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DRUID

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Responsibility study: Main illicit psychoactive substances among car drivers involved in fatal road crashes in France

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Executive summary

Introduction

In 1999, in France, before considering change in the drug legislation, the government wished to know more on the effect of illicit drugs on the risk of road crashes. A systematic screening of illicit drug on all drivers involved in fatal crashes between October 2001 and September 2003 was hence made compulsory.

The objective of this analysis is to evaluate the relative risk of being responsible for a fatal crash while driving under the influence of alcohol and the main illicit psychoactive substances, among car drivers, and to explore the dose-response relationship of cannabis and/or alcohol.

Material and method

Drivers involved in fatal road crashes, whether killed, injured or non-injured have been tested for alcohol and illicit drugs. Within the DRUID project, a responsibility analysis restricted to car drivers is conducted. In total, 7455 car drivers, with known drug and alcohol concentrations, are included. The study belongs to the framework of case-control studies in which the health event studied is "being responsible for a fatal crash". Responsibility is assessed with a method adapted from Robertson and Drummer. Cases are thus the 4946 car drivers who are responsible for the crash; the controls are 1986 car drivers selected from the 2509 non-responsible car drivers. The control group is chosen in order to be as close as possible to the driving population. For alcohol and illicit drugs, positivity is defined, from a blood dosage, according to DRUID common thresholds: for alcohol: 0.1g/L, cannabis: THC ≥ 1 ng/ml, amphetamines: 20 ng/ml, cocaine: 10 ng/ml and opiates: 10 ng/ml.

Results

Among car drivers, positive cannabis detection is associated with increased risk of responsibility. A significant dose effect is identified. The effect of cannabis remains significant after adjustment for age, sex and alcohol: adjusted odds ratio 1.89 [1.43-2.51]. For alcohol (≥0.1 g/l), crude and adjusted odds ratios of responsibility are very similar, and much higher than those associated to cannabis: adjusted odds ratio 8.39 [6.95-10.11]. No interaction is statistically significant between alcohol and cannabis. In other words, the odds ratio of responsibility associated to positivity to both cannabis and alcohol is merely the product of the respective odds ratios of cannabis and alochol: 1.89*8.39=15.86. For amphetamine, cocaine and opiates, adjusted odds ratios of responsibility are not significantly different from 1.

Discussion

The study finds similar odds ratios for alcohol as previously published. For cannabis, the significant odds ratio of 1.89 together with the significant dose-response effect indicate a causal relationship between cannabis and road crashes. There is no interaction between alcohol and cannabis on the higher risk of causing road crashes; in other words, there is merely a multiplicative effect between the two.

INTRODUCTION

In 1999 in France, before considering changes in the drug legislation, the French Government requested reliable epidemiological evaluations, especially on the role of cannabis in the occurrence of road crashes. Systematic screening of illicit drugs was hence made compulsory in France, from October 2001 to September 2003, for all drivers involved in fatal road crashes. This is the basis of the so-called SAM data and study (SAM=Stupéfiants et Accidents Mortels / illicit drugs and fatal crashes). A first analysis based on the responsibility approach including all drivers has already been conducted and published (Laumon et al. 2005). Here within the DRUID project, we conduct a responsibility study restricted to car drivers.

Cannabis intoxication of a driver may influence fatal crash occurrence in two ways: either by increasing the risk of causing a crash (resulting in death) or by increasing the risk of being killed (in a crash caused by himself/herself or by another driver) probably because of greater physiological vulnerability. Our study only deals with testing the first hypothesis. The second hypothesis implies that there is a selection bias in the non-responsible group; this is dealt with, through the construction of the control group.

We evaluate here the driver's risk of being responsible for a fatal crash. We look for a dose-response between cannabis concentration and responsibility, taking confounding factors into account (especially alcohol) ; we evaluate the representativeness of the cases and controls.

In short, the aims of this study are:

- to evaluate the relative risks of responsibility for fatal crashes while driving under the influence of alcohol and the main illicit psychoactive substances, among car drivers
- to explore the dose-response relationship of cannabis and/or alcohol on the risk of being responsible for a fatal crash, among car drivers

DATA

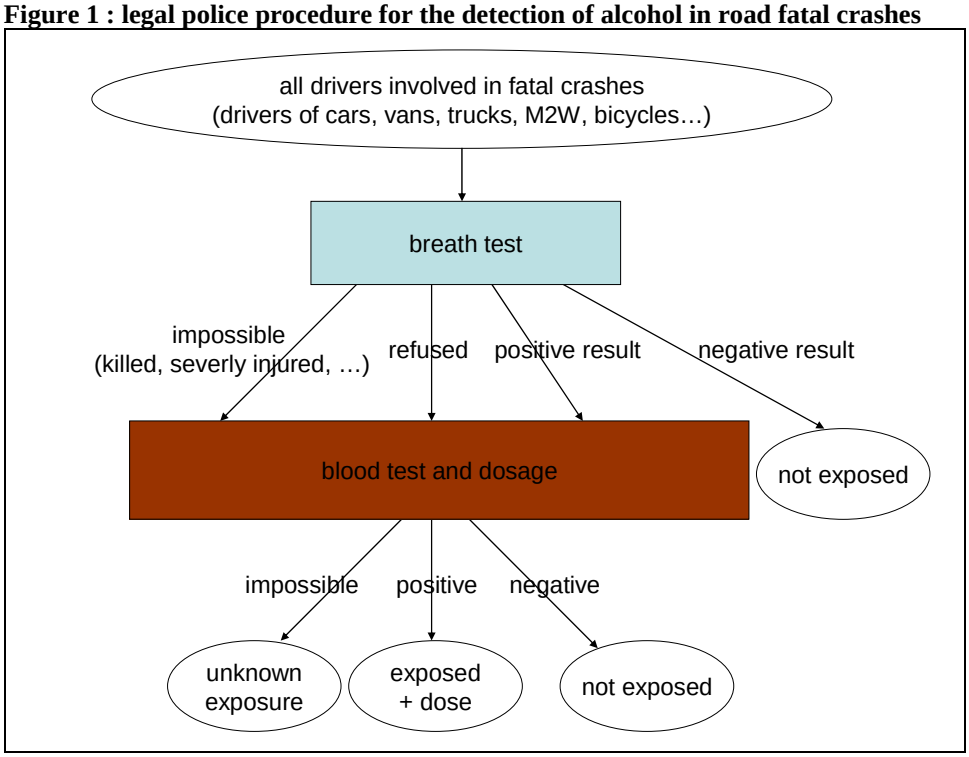
Legal procedure for data collection on alcohol

All drivers, riders and eventually pedestrians involved in a road injury crash (whether fatal or not) must be tested for the presence of alcohol by a breath test carried out by the police (article L 234-3 of the French traffic law, article L 3354-1 of the French public health regulation). If the alcohol concentration in breath is lower than 0.25 mg/l (which is equivalent to a blood alcohol concentration of 0.5 g/l), then the driver is considered to be negative to alcohol; the legal procedure ends there (in particular, no blood test/dosage is conducted).

If the breath test is positive, it is followed by a blood test and dosage.

If the driver refuses the test (rarely observed) or if the severity of the crash makes the test impossible (for someone killed or severely injured), then a blood test and dosage is conducted. It can be noted that, in these situations (i.e. as soon as a blood sample is taken), the blood alcohol concentration is precisely known, even for low doses under the French legal threshold of 0.5g/l.

