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Technical Note

Driving under the Influence of Psychotropic Substances: A Technical Interpretation

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Abstract: This technical clinical and forensic note is designed to interpret the influence that psychoactive (or psychotropic) substances may have on driving. The present interpretation is restricted to the four groups of substances (i.e., cannabinoids, cocaine and metabolites, opiates and amphetamines and derivatives) outlined in Annex V of Ordinance No. 902-B/2007 of 13 August and it is expected that can be extrapolated to other jurisdictions besides Portugal. This work is presented in a pragmatic and objective way, avoiding the clinical, physiological, pathophysiological, and toxicological aspects that would hinder understanding and impair the usefulness and applicability of its content. The evaluation of the state of influence by psychotropic substances is a complex clinical and forensic subject especially due interindividual variability and concomitant consumption of other substances that may predispose to pharmacological interactions.

Keywords: psychoactive substances; drugs; driving; influence; forensic and clinical implications

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1. Introduction

The legal framework for driving under the influence of psychoactive substances varies worldwide, but three approaches have usually been used: (i) zero-level tolerance laws—consider that road driving with any quantity of substances present in the body is illegal; (ii) laws that favor the state of influence (or homologous designations)—consider road driving illegal when the capabilities to do so are impaired by the action of psychoactive substances; and (iii) laws that favor minimum cutoff values in concentration—they consider road driving illegal when exceeding certain blood values of psychoactive substances. In Portugal, the zero-tolerance regime applies to cannabinoids, cocaine and metabolites, opiates and amphetamines and derivatives, which means that influence is not a necessary condition [1]. However, in any case, this regimen can only be applied to substances that are pharmacologically active, and the law incorporates others that are not. In other words, if it is reasonable and acceptable that the presence of a substance may imply influence, this is only potentially true for pharmacologically active substances. It is therefore justified to clarify this in detail. In other countries, such as the United Kingdom and Norway, a system that defines a critical concentration which is considered to be of influence is applied [2].

2. Methods and Applicable Legislation

This technical interpretation was based on the physiological and pathophysiological principles of medicine, pharmacology and toxicology, and was always complemented by the scientific literature of the specialty and Portuguese legislation in this subject:

(i) Decree Law No. 44/2005, of 23 February—regulates the Portuguese Road Code; (ii) Law No. 72 of 2013 of 3 September–amends the Portuguese Road Code; (iii) Law No. 18/2007 of 17 May—approves the regulation of surveillance of driving under the influence of alcohol or psychotropic substances; (iv) Ordinance No. 902-A/2007 of 13 August—approved the fees to be charged when driving under the influence of alcohol or psychotropic substances; and (v) Ordinance No. 902-B/2007 of 13 August— it sets out the requirements that quantitative analyzers must comply with, the procedures for collection, packaged and dispatched of blood for laboratory analysis, the procedures for laboratory analysis and the types of medical examinations to quantify the blood alcohol concentration (BAC) or detect the presence of psychotropic substances in blood. It is worth to be highlighted the inaccuracy, from the scientific point of view, of the title of the Law No. 18/2007 of 17 May. The inclusion of the conjugation "or" gives the idea that ethanol is not a psychotropic substance, which is not the case. Indeed, for the purposes of the Law and in comparison, to other psychotropic substances, ethanol follows a different forensic interpretation (i.e., with cutoff levels for BAC). The specific case of ethanol was not object of the present analysis.

3. Specific Aspects of Legislation

Driving under the influence of psychoactive substances is a major public health problem. For the purposes of the application of the Law on Road Surveillance under the Influence of Psychotropic Substances (Article 8 of Law No. 18/2007 of 17 May) and the provisions of Article 81 of the Portuguese Road Code, the following groups of compounds are specifically evaluated: (a) Cannabinoids; (b) Cocaine and metabolites; (c) Opiates; (d) Amphetamines and derivatives. The saliva screening test is considered positive when it reacts to one of the four groups of compounds mentioned above. Urine screening tests are carried out in public health facilities. The substances and concentrations provided in Table 2 of Annex V to Ordinance No 902-B/2007 of 13 August are taken into account, and the results are considered positive when the values obtained are equal to or greater than the cutoff concentrations indicated. Blood screening tests, carried out by the National Institute of Legal Medicine and Forensic Sciences (INMLCF, I.P.), when the previous tests are not performed, are considered positive when they show the presence of the substances present in Table 1 of Annex V (Article 17 of Ordinance No. 902-B/2007 of 13 August). However, in order to declare that psychotropic substances are present, a positive result in the confirmation blood test must reveal the presence of any of the xenobiotics provided for in Table 1 of Annex V to Ordinance No. 902-B/2007, of 13 August (Article 12 of Law No. 18/2007, 17) or any substance or product, with an analogous effect, capable of disturbing the physical, mental or psychological capacity of the person examined while driving safely (Article 8 of Law No. 18/2007, of 17 May, and Article 23 of Ordinance No. 902-B/2007 of August 13). The declaration that someone is being under the influence of psychotropic substances can also be made following a medical examination (Article 25 of Ordinance No. 902-B/2007 of 13 August).

