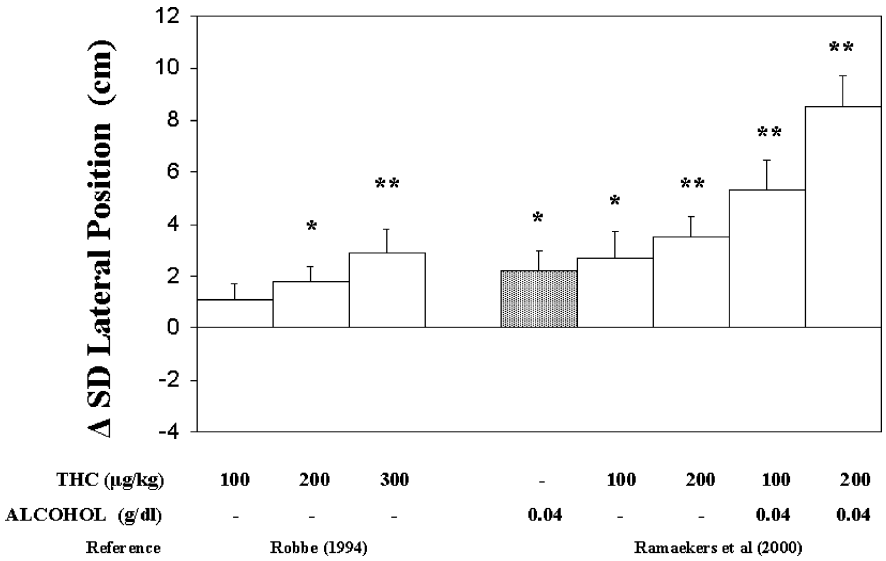

Fig. 2. Mean ΔSDLP (+SE) in the Road Tracking Test after incremental doses of THC alone and after THC combined with alcohol as measured in studies by Robbe (1) and Ramaekers et al. (31), respectively. Alcohol concentrations reflect the subjects' mean BACs while conducting the driving test. Significance of changes in SDLP is indicated as follows: $*P < 0.05$; $**P < 0.01$. Mean (range) plasma THC concentrations after 100, 200, and 300 μg/kg were 7.9 (0.8–17.2), 12.0 (1.5–27.1), and 16.1 (4.7–30.9) ng/ml (1).

Maastricht University, The Netherlands. Robbe (1994, 1998) investigated the effects of THC 0, 100, 200, and 300 μg/kg on performance in a 1 h Road Tracking Test and a 30 min Car-Following Test conducted on a primary highway, as well as the effects of alcohol and THC 100 μg/kg on performance in a City Driving Test. The combined effects of THC and alcohol on performance in the same tests were further investigated in subsequent studies (Robbe, 1998; Ramaekers et al., 2000; Lamers and Ramaekers, 2001). All subjects were recreational users of cannabis. THC produced a dose related increment in the standard deviation of lateral position (SDLP), a measure of lateral position variability or "weaving", during the Road Tracking Test. Reaction time to speed accelerations/decelerations of a leading vehicle and general driving proficiency were not affected by THC in the Car-Following Test and the City Driving Test, respectively. The effects of THC on lateral position variability were moderate and comparable to that of an alcohol dose producing a BAC of about 0.05 g/dl, the legal limit for driving under the influence in most European countries. However, its combination with a low dose of alcohol (i.e. BAC < 0.05 g/dl) produced severe performance impairment in the Road Tracking Test, and to lesser extents also in the Car-Following and City Driving Test. There was no significant interaction between alcohol and THC, indicating that the effects were additive. When compared to a previously established alcohol calibration curve (Louwerens et al., 1987), the combination of THC 100 and 200 μg/kg with alcohol produced a rise in mean SDLP the equivalent of that associated with BACs of 0.09 and 0.14 g/dl, respectively. A summary of the effects of THC and alcohol on lateral position variability is given in Fig. 2. Values on the *Y*-axis indicate change scores from placebo.