Figure 1 : legal police procedure for the detection of alcohol in road fatal crashes



Elapsed time between the crash and the dosage:
It was requested that the blood sample be taken as soon as possible after the crash. The elapsed time has no importance for immediately killed drivers because concentration of substance in the blood is unchanged after death. The elapsed time matters only for surviving drivers who get a blood alcohol dosage (n=1800, 17% of subjects). The time of blood sampling is not reported in 47% of these drivers. When it is reported, the distribution of elapsed time is less than 10% within 1 hour, and about: one quarter between 1 and 2 hours, one quarter between 2 and 3 hours, 20% between 3 and 4 hours, and 20% after 4 hours. Consequently, doses and prevalences are probably under-estimated.

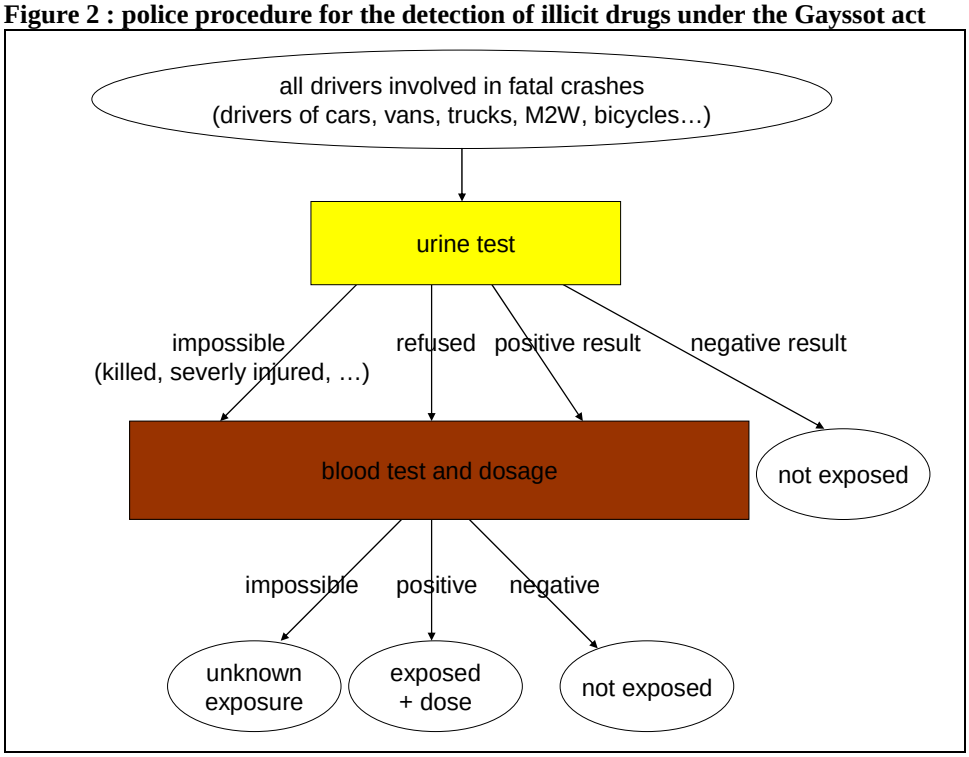
Missing information:

Alcohol exposure is known for 90% of drivers in our dataset (all drivers involved in fatal crashes between October 2001 and September 2003). Missing values correspond mainly to the following situations: the breath test was impossible or refused and no blood sample was taken (almost 90% the missing values); the result of the blood measure was not yet available at the time of data entry in the database (10%). There is also the very rare situation where drivers have a positive or unknown result from the breath test but no blood test or dosage (Biecheler et al. 2008).

Legal procedure for data collection of illicit drugs

For each driver or rider of a vehicle (whether motorised or not), involved in a crash that is immediately fatal, the presence of cannabis, amphetamines, opiates and cocaine is looked for. Pedestrians and passengers are not tested. The different steps of the illicit drugs screening procedure are defined in the Gayssot Act (loi du 18 juin 1999, décret du 27 août 2001, arrêtés des 4 et 5 septembre 2001). They are precisely described, and there is a clear distinction between what is ascribed to the police forces, to the physicians and to the biologists. The driver first undergoes a urinary testing. If it is negative, the procedure ends there. If it is positive, or if the testing is impossible or refused, a blood sample is taken, and a biological laboratory or a certified expert is then required for the testing and dosage of illicit drugs. The police forces are required to take the drivers to the appropriate medical places for the blood or urinary samples collection. The blood or urine uptakes must be done in the shortest time after the crash. Results of the tests are to be reported on dedicated forms and attached to the paper police report.

Figure 2 : police procedure for the detection of illicit drugs under the Gayssot act



Time elapsed between crash and blood sampling:
It was requested that the blood sample be taken as soon as possible after the crash. The elapsed time has no importance for immediately killed drivers (n=4933, 47% of subjects) because concentration of substance in the blood is unchanged after death. For surviving drivers, those who were negative to illicit drugs after a urinary test (n=3381, 32% of subjects) can really be considered as negative because these tests are very sensitive. In other words, they are built in such a way that there give very few false negatives. The elapsed time matters only for surviving drivers who get a blood dosage (n=2205, 21% of subjects). It is not excluded that, for some of these, the drug's measured concentration, and particularly the THC concentration, is significantly lower than the concentration at the time of the crash. Unfortunately, the time of the blood sampling is most often not reported (70% of missing values). For drivers where it is reported, the elapsed time is less than 10% within 1 hour, and about: one quarter between 1 and 2 hours, one quarter between 2 and 3 hours, 20% between 3 and 4 hours, and 20% after 4 hours. Consequently, doses and prevalences are probably somewhat under-estimated.

Missing information:
Illicit drugs exposure is unknown for about 35% of the drivers in our dataset (all drivers involved in fatal crashes between October 2001 and September 2003). Missing values appear in different situations. Most of the time (more than 50%), blood samples were not taken when the urine test was not possible or refused (although this last situation is very rare). A second common situation (one third of all missing values) is that urine tests were possible but were not carried out (one third) ; a third situation is that blood samples were taken but results were not provided (10%). It is important to note that the proportion, among missing values, of positive tests not followed by a confirmatory blood test or with an unknown blood result is low (2%). Physicians reported that reasons for not conducting a urine or blood test were (apart from the severity status of the casualty), most frequently a lack of appropriate equipment (Biecheler et al. 2008).

Legal procedure for data collection of medicines

In the Gayssot Act, it was clearly defined that psychoactive medicines suspecting to have an effect on driving skills will be tested only for drivers found positive to illicit drugs.
However, if we wish to use information about drivers' exposure to legal drugs (as an exposure of interest, or as confusion factor in a multivariate analysis), there should be no selection bias on who is tested. In other words, the information should be available for all drivers, or at least, on a random sample of the drivers.
As this was not the case, psychoactive medicine status (known for a non-randomly selected sample of only 5% of the drivers of our dataset) can not be used in the study.

Positivity thresholds

French positivity thresholds concerning illicit drugs have been defined by the Gayssot Act, and those concerning alcohol had been previously defined.

Table 1 : testing (yes/no) for psychoactive substance : French positivity thresholds

Substance	Body fluid	Threshold
Alcohol	Breath	0.25 mg/l*

Cannabis (THC-COOH)	Urine	50 ng/ml
Amphetamines	Urine	1000 ng/ml
Cocaine	Urine	300 ng/ml
Opiates	Urine	300 ng/ml

* **equivalent to 0.5 g/l of blood**

Table 2 : dosage for psychoactive substance: French positivity thresholds

Substance	Body fluid	Threshold
Alcohol	Blood	0.1 g/l
Cannabis (THC)	Blood	1 ng/ml
Amphetamines	Blood	50 ng/ml
Cocaine	Blood	50 ng/ml
Opiates	Blood	20 ng/ml

Drug blood dosages were conducted using a technique called gas-phase chromatography coupled with mass spectrometry.