In contrast with alcohol consumption, for which the legislation defines a certain BAC to forbid driving, positivity in the screening test for the above referred four groups of psychotropic substances does not automatically mean that we are in the presence of a very serious offence and as such does not automatically imply inhibition of driving for the expected legal period (2 to 24 months, Article 146(*m)* and Article 137(2) of the Portuguese Road Code). However, drivers, if the screening test is positive, are prevented from driving for a period of 48 h, unless, before that period, they have a negative result in a new screening test (the 157th of the Portuguese Road Code). Another difference between the penalty for alcohol consumption and that of other substances is the absence of a concentration cutoff limit for which psychotropic substances affect the capacities for driving. In other words, the law applies a zero-tolerance regime; that is, the positivity/presence of one of the four groups of psychoactive substances is a sufficient condition for the individual to be considered under the influence. Although this is legitimate and acceptable for illicit substances, the consumption of which is prohibited by Law No. 30/2000 of 20 November (which defines the

legal regimen applicable to the consumption of narcotic drugs and psychotropic substances, as well as the health and social protection of persons who consume such substances without a medical prescription), the truth is that this pragmatism of the Law contains limitations because the state of influence that is intended to be evaluated depends on several factors, which transcend this technical note.

4. Specific Interpretations

Although urine is an excellent sample for toxicological screening, there is no correlation between urinary concentrations found and the level of influence [3,4]. In other words, the presence of xenobiotics or their metabolites in urine indicates only previous exposure/consumption. Therefore, the concentrations presented for urine in Table 2 of Annex V of Ordinance No. 902-B/2007 on 13 August are in no way related to level of influence. Only a positive qualitative analysis for these xenobiotics in the blood can be related to sensory changes, since the blood is in close contact with the central nervous system (CNS). However, it is also important to note that there is no well-established correlation between the concentration of psychoactive substances in the blood and changes in performance.

Regardless, in several other jurisdictions, blood concentrations of certain substances have been used to assess the level of influence, but the interindividual variability is so great that they only represent approximations of function. It should also be noted that the positivity/presence of some of the substances referred to in Table 1 of Annex V to Ordinance No. 902-B/2007 of 13 August does not automatically means illicit consumption, since some of these are used in therapy and, as such, may be under medical prescription, such as morphine and, more recently, medicinal cannabis [5]. In the following highlights, a pragmatic interpretation regarding major psychoactive groups is presented to better serve the purpose of the technical note and its scientific application.

4.1. The Cannabinoids

Cannabinoids are the most prevalent illicit substances among influenced drivers, and their effect is dose-dependent [6]. In particular, cannabinoids increase the risk of accidents, cause drowsiness, euphoria or dysphoria, changes in memory, perception, stability, decision-making capacity, reasoning and reaction time, synesthesia, disorganized thoughts, confusion, paranoia, agitation, among other effects on the central nervous system [7]. The following are major technical aspects to be considered:

- The law defines Δ^9-tetrahydrocannabinol (Δ^9-THC) and its metabolites 11-hydroxy-Δ^9-tetrahydrocannabinol (THC-OH) and 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (THC-COOH) as illicit substances.
- While Δ^9-THC and THC-OH are pharmacologically active (i.e., they can influence cognitive abilities for road driving), THC-COOH is not, and as such, does not influence function.
- THC-COOH has a long half-life ($t_{1/2}$) and a large detection window, far beyond the manifestation of acute effects [8].
- In fact, in occasional cannabis smokers, THC-COOH was found up to 7 days after the last use [9].
- Therefore, THC-COOH is the compound within this group that is most often detected.
- Nevertheless, although it can be detected, its presence should not be used for the assessment of the state of influence, because it has no affinity for the cannabinoid receptor and therefore has no recognized psychoactive effect [10].
- In other words, it may be said that an in-control has concentrations of 18 ng/mL THC-COOH or 18 ng/mL Δ^9-THC in blood.
- However, it should be clarified that the THC-COOH positivity, undoubtedly means that a driver consumed Δ^9-THC.
- Tolerance to Δ^9-THC can be developed, meaning that for equal concentrations of Δ^9-THC, regular consumers may be less influenced than occasional consumers [11].
- Influence may occur 1 h after smoking or within 1 to 2 h after oral administration [12,13].