4. Discussion

The epidemiological literature has provided conflicting information on the role of THC in performance impairment and motor vehicle crashes. Among epidemiological studies, case-control studies are limited in number but generally provide evidence supporting an association between cannabis and increased crash risk. The majority of epidemiological studies are culpability studies and several of these show little evidence that drivers who only used cannabis are more likely to cause accidents than drug free drivers. In contrast, experimental studies have convincingly and repeatedly demonstrated that THC in doses up to 300 μg/kg causes impairment of various cognitive and psychomotor functions and of driving performance as measured in driving simulators or on-the-road tests. The magnitude of these performance impairments were comparable to alcohol induced performance impairment seen at BACs ≥ 0.05 g/dl, and should be considered as practically relevant. The reason for the apparent discrepancy between experimental and culpability studies is largely unknown but may be related to inadequate attribution of cannabis use to crashed drivers. These frequently relied on the detection of an inactive metabolite of THC in urine of drivers to establish the use of cannabis. However, this metabolite, THC–COOH, can be assessed in body fluids for hours and days and is not a reliable indication of recent cannabis use or impairment. Recent exposure to cannabis can only be safely assumed in the minority of culpability studies that determined cannabis use by the presence of THC in the blood. This latter procedure was only followed in two surveys. Culpability odds ratios in THC positives were generally higher than those in THC–COOH positives. Moreover, culpability odds ratios in THC positives were

three to six times as high as compared to drug free drivers, depending on the concentration of the drug detected in blood. Together, these data indicate that recent cannabis use may increase crash risk, whereas, past use of cannabis as determined by the presence of THC–COOH in drivers does not.

There are more general limitations to culpability studies that should be considered as well. The analysis assumes that drug free drivers involved in crashes are representative for the driving population at large. If so, culpability odds ratios may well establish reliable estimates of odds ratios that would be obtained in case-control studies using non crash drivers from the general driving population as control. However, this may not always be the case. Bates and Blakely (1999) pointed out that outcome misclassification may introduce bias. Determination of culpability status is not exact and there may be a tendency to misclassify drivers who are in fact responsible for the accident as not, or vice versa. However, it is noteworthy that studies that established cannabis use by measuring THC in blood (Hunter et al., 1998; Drummer et al., 2003b) all used an identical method for establishing driver culpability. The fact that one of these surveys reported increased culpability rates in injured drivers therefore most likely reflects the large THC concentrations found in these particular crash victims and not a structural difference in outcome classification between studies.

Bias may also occur if the control group of drug free cases is not controlled for confounding factors. Confounding could occur if there are lifestyle factors associated with cannabis use that are also independent risk factors for traffic crashes such as age, sex, time of accident or the use of alcohol. Confounding by alcohol is always avoided in culpability studies by excluding cases with alcohol present in their blood from statistical analyses of risk associated with cannabis. However, the potential role of other confounders is generally not taken in consideration. The possibility therefore exists that culpability studies identify an elevated risk of dying in road accidents if one is young, male and driving on weekends, instead of an elevated crash risk after recent use of THC as suggested. However this is not likely to be the case in the only culpability study so far that showed elevated crash risk in THC positive drivers. Drummer et al. (2003b) adjusted for potential confounders such as age, sex, crash type, jurisdiction and year of collection in their analysis, which provided extra support to their notion that the rise in culpability ratio was caused by cannabis and not by some other factor.

Recent epidemiological studies of the relation between cannabis and motor vehicle crashes have also involved a number of case control designs. The majority of these studies have suggested that cannabis is associated with twice the risk to become involved in traffic accidents. Two case-control studies seem of particular interest because they have used the classic study procedures that have previously been validated for alcohol in the Grand Rapids study (Borkenstein et al., 1974). Basically these studies have compared the prevalence of cannabis use among crashed drivers to the prevalence of cannabis among the drivers who were passing the same roads in same time period. This approach is generally accepted as a very reliable and solid method for establishing drug related crash risk. Epidemiologists have however long refrained from conducting such studies in cannabis research because of the participation problem. That is, identification of cannabis would require a blood sample from control drivers on a voluntary basis. Because cannabis is an illegal drug it is likely that drug users would be less willing to participate in the study than non-drug users. This would potentially bias study results and inflate odds ratios. Possible alternatives to blood sampling would be to collect non-invasive matrices such urine and saliva as applied in the studies by Dussault et al. (2002) and Movig et al. (2003). In both studies the response rates among controls were reasonably high, i.e. around 80–85%, which indicates that most controls are willing to cooperate in roadside drugs testing. Though not optimal, these numbers should increase confidence in the feasibility of case control designs for establishing the relation between cannabis and crash risk.