Table 3 : commonly –defined DRUID thresholds

Psychoactive substance	Threshold
Alcohol	0.1 g/l
Cannabis (THC)	1 ng/ml
Amphetamines	20 ng/ml
Cocaine	10 ng/ml
Opiates	10 ng/ml

For each of the five psychoactive substances except cannabis, the DRUID threshold is lower than the French legal threshold; this implies that we miss some positive drivers: those who are in the range between the DRUID threshold and the French legal threshold. As a consequence, the prevalences using the DRUID thresholds are under-estimates of the true prevalences. Because of this misclassification effect, and more precisely this dilution effect, corresponding odds-ratios are under-estimates of the true odds-ratios.

For alcohol, 0.1 g/l is the DRUID threshold and 0.5 g/l is the French legal threshold. There are only two very specific situations where it is nevertheless possible to measure a dose of alcohol within the range 0.1-0.5 (when it is truly in this dose range, of course). The first and most common situation is when drivers are killed or very seriously injured so that it is impossible to conduct a breath test; hence a blood test and dosage is directly conducted (with lower detection threshold at 0.1g/l). The second situation is when the true value is almost at 0.5, and that the breath test (which is more sensitive than the blood test) leads to a positive result and hence a blood test is conducted. For all other drivers with a negative breath test, there is no blood test or dosage, so that it is not possible to know where the true value of the blood alcohol concentration stands between 0 and 0.5 g/l. It is however very likely that most of these doses are true zeros. All of these drivers are categorised in the dose group "[0-0.1[g/l" and none in the dose group [0.1-0.5[g/l.

Police reports collection

Police forces were informed by decree of their obligation to send to OFDT, the French monitoring centre for drugs and drug addiction, a copy of all police reports dealing with immediately fatal road accidents that occurred during the study period. The OFDT, as study coordinator, was in charge of sending these paper police reports to the CEESAR, one of the partner in the project, in order for these paper reports to be coded and registered. The data were then sent as an electronic file to our research team. However, despite of the mandatory aspect of the request, a number of immediately fatal accidents were missing from the paper police reports received by OFDT. These missing police reports were identified by comparison with the national database of road crashes, which consists of records of all police reports of road (injury) crashes, whether fatal or non-fatal. This identification enabled OFDT to send some reminders to the police forces. As a result, 95% of police reports of immediately fatal crashes were finally received at OFDT (two thirds after a reminder). In the end, 10,671 police reports were collected. However, some were highly incomplete and hence 10,614 could be used. These 10,614 fatal crashes correspond to 17,228 drivers (or riders).

Record-linkage with the national police database

All the police reports of road crashes are supposed to be registered in the national police crash database. Each paper police report is registered into an electronic record; a number of pre-defined characteristics are coded. In order to use this readily available information, we restricted the analysis to the drivers that were also registered in this database; this means that instead of basing the analysis on 17,228 drivers, it is based on 16,728 drivers.

Selection of subjects

Selected crashes are crashes that are immediately fatal, and that occurred in France between October 2001 and September 2003. The statistical unit is the driver (not the crash).

We excluded drivers with unknown age (23 of them). We further excluded drivers with missing data on alcohol and illicit drugs. This left us with 10,748 drivers.

We excluded drivers with unknown age (23 of them). We further excluded drivers with missing data on alcohol or illicit drugs.

Within the DRUID project, we focus on car drivers. We hence selected all car drivers involved in fatal crashes, whatever the antagonist: none, another car driver, a pedestrian, a cyclist, a M2W user, a van/truck driver…

Alcohol status is unknown for 10% of the subjects. More precisely, it is unknown for 3% of the surviving drivers and for 17% of the killed drivers. Since it is tested for almost all surviving drivers, one can not suspect the police forces to select drivers for testing based on their behaviour (whether it may indicate being under influence). Concerning the proportion of missing alcohol status in killed drivers, one may suspect some technical/medical difficulties.

Illicit drug status is unknown for 36% of the drivers involved in fatal crashes. According to paper police reports, most of the missing data are due to a lack of appropriate equipment for conducting the test (as reported by the physicians). Indeed, the procedure for testing illegal drugs was new to them, whereas alcohol testing has been mandatory in France for all injury road crashes since the 70's.

We have compared drivers with known drug/alcohol status to drivers with missing drug/alcohol status, separately for killed drivers and for surviving drivers, in terms of age and sex. We sometimes find some slight differences but nothing systematic.

From these elements, we can say that the missing data mechanism is not "missing completely at random" (MCAR), but merely "missing at random" (MAR); this means, that excluding subject with missing data on alcohol or drug will not create bias in the regression analysis where alcohol and drug are explicative variables (Allison 2010).

Excluding drivers with unknown drug or alcohol status leaves us with 10,748 subjects.

Among the 10,748 drivers with known exposure on illicit drug and alcohol, there are 7514 car drivers (we excluded 30 drivers of small low-speed "cars" that do not require a driving licence).

In order that our analysis follows the DRUID framework, we further excluded drivers below 18 years old. This led us to 7455 car drivers.

METHOD

Culpability and Responsibility studies

Culpability and responsibility studies are the same type of studies. The principle is to compare drivers who are responsible for the crash with drivers who are not responsible for the crash.

Within the DRUID project, WP2 (minutes of the WP2 meeting "other studies", 23-24 march 2009) we agreed that culpability for the crash is defined in terms of legal regulation (and usually assessed by the police) whereas responsibility is defined in terms of accident causation (and usually assessed by accidentology experts).

We conduct here a responsibility study.

Assessment of crash responsibility

A first way of obtaining the responsibility status of drivers involved in crashes is to request some accidentology experts to assess it. Such experts will analyze the police reports in the view of understanding why and how the crash happened.

The drawbacks of using experts' assessments are two types: there is no external validation; in particular there is no international validation; secondly, it is a very heavy procedure to implement for a great number of drivers.

A second way of assessing the responsibility status is to use automated assessment procedures. Some have already been developed; one is proposed by Robertson and Drummer (Robertson 1992). This method consists in computing a responsibility score, based on information from 8 groups of characteristics: road conditions, traffic conditions, vehicle conditions, crash type, complexity of the driving task, complexity of traffic regulation, tiredness of the driver, and witnesses comments.

This Robertson and Drummer method has many advantages: it is very easy to implement, it can be used for any type of crash and moreover it has been used by several research teams worldwide. It has some drawbacks: firstly, it is based on pieces of information that are not always found in police reports; secondly, it uses information on driving offences, and in particular the blood alcohol status. This is problematic because this is a confounding factor: we want to account for its correlation with the risk of being responsible in a fatal crash: its correlation in terms of impairment, of taking more risk, not its correlation in terms of legal sense. At the same time, it is easy to disregard this data (alcohol status) in the automated assessment of responsibility. This is what we did.

We dropped some other items from the method, for other reasons. The item "comments from possible witnesses" it is not part of the recorded police reports. The item "level of tiredness of the driver" is not reliable.

The other six types of characteristics of the Robertson and Drummer method were adapted to the French available police data. It can be pointed out that two items play a strong role in the score: "driving offences" (except alcohol status, excluded from the procedure) and being "declared responsible by the police" (this concerns crashes involving 2 vehicles or more).

The obtained responsibility score is divided into 3 categories: (fully) responsible, partially responsible and non-responsible. In the analysis, partially responsible drivers are grouped together with fully responsible drivers.