- Some studies have proposed interpretations based on blood concentrations that are listed below because the state of influence is largely dependent on biological concentrations [14].
- In occasional consumers and in the case of recent consumption, Δ^9-THC concentrations of 2–5 ng/mL are usually associated with states of influence [15].
- Concentrations greater than 5 ng/mL are equivalent to an accident risk approximately equal to the alcohol rate of 1.5 g/L [16].
- Concentrations of 7–10 ng/mL Δ^9-THC in serum (3.5–5 ng/mL in whole blood) cause a state of influence similar to BAC of 0.5 g/L [17].
- The state of influence increases 2.4, 2.5 and 3.2 for concentrations of Δ^9-THC in the blood of 3.0–4.8, 4.9–10.1 and >10.2 ng/mL, respectively [11].
- Values below 2 ng/mL indicate no influence [14].
- For concentrations greater than 2 ng/mL, performance impairment was seen for some, but not all, driving-related tasks [14].
- For concentrations of 2–5 ng/mL Δ^9-THC, 71% of influenced individuals; for 5–10 ng/mL, 75–90% of individuals are influenced, and for concentrations greater than 30 ng/mL, 100% are influenced [14].
- In some countries, such as the United Kingdom, limits of 2 µg/L for Δ^9-THC have been set so as not to accidentally penalize drivers exposed to passive consumption and due to the inherent analytical difficulties associated with enforcing a 0.0000 µg/L limit.

4.2. Cocaine and Metabolites

Among the effects of cocaine that may influence driving, the following stand out: mydriasis, convulsions, tachycardia, euphoria, increased self-confidence, anxiety, increased reaction capacity followed by a marked reduction of this cognitive capacity, hallucinations and sudden death [18]. The following are major technical aspects to be considered:

- Cocaine use is associated with an average of 2 to 10 times higher risk of serious injury or fatality in road accidents, according to the findings of the Project Driving Under the Influence of Drugs, Alcohol and Medicines (DRUID) [19].
- This risk is similar to driving with a BAC between 0.5 g/L and 0.8 g/L [20].
- Cocaine is mainly metabolized by 2 pathways: major benzoylecgonine and ecgonin methyl ester metabolites and several other minor metabolites.
- For the purposes of Law No. 18/2007 of 17 May, only cocaine and its main metabolite, benzoylecgonine, which comes from spontaneous hydrolysis or the action of human carboxylesterase 1, were analyzed [21].
- Since benzoylecgonine is inactive this is a method of detoxification and lacks psychoactive activity [22]. Thus, if this compound is found (and with negative cocaine) it does not mean that the individual is under the influence of this psychoactive substance.
- However, it should be clarified that benzoylecgonine positivity undoubtedly means that the driver is a consumer of illicit substances, specifically cocaine.
- Reported concentrations of cocaine in the blood range from 0.076 to 0.109 mg/L [23,24].
- Benzoylecgonine is more likely to be found in the blood than cocaine because it has a higher $t_{1/2}$ (i.e., 4–7 h versus 0.5–1 h of cocaine), depending on whether the consumer is a naïve or chronic user [21,25,26].
- In other words, while cocaine may be absent from a blood sample after 4 to 6 h, benzoylecgonine may be present for up to 6 days after cocaine administration, especially in chronic users.
- In some countries, such as the United Kingdom, limits of 50 µg/L benzoylecgonine and 10 µg/L cocaine have been defined so as not to penalize accidentally exposed drivers, because of passive consumption.

4.3. Opiates

Among the effects that may alter driving by opiates, the following stand out: drowsiness, increased reaction time, confusion, agitation, fear, hallucinations, lack of motor coordination, mood alteration, myosis, tremor and convulsions [27–29]. The following are major technical aspects to be considered:

- The law defines the presence of a subset of opiates, morphine and 6-acetylmorphine as illicit compounds [30]. In other words, morphine and 6-acetylmorphine are surveilled [31–34].
- Consideration should be given to the fact that many pharmaceutical formulations (e.g., used as analgesics and antitussives) have codeine and morphine, and therefore may produce a positive opiate but not due to illicit consumption. Despite being an omitted legislation, in these cases, the licit consumption can be easily attested by a medical prescription.
- For example, codeine undergoes *O*-demethylation, catalyzed by CYP2D6 and 2D7, resulting in morphine. Thus, morphine is present when patients are administering codeine [31]. It is even plausible that morphine has been administered *per se*, especially in hospital for the for severe pain in cases of extensive traumatic injuries.
- In this case, it is necessary, when possible, that the collection of biological samples be made before starting therapeutic measures.
- The presence of 6-acetylmorphine (6-AM) is evidence of recent heroin use, since it results from hydrolysis of heroin catalyzed by human carboxyesterase-1 and 2 in the liver and brain and plasma butyrylcholinesterase [31].
- Both heroin and 6-acetylmorphine reduce $t_{1/2}$ by 1–2 min and 10–25 min, respectively [35–40].
- This means that the metabolite is no longer relevant for documenting heroin use because it is not found after 8–10 h in urine and 0.5 to 2 h in the blood [35–40].
- The very reduced $t_{1/2}$ of heroin means it cannot be used for analysis to document its consumption.
- For morphine, its $t_{1/2}$ of approximately 1 to 3 h extends its blood window of detection to 10 to 15 h after ingestion [41].
- In some countries, such as the United Kingdom, even applying a zero-tolerance regime, the limit of 5 μg/L for 6-acetylmorphine is used so as not to penalize accidentally exposed drivers, because of passive consumption or high values of 80 μg/L for morphine because of its large therapeutic application [42].