Experimental and epidemiological research converges on the fact that the association between THC and driver impairment is dose related. Odds ratios for accident culpability were shown to increase with increasing concentrations of THC in the blood of (fatally) injured drivers. Likewise, performance impairments in psychomotor or cognitive tests and lateral position variability in experimental driving tests were shown to gradually increase with increasing doses of THC. This may prove relevant since it has been argued that most THC doses employed in experimental research have been less than those used for recreational purposes in real-life. In a dose finding study by Robbe (1994) 23 subjects who were all recreational users of THC indicated that they had achieved their desired psychological effect after smoking a mean dose of 300 μg/kg THC.[1] The range of this preferred dose varied between 194 and 524 μg/kg THC indicating considerable inter-individual variation. It is thus likely that drivers in the general population will at times use doses that are higher than the ones used in experimental studies or associated with average concentrations detected in epidemiological surveys. It can be predicted from the currently available experimental data that the use of higher doses (i.e. >300 μg/kg THC) will be associated with severe driving impairment, equivalent to BACs > 0.08 g/dl.

The clear dose/concentration-effect relation between cannabis and driver impairment or crash risk raises the question whether a ‘per se’ limit could be identified above which drivers are always at risk. Meta-analyses of experimental performance data provide some good indication that maximal performance impairment will be achieved at THC concentrations >14 ng/ml in plasma (or >7 ng/ml when measured in whole blood). However, it has not been

[1] For comparison: identical to smoking a marijuana cigarette of 767 mg containing 2.6% or about 20 mg THC by a person of average weight.

established yet whether performance impairment observed at such a concentration also coincides with an elevated crash risk. The elevated culpability ratio's observed in Drummer et al.'s (2003a,b) analyses applied to a large group of THC positives with widely varying plasma concentrations, i.e. between 1 and 100 ng/ml THC in blood. It is impossible to tell which part of the distribution was actually responsible for the elevated OR observed in this sample. The elevated mean OR pertains to the whole distribution range and may be much less in cases with low THC concentrations and much higher in cases at the opposite end of the distribution. What is needed is a detailed analysis of the crash risk for THC positives as a function of THC concentration. Hunter et al. (1998) provided a first indication of a dose related effect of cannabis on culpability ratio but primarily for THC concentration ranges below 2 ng/ml. Their approach should now also be extended to cases with higher THC concentrations in order to confirm and support current notions on per se limits from experimental performance data.

It is also absolutely clear from epidemiological and experimental studies that the combination of alcohol and THC plays a major role in performance impairment and motor vehicle crashes. The epidemiological evidence shows that the combination of alcohol and THC is over-represented in injured and dead drivers, and particular in those responsible for the accident to occur. Experimental studies have shown that alcohol and THC combined can produce severe performance impairment even when given at low doses. The combined effect of alcohol and cannabis on performance and crash risk appeared additive in nature, i.e. the effects of alcohol and cannabis combined were always comparable to the sum of the effects of alcohol and THC when given alone.

Experimental studies furthermore indicate that not all driving tasks are equally sensitive to the detrimental effects of THC. Performance was always worst in tests measuring driving skills at the operational level, i.e. tracking and speed adjustment, as compared to performance in tests measuring driving performance at the maneuvering level, i.e. distance keeping and braking, and the strategic level, i.e. observation and understanding of traffic, risk assessment and planning. Strategic and maneuvering levels are particularly demanding of resources in that they require effortful processing and attention. Thus, processing is relatively slow and flexible. In contrast, the operational level is considered to be an automatic, routine process, which is fast and relatively inflexible. Drivers may be particularly vulnerable to detrimental effects of THC in traffic situations were they specifically employ driving skills that are operated at lower automated levels, such as during highway driving. The implication might be that drivers under the influence of THC might be more likely to be involved in specific types of traffic accidents such as single vehicle crashes. Culpability studies by definition have neglected this possibility, since drivers involved in this type of accident are practically always responsible, irrespective of drug use.