The adapted Robertson and Drummer method has been applied on all drivers included in the study. In order to validate (or not) the adapted method, we compared its results with an experts' group assessment. This was done in a blind way i.e. the experts were not given the results from the adapted automated method. Also, information on alcohol, drug status were NOT provided to them; age and sex data were also hidden as they are correlated with alcohol and drug status.

This experts assessment was conducted on a sub-sample of 3024 drivers, involved in crashes involving two or more vehicles. The two responsibility assessments were compared for this common sub-group. We found a kappa score of 0.67 (agreement score), with 95% CI=[0.65-0.70]). It was concluded that they were similar enough to validate the adapted Robertson and Drummer method (Laumon et al. in press).

Responsibility study = a case-control study

Case-control studies are a classic design of studies in epidemiology; typically one compares people with a health event (cases) to people without the health event (controls), to identify

which and how some characteristics differ between the two groups. Association between characteristics and the illness is measured by odd-ratios, and statistically tested. When there is a positive association, one uses the terminology of 'risk factor' (for a negative association one uses the terminology of 'protective factor').

Among these characteristics, one may focus on exposure to a specific product (tobacco for instance). This is called the exposure variable.

The health event can be called the "outcome of interest". Presence of the outcome of interest defines cases; absence of it defines controls.

The target population is usually the whole population; in others words, one typically wants to find results that apply to the whole population.

The source population, ie the population used to sample and contact people is often the hospitalised population: people are easy to contact, and usually rather receptive for participating. For instance, in cancer epidemiology, if one wants to study the effect of tobacco on bladder cancer, people with bladder cancer will be recruited from oncology departments (at hospitals); controls can be recruited from other hospital departments.

Case-control studies have later been used in the field of injury epidemiology. In this situation the health event is being killed or being injured in a road crash. Cases are hence defined as injured or killed people in a road crash; controls are uninjured people.

Controls are usually sampled from circulating drivers (at best: at the same place and time as the crash happened).

It is however quite difficult to request circulating drivers to stop and to take part in a study; one usually needs the police participation. Therefore, very few research teams succeed in carrying out such studies at the time when alcohol was studied (Borkenstein et al. 1974) and even now, for drugs.

Because of these difficulties, some researchers have set up culpability or responsibility studies. One works on the population of people involved in crashes. The principle is to compare drivers who are responsible for the crash to drivers who are not, and explore which characteristics are associated with being responsible for the crash. An underlying assumption is that non-responsible drivers are involved in the crash "by chance", independently from the nature of their journey and from the consumption or not of drugs, and hence are a good sample (i.e. representative) of the general driving population. It is not always so (see further). This approach is developed by some authors as "induced exposure" (Lenguerrand et al. 2007; Sacco et al. 1999; Stamatiadis & Deacon 1997).

We explain now why a culpability study belongs to the framework of the case-control studies. The outcome of interest is here "being responsible for the crash". Cases and controls are defined according to it: cases are made up from responsible drivers and controls from non-responsible drivers. The source population is the population of drivers involved in crashes. We compare the characteristics of the two groups (in the same way as in a "typical" case-control study) in order to identify risk factors for being responsible of the crash (or protective factors). We estimate odd ratios to measure the association between characteristics and the outcome of interest.

Including the responsibility study in the general framework of case-control studies has been used in the paper from our research team, which has been peer-reviewed and accepted by the British Medical Journal (Laumon et al. 2005).

Other research teams have based their study design on the case-control study with responsibility as the outcome of interest. In 2000, a paper about health conditions, medication and car crashes in the elderly, from a team of US epidemiologists and clinicians was published in the highly valuable American Journal of Epidemiology (impact factor=4.454 in 2010), explicitly using a case-control design (McGwin et al. 2000). Cases were "at fault-drivers involved in crashes", and two control groups were constructed: a group of "not at-fault drivers involved in crashes" and a group of "drivers not involved in crashes" (analyses were conducted using one control group alternatively).

In 2006, a paper on the same subject on all adults, from a research team from the Norwegian Institute of Transport Economics (TØI), was published in Accident Analysis and Prevention (Sagberg 2006); it also explicitly states : "cases and controls were identified from an insurance company database of crash-involved drivers, on the basis of culpability for the crash".

For a number of reasons (at least, for using odds ratios as approximations of relative risks), it is best that the control group is as close as possible to the general population, in others words that it is representative of the general population. Therefore, we paid much attention to the selection of controls (see below).

Selection of cases and controls

The cases are the 4946 car drivers responsible for the crash and below 18 years old. The controls are selected as a sub-sample from the 2509 non-responsible car drivers below 18 years old.

Such a sub-selection of non-responsible drivers is needed. Indeed, in a case-control study, relative risks (RR) can not be estimated but odds ratios (OR) can. However relative risks are much easier to interpret than odds-ratios. Relative risks can be approximated by odds-ratios if the three following conditions are all met: 1) the controls are a representative sample of the whole population, 2) the outcome of interest is a rare event, 3) the value of the odds ratio is not too big. It implies here that the controls should be as close as possible to the whole driving population (NB: in this population, the event "being responsible for a fatal crash" becomes a rare event).

As previously found with alcohol (Evans 1991), preliminary analysis of the data (Laumon et al. in press) showed a significant increase in the risk of death of non-responsible drivers who tested positive to cannabis. In other words, cannabis is a risk factor for a fatal outcome once the person is injured (all other things being equal), maybe because of higher physiological vulnerability, riskier behaviour, etc. Because this phenomenon would lead to a selection bias in comparison with the driving population, due to the over-representation of crashes in which the only victim killed is a driver detected as cannabis (or alcohol)-positive, we excluded non-responsible drivers who were the sole fatally injured victim in the crash (523 of them, among car drivers above 18 years old). Controls are hence selected as non-responsible drivers, who

were not the only fatally injured party. The control group of car drivers hence includes 1986 subjects.

This is analogous to what is done in other fields of epidemiology. In cancer epidemiology: cases are cancer patients, and controls are usually recruited among other hospitalized persons. For instance, if a study aims at exploring the effect of tobacco on bladder cancer, the selection of hospital controls will exclude patients suffering from diseases known to be related with tobacco. Otherwise the controls will display a higher proportion of smokers than the general population.

We are aware that this sub-selection is not trivial. It has already been used in the French SAM study based on all drivers (i.e. not restricted on car drivers) ; the corresponding paper has been peer-reviewed and accepted (Laumon et al. 2005) by the British Medical Journal, an international journal that is highly valuable, in the field of epidemiology (impact factor=12.8, source=ISI, Web of Science).

Validation of the selection of cases and controls

The table below provides the prevalence of psychoactive substances in the cases, in the controls and in the non-responsible drivers that have been excluded from the control group (those who are the sole fatality in the crash). The table does show that the prevalence is much higher (for cannabis and alcohol) among the excluded non-responsible drivers than among the controls.

Table 4 : prevalence of psychoactive substance according to responsibility status for the fatal crash, CAR drivers over 18 years old, France, 2001-2003, n=7455

Psychoactive substance	prevalence in cases (n=4946)	prevalence in excluded non-responsible (n=523)	prevalence in controls (n=1986)
Alcohol (≥0.1g/l)	37.6%	24.5 %	6.8 %
Cannabis (THC≥1 ng/ml)	9.4%	5.9 %	3.3 %
Amphetamines (≥20ng/ml)	1.0%	0.4 %	0.4 %
Cocaine (≥10 ng/ml)	0.6%	0.6 %	0.3 %
Opiates (≥10 ng/ml)	0.9%	1.1 %	1.2 %

The representativeness of our controls can be discussed on the basis of a comparison, between these estimated prevalences and those estimated elsewhere for the whole driving population using other methods. These comparisons are available for all drivers types, but prevalences for car drivers are not very different from all drivers (Amoros & Gadegbeku 2010). For alcohol, in the same period, the prevalence of alcohol above 0.5 g/l in the driving population in France was found to be 2.5% (ONISR 2004) whereas the corresponding estimation in our control group is equal to 2.7%.

We can also consider drivers involved in slight crashes as close to drivers in the driving population and standardize prevalences obtained in the control group on the characteristics of these drivers. Comparing our controls with non-responsible drivers involved in a slight injury crash allowed us to identify their distinguishing characteristics: driver's sex and age; type of

vehicle; and place, time, and type of crash. The prevalence of cannabis (above 1 ng/ml) in our controls was 2.8%, compared with 2.9% when standardised for these variables; both these prevalences were 2.7% for alcohol (above 0.5 g/l) (Laumon et al. 2005).
These similarities contribute to validate our control group as close as possible to the driving population.

Estimation of odds ratio and relative risks

We conduct a case-control study, where cases and controls are defined according to their crash–involvement responsibility, among car drivers. This is analysed using a logistic regression, with SAS software.

A logistic regression provides odds ratios estimates. Since controls have been selected in order to be representative of the driving population (by excluding the non-responsible who are the only fatality in the crash), the event of interest (being responsible for a fatal crash) is a rare event. The first two conditions for using odds ratio estimates as approximate of Relative risk estimates are met. The last condition is that the estimates should be close to the value 1.

Relative risks are much easier to interpret than odds ratios. The relative risk is the ratio of two risks: the risk of the health event for exposed subjects and the risk of the health event for non –exposed subjects. The risk of the health event among exposed subjects (respectively among non-exposed subjects) is measured by the probability of the health event among exposed subjects (resp. among non-exposed subjects). For instance a relative risk of 1.5 (and significantly different from 1) means that exposed people are 1.5 more likely at risk of the health event than non-exposed people (or, in other words, exposed subjects have 50% (=(1.5-1.0)*100) more risk to suffer the health event than non-exposed subjects.

Odd ratio is the ratio of two odds, the odd of the health event among exposed people and the odd of the health event among unexposed people. Each odd is the ratio between the risk of having the health event and the risk of not having the health event.

It is hence rather difficult to interpret, and many people interpret it as if it was a relative risk, which is not always valid (see above the conditions under which the odds ratio is a good estimate of the relative risk).

An odd ratio is significantly different from 1 if its confidence interval do not contains the value 1. The confidence intervals given in this report are all computed with a risk α equal to 5%. In other words, the confidence intervals have 95% of chance of containing the true value of the odd ratio.

The main exposure variable of interest is cannabis intoxication. Other exposures to illicit drug are considered: amphetamines, opiates, and cocaine. However, due to the small number of drivers who are positive for these substances, it is not be possible to study a dose-effect for these substances but only the effect of negative/positive detection.

The THC cutpoints commonly defined within the DRUID project are: 1 / 3/ 5 (ng/ml). The reference category is the [0 -1[category.

Confounding factors

One major confounding factor is alcohol. As a reminder, in the field of epidemiology, a characteristic is called a confounder if it is correlated with both the exposure of interest on the one hand, and with the outcome of interest on the other hand. Alcohol consumption is (positively) correlated with cannabis consumption (the exposure of interest); for instance, among people who are positive to cannabis, a high proportion, 50% (Amoros & Gadegbeku 2010) are also positive to alcohol. Another way to see this correlation is through the age characteristic: cannabis consumption is more frequent in young people, and so is alcohol (for men, who are the most numerous in this study).

On the other hand, alcohol consumption is correlated with being responsible of fatal road crash; this has been established by numerous studies.

Because of these two associations, analysis on the effect of cannabis must take alcohol consumption into account, as a confusion factor at least. Before doing that, one should however test whether there is an interaction between cannabis and alcohol consumption (on the effect of being responsible of a fatal crash).

In the epidemiological sense, interaction between two exposures, say A and B, means that the own effect of exposure to A on the outcome of interest is not the same whether there is also exposure to substance B or not. In other words, there is interaction if the effect of both substances (compared to none of the two) on the outcome of interest is not multiplicative: if it is greater than the multiplicative effect or if it is smaller. The multiplicative effect is merely obtained by multiplying the adjusted OR for exposure A with the adjusted OR for exposure B (the adjustment being at least on the other exposure). The interaction OR is obtained by including an interaction term in the regression model instead of the two exposures (see Annex, tables 20 and 21; for two dichotomous exposures A and B, it means that instead of including variable A (in 2 categories: yes/no) and variable B (in 2 categories : yes/no), one includes one variable constructed on variables A and B, as such, in 4 categories: A=no and B=no / A=yes and B=no / A=no and B=yes / A=yes and B=yes; the interaction OR is the one between the last category (A=yes and B=yes) and the first category (A=no and B=no)).

Here, this would mean: the combined effect of cannabis and alcohol consumption on being responsible of a fatal crash is greater (or smaller) than the multiplicative effect of the two. A formal statistical test exists, that checks whether the OR obtained by multiplying the cannabis adjusted OR with the alcohol adjusted OR is different than the OR of both cannabis and alcohol obtained from a regression model with an interaction term.

This test has been conducted and the hypothesis of equality between the interaction effect and the multiplicative effect is not rejected (see results and annex sections); in other words it is not shown that there is an interaction between cannabis and alcohol. It means that the effect of both can be considered as merely multiplicative.

In terms of modelling, it means that it is only needed to adjust for the confounding effect of alcohol on cannabis: i.e. it is only needed to include the alcohol variable in the regression model (as a main factor).

Furthermore, the inclusion of alcohol in the model enables some validation of the results: by comparing the results that we obtain for alcohol to the results already published (large literature on this). The dose-effect is also estimated for alcohol.

The DRUID cutpoints for alcohol that have been chosen for the DRUID project are the following ones: 0.1 / 0.5 / 0.8 / 1.2 (g/l). The reference category is the [0-0.1[.

The other potential confounding factors taken into account are: the drivers' age and gender. Age is a confounding factor, because on the one hand, younger age is associated (positively correlated) with higher risk of fatal crash, and on the other hand, younger age is associated with higher consumption of cannabis (Amoros & Gadegbeku 2010). Gender is a confounding factor as on the one hand it is associated with fatal crash: men are more likely to be responsible for a fatal crash than women (Martin et al. 2004), and on the other hand, gender is associated with cannabis consumption: men are more often cannabis consumers than women (Ravera & de Gier 2008). The common DRUID cut-points defined for age are: 18, 25, 35 and 50 years old.

RESULTS

Before displaying the odds ratios, we remind the reader about the estimated prevalences of the psycho-active substances in the cases and controls group (Amoros & Gadegbeku 2010).

Table 5 : prevalence of psychoactive substance according to responsibility status for the fatal crash, among CAR drivers above 18 years old, France, 2001-2003, n=6932

Psychoactive substance	prevalence in cases (n=4946)	prevalence in controls (n=1986)
Alcohol (≥0.1g/l)	37.6%	6.8 %
Cannabis (THC≥1 ng/ml)	9.4%	3.3 %
Amphetamines (≥20ng/ml)	1.0%	0.4 %
Cocaine (≥10 ng/ml)	0.6%	0.3 %
Opiates (≥10 ng/ml)	0.9%	1.2 %

The prevalences in the case group are much higher than the prevalences in the control group: 5.5 times higher for alcohol, 2.8 times higher for cannabis, 2.5 times higher for amphetamines and 2 times higher for cocaine. However this is a descriptive analysis (no statistical test) and a univariate analysis (no confounding effect taken into account).

In the following, we only interpret odd ratios that are statistically different from the value 1.