5. Conclusions

- THC has been shown to impair cognition, psychomotor function, and actual driving performance in a dose related manner.
- The degrees of impairment observed in laboratory or actual driving tests after doses up to 300 μg/kg THC were comparable to the impairing effects of an alcohol dose producing a BAC $\geq$ 0.05g/dl, the legal limit for driving under the influence in most European countries.
- There is no indication that *past use* of THC alone affects crash risks, but there is growing evidence that *recent use* of THC increases the risk for motor vehicle accidents compared to drug free drivers, particularly at higher concentrations.
- Detrimental effects of THC appear more prominent in highly automated driving behavior, as compared to more complex driving tasks that require conscious control.
- The effects of THC and alcohol on driving performance and risk of motor vehicle crashes appear to be additive, but the sum can be large and potentially dangerous. Combined use of THC and alcohol produces severe driving impairment and sharply increases the risk of drivers' accident culpability as compared to drug free drivers, even at low doses.

References

Attwood, D.A., Williams, R.D., Bowser, J.S., McBurney, L.J., Frecker, R.C., 1981. The effects of moderate levels of alcohol and marijuana, alone and in combination on closed-course driving performance. ((81-RSU-17)), Defence and Civil Institute of Environmental Medicine, Downsview, Ontario.

Bates, M.N., Blakely, T.A., 1999. Role of cannabis in motor vehicle crashes. Epidemiol. Rev. 21, 222–232.

Berghaus, G., Schultz, E., Szegedi, A., 1998a. Cannabis und fahrtû chtigkeit. Ergebnisse der experimentelle forschung. In: Berghaus, G., Krûger, H.P. (Eds.), Cannabis im Straßenverkehr, Gustav Fisher Verlag, Stuttgart, pp. 73–97.

Berghaus, G., Krûger, H.P., Vollrath, M., 1998b. Beeinträchtigung fahrrelevanter leistungen nach rauchen von cannabis und alcoholconsum. Eine vergleichende metaanalyse experimenteller studien. In: Berghaus, G., Krûger, H.P. (Eds.) Cannabis im Straßenverkehr, Gustav Fisher Verlag, Stuttgart, pp. 99–111.

Borkenstein, R.F., Crowther, R.F., Shumate, R.P., Ziel, W.B., Zylman, R., 1974. The role of the drinking driver in traffic accidents (the Grand Rapids study). Blutalcohol 11, s7–s13.

Budd, R.D., Muto, J.J., Wong, J.K., 1989. Drugs of abuse found in fatally injured drivers in Los Angeles County. Drug Alcohol Depend 23 (2), 153–158.

Casswell, S., 1979. Cannabis and alcohol: effects on closed course driving behaviour. In: Proceedings of the Seventh International Conference on Alcohol, Drugs and Traffic Safety. Melbourne 23–28 January 1977.

Chait, L.D., Pierri, J., 1992. Effects of smoked marijuana on human performance: a critical review. In: Murphy, L., Bartke, A. (Eds.), Marijuana/cannabinoids: neurobiology and neurophysiology. CRC Press, Boca Raton, pp. 387–423.

Chesher, G.B., Starmer, G.A., 1983. Cannabis and Human Performance Skills (Grand Report Series). Drug and Alcohol Authority Research, Sydney, NSW, Australia.

Chesher, G.B., 1986. The effects of alcohol and marijuana in combination: a review. Alcohol, Drugs Driving 2, 105–200.

Cimbura, G., Lucas, D.M., Bennett, R.C., Warren, R.A., Simpson, H.M., 1982. Incidence and toxicological aspects of drugs detected in 484 fatally injured drivers and pedestrians in Ontario. J. Forensic. Sci. 27 (4), 855–867.

Cimbura, G., Lucas, D.M., Bennet, R.C., Donelson, A.C., 1990. Incidence and toxicological aspects of cannabis and ethanol detected in 1394 fatally injured drivers and pedestrians in Ontario (1982–1984). J. Forensic. Sci. 35, 1035–1041.

Daldrup, T., Reudenbach, G., Kimm, K., 1987. Cannabis und Alkohol im Strassenverkehr [Cannabis and alcohol in traffic]. Blutalkohol 24 (2), 144–156.

Donelson, A.C., Cimbura, G., Bennett, R.C., Lucas, D.M., 1985. The Ontario monitoring project: Cannabis and alcohol use among drivers and pedestrians fatally injured in motor vehicle accidents from March 1982 through July 1984. Traffic Injury Research Foundation of Canada, Ottawa, Canada.