Alcohol

Table 6 : OR for alcohol consumption (yes vs no) of the risk of being responsible of a fatal crash, for car drivers above 18 years old, France, 2001-2003, n=6932

Psychoactive substance	Number of positive	Crude OR	95% CI	Adjusted OR	95% CI
Alcohol (yes vs. no)	1 997	8.28	6.89 - 9.95	8.39	6.95-10.11

Alcohol positivity: blood alcohol concentration ≥ 0.1 g/l
adjusted on THC(yes/no), age, gender

Crude and adjusted odds ratios for alcohol (in a yes/no categorisation) are very similar, and are quite high, at around 8.

Table 7 : OR for alcohol consumption (5 dose categories) of the risk of being responsible of a fatal crash for car drivers above 18 years old, France, 2001-2003, n=6932

Psychoactive substance	Number of drivers	Crude OR	95% CI	Adjusted OR	95% CI
0 ≤ Alcohol < 0.1 g/l	4935	1.00		1.00	
0.1 ≤ Alcohol < 0.5 g/l	327	2.57	1.93-3.40	2.45	1.84-3.26
0.5 ≤ Alcohol < 0.8 g/l	162	6.35	3.66-11.01	6.14	3.52-10.69
0.8 ≤ Alcohol < 1.2 g/l	251	7.33	4.58-11.74	6.92	4.30-11.13
1.2 ≤ Alcohol	1257	18.26	13.26-25.15	19.32	13.99-26.69

adjusted on THC (in 4 dose categories), age, gender

When alcohol is categorised according to its concentration in the blood, the odds ratios increase according to the dose of alcohol.

For low doses below the French legal threshold ([0.1-0.5[), the OR for car driver of being responsible of the crash is significantly higher than 1, but much lower than for other doses.

The odds ratio for alcohol above 1.2 g/l is very high. However this last category is very wide. About one half of the drivers of this category are in fact above 2.0 g/l, where the odds ratio is extremely high: OR=39.6, 95% CI= [22.7-68.9] (Laumon et al. in press). That explains the very high level of risk in the 1.2+ category.

Cannabis

Table 8 : OR for cannabis (THC) consumption (yes vs no) of the risk of being responsible of a fatal crash for car drivers above 18 years old, France, 2001-2003, n=6932

Psychoactive substance	Number of positive	Crude OR	95% CI	Adjusted OR	95% CI
THC (yes vs. no)	529	3.00	2.31 - 3.91	1.89	1.43-2.51

Cannabis positivity: THC in the blood ≥ 1 ng/ml
adjusted on alcohol (yes/no), age, gender

The crude OR for cannabis is estimated at 3, and the adjusted OR is estimated at a lower value of 1.89.

In others words, car drivers under the influence of cannabis have 1.89 times more risk of being responsible of a fatal crash than non-intoxicated drivers (all other things being equal).

Table 9 : OR for cannabis intoxication (4 dose categories) of the risk of being responsible of a fatal crash for car drivers above 18 years old, France, 2001-2003, n=6932

Psychoactive substance	Number of drivers	Crude OR	95% CI	Adjusted OR	95% CI
0 ≤ THC < 1 ng/ml	6403	1.00	-	1.00	-
1 ≤ THC < 3 ng/ml	220	2.26	1.57-3.26	1.53	1.03-2.27
3 ≤ THC < 5 ng/ml	116	4.54	2.37-8.70	2.84	1.44-5.60
5 ≤ THC	193	3.51	2.22-5.54	2.01	1.24-3.27

adjusted on alcohol (in 5 dose categories), age, gender

When we explore a dose-level for cannabis intoxication, again, the adjusted odd ratios are estimated at a lower value than the crude odds ratios. The trend test rejects the null hypothesis (of equality of the odds-ratios associated with different dose categories) at $p<0.001$; there is an increased risk of responsibility for fatal crashes with increasing cannabis dose.

However, one can notice that the confidence interval for the 3 to 5 ng/ml category is wider than the other two, certainly due to the very small number of drivers ; in other words, the precision of the estimate is not very good in this category.

Table 10 : OR for cannabis intoxication (3 dose categories) of the risk of being responsible of a fatal crash for car drivers above 18 years old, France, 2001-2003, n=6932

Psychoactive substance	Number of drivers	Crude OR	95% CI	Adjusted OR	95% CI
0 ≤THC < 1 ng/ml	6403	1.00	-	1.00	-
1 ≤ THC < 5 ng/ml	336	2.77	2.01-3.81	1.82	1.29-2.57
5 ≤ THC	193	3.51	2.22-5.53	2.00	1.24-3.27

adjusted on alcohol (in 5 dose categories), age, gender

The frequencies are more balanced between the two positive categories. This allows us to have smaller confidence intervals.

The trend test rejects the null hypothesis (of equality of the odds-ratios associated with different dose categories) at $p<0.001$; there is an increased risk of responsibility for fatal crashes with increasing cannabis dose.

Association between alcohol and cannabis

The own (=adjusted) effect of alcohol on the risk of being responsible for a fatal crash is estimated at 8.39 and the own (=adjusted) effect of cannabis is estimated at 1.89. If there is no interaction between the two, cannabis effect remains the same whether the driver is positive or not to alcohol. Thus, in this case, the effect of the association of both cannabis and alcohol is a multiplicative effect between the two. The odd ratio of being both under the influence of alcohol and cannabis on the risk of being responsible for a fatal crash (compared to drivers not exposed to cannabis nor to alcohol) is estimated at 8.39*1.89=15.86.

The model which includes an interaction effect (see annex), provides an OR of 10.87 for exposure to both alcohol and cannabis (compared to no exposure to cannabis nor alcohol). The test of the null hypothesis that the interaction effect is equal to the multiplicative effect yields a p-value of 0.13 (greater than the 5% error level): the null hypothesis is not rejected. In other words, the model does not indicate an interaction between cannabis and alcohol intoxication, only a multiplicative effect.

Amphetamines

Table 11 : OR for amphetamines consumption (yes vs no) of the risk of being responsible of a fatal crash for car drivers above 18 years old, France, 2001-2003, n=6932

Psychoactive substance	Number of positive	Crude OR	95% CI	Adjusted OR	95% CI
Amphetamines (yes vs. no)	54	2.71	1.22 – 6.01	(1.54)	0.66-3.56

Amphetamine positivity: blood concentration ≥ 20 ng/ml
Adjusted on alcohol (doses), Cannabis (doses) age, gender

The crude odd ratio for the influence of amphetamines on responsibility for a fatal crash is significantly above 1, i.e. indicating a higher risk. However, when adjusting for confounding effects from alcohol, cannabis, age and gender, the odds ratio is estimated at 1.5 and it is no longer different from 1. The confidence interval is somewhat wide.

We remind the reader that because of the small frequency of car drivers (involved in fatal crashes) who are positive to amphetamines, it was not possible to conduct a dose-level analysis on amphetamines.

Cocaine

Table 12 : OR for cocaine consumption (yes vs no) of the risk of being responsible of a fatal crash for car drivers above 18 years old, France, 2001-2003, n=6932

Psychoactive substance	Number of positive	Crude OR	95% CI	Adjusted OR	95% CI
Cocaine (yes vs. no)	34	(1.87)	0.78 – 4.53	(1.17)	0.45-3.02

Cocaine positivity: blood concentration ≥ 10 ng/ml
adjusted on alcohol (doses), Cannabis (doses) age, gender

Both the crude and adjusted odd ratio for cocaine are not significantly different from the value 1. In other words, the analysis does not show an effect of cocaine on being responsible for a fatal crash.

Opiates

Table 13 : OR for cocaine consumption (yes vs no) of the risk of being responsible of a fatal crash for car drivers above 18 years old, France, 2001-2003, n=6932

Psychoactive substance	Number positive	Crude OR	95% CI	Adjusted OR	95% CI
Opiates (yes vs. no)	69	(0.80)	0.48 – 1.33	(0.76)	0.44-1.32

Opiates positivity: blood concentration ≥ 10 ng/ml
adjustement on alcohol (doses), Cannabis (doses) age, gender

Crude and adjusted odd ratios for opiates are estimated at the same value and are not different from 1. In other words, the analysis does not show an effect of opiates on being responsible for a fatal crash.

DISCUSSION

Strengths and weaknesses

The study has been possible thanks to a specific law in France: it was made compulsory for each fatal crash, that all the involved drivers be tested for illegal drugs. Alcohol was already being tested on all drivers involved in any injury road crash.

Drug status is missing on 35% of the subjects, and alcohol is missing on 10% of the subjects (36% altogether). The missing mechanism seem mostly a lack of appropriate equipment and some technical difficulties. Excluding drivers with missing data on drug and/or alcohol should hence have little effect on the results.

The study is based on a large number of subjects, about 7,000 of them. This means a rather good statistical power.

This is a responsibility study. We have also explained that it belongs to the framework of the case-control design, where the outcome of interest, by broadening the definition of "health event" becomes "being responsible for a fatal road crash", the exposure of interest is cannabis, and the possible confounding factors are alcohol, age and gender.

Responsibility has been assessed by the automated method of Robertson and Drummer (Robertson 1992). The high level of concordance with the expert responsibility assessment validates the automated method.

The sub-selection of the control group (excluding non-responsible drivers who are the sole fatality in the crash) may create wonder: this is done in order to have a control group as close as possible to the driving population, and hence use the estimated odds ratios as good approximations of relative risks. It is completely analogous to what is done in others fields of epidemiology. Furthermore, the obtained estimates of prevalences and odd ratios are fully coherent with other estimations, from other studies. There are much fewer controls than there are cases (because of the single-vehicle crashes where the driver is responsible most of the time); this does not prevent the study from obtaining significant results for cannabis.

Time between crash and blood sampling

The legal procedure requested that the blood sampling to be conducted as soon as possible after the crash. The time elapsed between the two matters only for surviving drivers. It is unknown most of the time (and when it is known it is mostly within 1 and 4 hours). Consequently, doses and hence prevalences are probably somewhat under-estimated.

Opiates and morphine

No significant effect is noticed for opiates, neither in univariate nor in the adjusted model. On the one hand, this can be due to a lack of statistical power, the number of positives drivers being very low. On the other hand, some severely injured drivers were given morphine as a pain treatment. Most of the time, such information was written in the police report, and in this situation the positivity to the test was not considered. However if a number of non responsible drivers had a false positive information concerning opiates, it could bias the odd ratio downwards. This hypothesis can not completely be excluded.

No analysis on medicines

There has not been a systematic screening of psychoactive medicines of the drivers involved in fatal crashes (only in those already positive to illicit drugs, which introduces a selection bias). We could hence not study the effect of medicines on the crash responsibility; we could neither adjust for it.

We did perform a sensibility analysis: exclude drivers who are positive to psychoactive medicine and check whether the results change and by how much. For cars drivers, only 64 were tested positive to medicines. By excluding them, we get very similar results: adjusted OR for cannabis: 1.97, 95% IC=[1.46-2.65] instead of 1.89, 95% IC=[1.43-2.51], and adjusted OR for alcohol: 8.50, 95% IC=[7.03-10.3] instead of 8.39, 95% IC=[6,95-10.1]. The same pattern was observed for the group of all drivers (Laumon et al. in press).

Similarity of our results on alcohol with previous studies

We used alcohol as an indicator of plausibility for the results obtained: our study concurs with previous studies on crash risk related to alcohol (Drummer et al. 2004; Dussault et al. 2002; Longo et al. 2000). This backs up our methodological choices.

We confirm the confounding role of alcohol on cannabis; we do not detect any interaction between the two: consumption of both cannabis and alcohol merely multiplies the risks related to consumption of either cannabis or alcohol alone (the evidence of no interaction is even greater when drivers of all vehicles types are studied (Laumon et al. in press). This result consolidates several previous experimental and epidemiological studies (Inserm 2008).

Similarity of our results on cannabis with studies using detection of THC in the blood

Our result on the effect of cannabis (OR=1.89, 95% IC=[1.43-2.51] is coherent with the study of Drummer where OR=2.7, 95% CI= [1.0-7.0] (Drummer et al. 2004) which is a study that assessed cannabis status from the presence of THC in the blood, and not from THC-CCOH in urine. THC in the blood is a good indicator of being under the influence of cannabis when the crash occurred, whereas THC-COOH is only a indicator of past-exposure to cannabis, up to several days ago. In other words, THC in the blood allows identifying people who were under the influence of cannabis at the time of crash whereas THC-COOH in urine identifies cannabis consumers, who may not have been under the influence of cannabis at the time of the crash.

Study population=involved in fatal crashes versus fatally injured involved drivers

We did not restrict the study population to killed drivers only; we kept all car drivers whether killed, injured or non-injured. This implies that we evaluate the overall increase in cannabis related risk in causing crashes that are fatal to either the individual himself or to others (risk of being responsible for a fatal crash and risk of dying from an injury crash). This explains why we find higher odds ratios than in studies that only included fatally injured drivers (Drummer et al. 2004; Dussault et al. 2002).

Odds ratio when comparing responsible to all non responsible drivers

When comparing the responsible drivers to all non responsible drivers, without doing any selection in the controls, odds ratio are lower (for cannabis and for alcohol) than those obtained with the controls restricted to non-responsible drivers who are not the sole fatally in the crash. Thus, for all drivers, adjusted OR of responsibility for cannabis (THC>0) is 1.43, 95% CI=[1.19-1.73] when comparing responsible to non-responsible, and 1.78, 95% CI=[1.40-2.25] when selecting controls (Laumon et al. in press).

Cannabis and fatal crash responsibility: a dose-effect response

The analysis shows a dose-effect between cannabis and the risk of responsibility for fatal traffic crashes; this is strongly in favour of a causal relationship between cannabis and road crashes. The same dose-response effect is found when the analysis is not restricted to car drivers, but using drivers of all vehicles types (Laumon et al. 2005).

OR estimated with DRUID thresholds have lower values than OR estimated using French thresholds (results in annex)

For alcohol, amphetamines, cocaine and opiates, the DRUID thresholds are lower than the French legal thresholds. Thus, concentrations above the DRUID thresholds but under the French ones are not systematically searched for, nor written down. This leads to under-estimating the number of drivers positive to low doses (between the DRUID threshold and the French one).

The fact that the DRUID thresholds are lower than the French legal thresholds is problematic when focusing on odds ratios associated to dose category between the two thresholds. This is an issue for alcohol (where the DRUID threshold is 0.1g/l and the French legal was 0.5 g/l). For some drivers, only a breath test with a negative result is provided. Indeed, in this case, no blood sample is taken and it is hence impossible to obtain a dose that is lower than the French legal threshold. Moreover, this concerns mostly uninjured or slightly injured drivers (since killed or severely injured drivers, who can not undergo a breath test are directly tested with a blood test). It has to be kept in mind when comparing cases versus controls, because the proportion of uninjured or slightly injured drivers is higher in non-responsible drivers than in responsible ones (Amoros & Gadegbeku 2010). Therefore, the under-estimation of positive drivers is more important in non-responsible drivers than in responsible ones. This leads to have an artificial high odds ratio associated to this category. This phenomenon is described in details in the SAM report (Laumon et al. in press) focusing on low doses of alcohol.