Drummer, O.H., 1994. Drugs in drivers killed in Australian road traffic accidents. Victorian Institute of Forensic Pathology, Institute of Forensic Medicine, Monash University, Melbourne, Australia (report no 0594).

Drummer, O.H., Gerostamoulos, J., Batziris, H., Chu, M., Caplehorn, J., Robertson, M.D., Swann, P., 2003a. The incidence of drugs in drivers killed in Australian road traffic crashes. Forensic. Sci. Int. 8, 154–162.

Drummer, O.H., Gerostamoulos, J., Batziris, H., Chu, M., Caplehorn, J., Robertson, M.D., Swann, P., 2003b. The involvement of drugs in drivers of motor vehicles killed in Australian road traffic crashes. Accid. Anal. Prev., in press.

Dussault, C., Brault, M., Bouchard, J., Lemire, A.M., 2002. The contribution of alcohol and other drugs among fatally injured drivers in Quebec: some preliminary results. In: Proceedings of the 16th International Conference on Alcohol, Drugs and Traffic Safety T2002, Montreal, pp. 423–430.

European Monitoring Centre for Drugs and Drug Addiction, 1999. Literature Review on the Relation between Drug Use, Impaired Driving and Traffic Accidents. (CT.97.EP.14) Lisbon: EMCDDA.

Fergusson, D.M., Horwood, L.J., 2001. Cannabis use and traffic accidents in a birth cohort of young adults. Accid. Anal. Prev. 33, 703–711.

Garriott, J.C., Di Maio, V.J., Rodriguez, R.G., 1986. Detection of cannabinoids in homicide victims and motor vehicle fatalities. J. Forensic. Sci. 31 (4), 1274–1282.

Gerberich Goodwin, S., Sidney, S., Braun, B.L., Tekawa, T., Tolan, K.K., Quesenberry, C.P., 2003. Marijana use and injury events resulting in hospitalisation. Ann. Epidemiol. 13, 230–237.

Hingson, R., Heeren, T., Mangione, T., Morelock, S., Mucatel, M., 1982. Teenage driving after using marijuana or drinking and traffic accident involvement. J. Safety Res. 13, 33–38.

Hunter, C.E., Lokan, R.J., Longo, M.C., et al., 1998. The prevalence and role of alcohol, cannabinoids, benzodiazepines and stimulants in non-fatal crashes. Forensic Science, Department for Administrative and Information Services, Adelaide, South Australia.

Klonoff, H., 1974. Marijuana and driving in real-life situations. Science 186, 317–323.

Lamers, C.T.J., Ramaekers, J.G., 2001. Visual search and urban city driving under the influence of marijuana and alcohol. Hum. Psychopharmacol. Clin. Exp. 16, 393–401.

Logan, B.K., Schwilke, E.W., 1996. Drug and alcohol use in fatally injured drivers in Washington State. J. Forensic. Sci. 41, 505–510.

Longo, M.C., Hunter, C.E., Lokan, R.J., White, J.M., White, M.A., 2000. The prevalence of alcohol, cannabinoids, benzodiazepines and stimulants amongst injured drivers and their role in driver culpability. Part II: the relation between drug prevalence and drug concentration, and driver culpability. Accid. Anal. Prev. 32, 623–632.

Louwerens, J.W., Gloerich, A.B.M., De Vries, G., et al., 1987. The relationship between drivers' blood alcohol concentration and actual driving performance. In: Noordzij, P.C., Roszbach, R. (Eds.), Alcohol, drugs and Traffic Safety-T86, pp. 183–192.

Lowenstein, S.R., Koziol-Mclain, J., 2001. Drugs and traffic crash responsibility: a study of injured motorists in Colorado. J. Trauma 50, 313–320.

Mason, A.P., McBay, A.J., 1984. Ethanol, marijuana and other drug use in 600 drivers killed in single-vehicle crashes in North Carolina, 1978–1981. J. Forensic. Sci. 29, 987–1026.

McLean, S., Parsons, R.S., Chesterman, R.B., Dineen, R., Johnson, M.G., Davies, N.W., 1987. Drugs, alcohol and road accidents in Tasmania. Med. J. Aust. 147 (1), 6–11.

Mercer, G.W., Jeffery, W.K., 1995. Alcohol, drugs, and impairment in fatal traffic accidents in British Columbia. Accid Anal. Prev. 27, 335–343.