When comparing the results obtained with DRUID thresholds with those obtained with the French ones, the conclusion is that taking lower thresholds lead us to have lower odds ratios. This phenomenon is probably due to lower impairment at lower doses.

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ANNEXES

Results using French legal thresholds

Table 14 : prevalence of psychoactive substance according to responsibility status for the fatal crash, among CAR drivers over 18 years old, using French legal thresholds, France, 2001-2003, n=6932

Psychoactive substance	prevalence in cases (n=4946)	prevalence in controls (n=1986)
Alcohol (≥0.5g/l)	32.3 %	3.7 %
Cannabis (THC≥1 ng/ml)	9.4 %	3.3 %
Amphetamines (≥50ng/ml)	0.7 %	0.2 %
Cocaine (≥50 ng/ml)	0.3 %	0.1 %
Opiates (≥20 ng/ml)	0.9 %	1.2 %

Alcohol

Table 15 : OR for alcohol consumption (yes vs no) of the risk of being responsible of a fatal crash for CAR drivers over 18 years old, using French legal thresholds, France, 2001-2003, n=6932

Psychoactive substance	Crude OR	95% CI	Adjusted OR	95% CI
Alcohol (yes vs. no)	12.49	9.81-15.89	12.89	10.10-16.46

Alcohol positivity: blood alcohol concentration ≥ 0.5 g/l
adjusted on THC(yes/no), age, gender

Table 16 : OR for alcohol consumption (4 dose categories) of the risk of being responsible of a fatal crash, for CAR drivers over 18 years old, using French legal thresholds, France, 2001-2003, n=6932

Psychoactive substance	Crude OR	95% CI	Adjusted OR	95% CI
0 ≤ Alcohol < 0.5 g/l	1.00	-	1.00	-
0.5 ≤ Alcohol < 0.8 g/l	6.04	3.48-10.48	5.83	3.35-10.16
0.8 ≤ Alcohol < 1.2 g/l	6.98	4.36-11.17	6.58	4.09-10.58
1.2 ≤ Alcohol	17.38	12.62-23.93	18.36	13.30-25.35

adjusted on THC (in 4 dose categories), age, gender

Cannabis

Table 17 : OR for cannabis (THC) consumption (yes vs no) of the risk of being responsible of a fatal crash, for CAR drivers over 18 years old, using French legal thresholds, France, 2001-2003, n=6932

Psychoactive substance	Crude OR	95% CI	Adjusted OR	95% CI
THC (yes vs. no)	3.00	2.31-3.91	1.96	1.47-2.60

Cannabis positivity: THC in the blood ≥ 1 ng/ml
adjusted on alcohol (yes/no), age, gender

Table 18 : OR for cannabis intoxication (4 dose categories) of the risk of being responsible of a fatal crash, for CAR drivers over 18 years old, using French legal thresholds, France, 2001-2003, n=6932

Psychoactive substance	Crude OR	95% CI	Adjusted OR	95% CI
0 ≤ THC < 1 ng/ml	1.00	-	1.00	-
1 ≤ THC <3 ng/ml	2.26	1.57-3.26	1.51	1.04-2.29
3 ≤ THC < 5 ng/ml	4.54	2.37-8.70	2.91	1.48-5.76
5 ≤ THC	3.51	2.22-5.54	2.15	1.33-3.48

adjusted on alcohol (in 5 dose categories), age, gender

Table 19 : OR for cannabis intoxication (3 dose categories) of the risk of being responsible of a fatal crash, for CAR drivers over 18 years old, using French legal thresholds, France, 2001-2003, n=6932

Psychoactive substance	Crude OR	95% CI	Adjusted OR	95% CI
0 ≤ THC < 1 ng/ml	1.00	-	1.00	-
1 ≤ THC < 5 ng/ml	2.77	2.01-3.81	1.85	1.31-2.60
5 ≤ THC	3.51	2.22-5.53	2.15	1.33-3.48

adjusted on alcohol (in 5 dose categories), age, gender

Amphetamines

Table 20 : OR for amphetamine consumption (yes vs no) of the risk of being responsible of a fatal crash, for CAR drivers over 18 years old, using French legal thresholds, France, 2001-2003, n=6932

Psychoactive substance	Crude OR	95% CI	Adjusted OR	95% CI
Amphetamine (yes vs. no)	3.53	1.25-9.94	2.24	0.76-6.63

Amphetamine positivity: blood concentration ≥ 50 ng/ml
Adjusted on alcohol (doses), Cannabis (doses), age, gender

Cocaine

Table 21 : OR for cocaine consumption (yes vs no) of the risk of being responsible of a fatal crash, for CAR drivers over 18 years old, using French legal thresholds, France, 2001-2003, n=6932

Psychoactive substance	Crude OR	95% CI	Adjusted OR	95% CI
Cocaine (yes vs. no)	2.61	0.59-11.59	1.67	0.35-7.92

Cocaine positivity: blood concentration ≥ 50 ng/ml
adjusted on alcohol (doses), Cannabis (doses), age, gender

Opiates

Table 22 : OR for cocaine consumption (yes vs no) of the risk of being responsible of a fatal crash, for CAR drivers over 18 years old, using French legal thresholds, France, 2001-2003, n=6932

Psychoactive substance	Crude OR	95% CI	Adjusted OR	95% CI
Opiates (yes vs. no)	0.80	0.48-1.33	0.82	0.48-1.41

Opiates positivity: blood concentration ≥ 20 ng/ml
adjustement on alcohol (doses), Cannabis (doses), age, gender

Regression models with or without interaction between alcohol and cannabis

Table 23 : logistic regression model with main effects of the risk of being responsible of a fatal crash, for CAR drivers over 18 years old, using DRUID thresholds, France, 2001-2003, n=6932

Variables	Adjusted OR	95% CI
Alcohol=no	1.00	-
Alcohol=yes	8.39	6.95-10.12
THC=no	1.00	-
THC=yes	1.89	1.43-2.51
18 ≤ age ≤ 24	2.14	1.82-2.52
25 ≤ age ≤ 34	1.10	0.94-1.28
35 ≤ age ≤ 49	1.00	-
50 ≤ age	1.53	1.32-1.78
Gender=female	1.00	
Gender=male	0.90	0.79-1.03

Alcohol=yes (≥ 0.1 g/l) – THC=yes (≥1 ng/ml) ,blood dosages

According to the above model with main effects only (no interaction term), car drivers who are intoxicated with both alcohol and cannabis, have an odds ratio of 8.37*1.89=15.82 for the risk of being responsible for a fatal crash, compared to drivers who are not intoxicated to alcohol NOR cannabis.

Table 24 : logistic regression model with interaction of the risk of being responsible of a fatal crash, for CAR drivers over 18 years old, using DRUID thresholds, France, 2001-2003, n=6932

Variables	Adjusted OR	95% CI
Alcohol=no & THC=no	1.00	-
Alcohol=yes & THC=no	8.72	7.17-10.62
Alcohol=no & THC=yes	2.09	1.52-2.87
Alcohol=yes & THC=yes	**10.87**	**6.18-19.12**
18 ≤ age ≤ 24	2.14	1.82-2.52
25 ≤ age ≤ 34	1.10	0.94-1.28
35 ≤ age ≤ 49	1.00	-
50 ≤ age	1.54	1.32-1.79
Gender=female	1.00	
Gender=male	0.90	0.79-1.03

Alcohol=yes (≥ 0.1 g/l) – THC=yes (≥1 ng/ml), blood dosages