Moskowitz, H., 1985. Marijuana and driving. Accid. Anal. Prev. 17, 323–346.

Movig, K.L.L., Matthijssen, M.P.M., Nagel, P.H.A., Van Egmond, T., de Gier, J.J., Leufkens, H.G.M., Egberts, A.C.G., 2003. Psychoactive substance use and the risk of motor vehicle accidents, Accid. Anal. Prev., in press.

Mura, P., Kintz, P., Ludes, B., Gaulier, J., Marquet, P., 2003. Comparison of the prevalence of alcohol, cannabis and other drugs between 900 injured drivers and 900 control subject: results of a French collaborative study. Forens. Sci. Int. 133, 79–2003.

O'Kane, Tutt, D.C., Bauer, L.A., 2002. Cannabis and driving: a new perspective. Emerg. Med. 14, 296–303.

Peck, R.C., Biasotti, A., Boland, P.N., Mallory, C., et al., 1986. The effects of marijuana and alcohol on actual driving performance. Alcohol, Drugs Driving 2 (3–4), 135–154.

Ramaekers, J.G., Robbe, H.W.J., O'Hanlon, J.F., 2000. Marijuana, alcohol and actual driving performance. Hum. Psychopharmacol. Clin. Exp. 15, 551–558.

Robbe, H.W.J., 1994. Influence of Marijuana on Driving. University of Limburg, Maastricht, The Netherlands.

Robbe, H.W.J., 1998. Marijuana's impairing effects on driving are moderate when taken alone but severe when combined with alcohol. Hum. Psychopharmacol. Clin. Exp. 13, s70–s78.

Sexton, B.F., Turnbridge, R.J., Brook-Carter, N., Jackson, P.G., Wright, K., Stark, M.M., Englehart, K., 2000. The influence of cannabis on driving. Technical report 477, Transport Research Foundation Limited (TRL), United Kingdom.

Smiley, A., 1986. Marijuana: On-road and driving simulator studies. Alcohol, Drugs Driving 2 (3–4), 121–134.

Smiley, A.M., Moskowitz, H., Ziedman, K., 1981, Driving simulator studies of marijuana alone and in combination with alcohol. In: Proceedings of the 25th Conference of the American Association for Automotive Medicine, pp. 107–116.

Soderstrom, C.A., Trifillis, A.L., Shankar, B.S., Clark, We., Cowley, R.A., 1988. Marijuana and alcohol use among 1023 trauma patients. Arch. Surg. 123, 733–737.

Soderstrom, C.A., Dischinger, P.C., Kerns, T.J., Trifillis, A.L., 1995. Marijuana and other drug use among automobile and motorcycle drivers treated at a trauma center. Accid. Anal. Prev. 27, 131–135.

Solowij, N., 1998. Cannabis and cognitive functioning. Cambridge University Press, Cambridge, England.

Stein, A.C., Allen, R.W., Cook, M.L., Karl, R.L., 1983. A Simulator Study of the Combined Effects of Alcohol and Marijuana on Driving Behavior (DOT HS 806 405). System Technology Inc., Hawthorne, CA.

Sticht, G., Käferstein, H.K., 1998. Grundbegriffe, Toxikokinetik and toxikodynamik. In: Berghaus, G., Krûger, H.P. (Eds.), Canna-

bis im Straßenverkehr. Gustav Fisher Verlag, Stuttgart, pp. 1–11.

Terhune, K.W., Fell, J.C., 1982. The role of alcohol, marijuana and other drugs in the accidents of injured drivers. (Tech. Rep. under Contract No. DOT-HS-5-01179). Calspan Field Services Inc., Buffalo, New York.

Terhune, K.W., Ippolito, C.A., Hendriks, D.L., Michalovic, J.G., 1992. The incidence and role of drugs in fatally injured drivers. National Highway Traffic Safety Administration, Final Report under Contract No. DTNH 22-88-C-07069.

Watson, S.J., Benson, J.A., Joy, J.E., 2000. Marijuana and medicine: assessing the science base. A summary of the 1999 Institute of Medicine report. Arch. Gen. Psychiatry 57, 547–552.

Williams, A.F., Peat, M.A., Crouch, D.J., Wells, J.K., Finkle, B.S., 1985. Drugs in fatally injured young male drivers. Public Health Rep. 100 (1), 19–25.