4.4. Amphetamines and Derivatives

Among the effects that may alter driving after the administration of amphetamines and derivatives the following stand out: mydriasis, irritability, convulsions, insomnia, euphoria, impulsivity, confusion, psychoses, and aggressive behavior [43,44]. The following are major technical aspects to be considered:

- The interpretation for this group is more obvious, since the compounds considered in Law No. 18/2007 of 17 May are all pharmacologically active.
- Nevertheless, it is important to highlight the fact that methamphetamine is metabolized to amphetamine and 3,4-methylenedioxymetamphetamine (i.e., MDMA or ecstasy) and 3,4-methylenedioxyethylamphetamine (MDEA or MDE) are metabolized into 3,4-methylenedioxyamphetamine (MDA) [45], which is more potent than the former [46].
- Therefore, the assessment of these compounds may give rise to erroneous presumptions regarding the type of substance that was consumed.
- 1,3-benzodioxolil-N-methylbutanamine (i.e., 3,4-methylenedioxy-N-methyl-α-ethylphenylethylamine; MBDB) has little or no expression (including compared to other substances not included in the law) and is metabolized to its active metabolite 1-(3,4-methylenedioxyphenyl)-2-butanamine (BDB) [47].

- Blood-cut-off concentrations, ranging from 20 to 600 ng/mL for amphetamine, from 20 to 200 ng/mL for methamphetamine and from 20 to 300 ng/mL for MDMA have been proposed [48,49].
- In some countries, such as the United Kingdom, even applying a zero-tolerance regime, a limit of 250 µg/L for amphetamine has been established by recognizing its therapeutic applications (e.g., attention deficit hyperactivity disorder and narcolepsy). Despite the potential therapeutic application, it should be highlighted that it does not mean they are safe in terms of driving. For methamphetamine and 3,4-methylenedioxyamfetamine, minimum limits of 10 µg/L were set so as not to be penalized due to accidental exposure.

5. About the Inclusion of Other Compounds

The problem with the inclusion of other substances, in addition to the abovementioned illicit substances, arises because there is disagreement among experts, lawyers and judges, regarding whether these substances are legal [50]. It should be noted that although the law includes other substances, screening tests are performed to analyze only the substances in the four groups referred to above. More surprising is the fact (justifying reflection) that when screening indicates the presence of other compounds, such as benzodiazepines, this does not require further confirmatory analysis, because it is erroneously considered that these substances are not prohibited when driving. Indeed, it is important to highlight that in addition to the four groups of substances described above, the law also considers that individuals may be declared influenced by psychotropic substances or products, with similar effects capable of disturbing the physical, mental or psychological capacity of the examinee when operating a motor vehicle driving safely, are present in the blood (Article 8 of Law No. 18/2007, 17 May, and Article 23 of Ordinance No. 902-B/2007 of August. However, this does not invalidate a blood test ordered by the court if blood was previously obtained (e.g., for the purpose of supervising alcohol or the four groups of psychotropic substances described above) and stored in the forensic toxicology services of INMLCF, I.P. This analysis can be carried out to exclude the presence of other illicit psychoactive substances (e.g., lysergic acid diethylamide (LSD)) and several other licit substances. Indeed, there are many possibilities for substances (many of them drugs/medicines) that, alone or in combination, may influence cognitive abilities when driving a motor vehicle, such as opioid analgesics, antitussives, anxiolytics, sedatives and hypnotics, antidepressants, antipsychotics, central stimulants, antiepileptics, antihistamines H_1, antiarrhythmics, eye drops, anti-parkinsonian and antimigraine drugs, psychedelics, and dissociative anesthetics, among others. The review of these references [50,51] aims to summarize several of the other psychoactive substances that may influence driving due to the effects they have on the central nervous system. In some countries, such as the United Kingdom and Norway, limits have been set for some drugs and are adjusted to relatively high levels to avoid the noncompliance with prescribed therapy [52]. The individualized interpretation of each of the substances provided for in Article 12 of Law No. 18/2007 of 17 December 2007 was not the objective of this technical note.

6. Conclusions

The evaluation of states of influence by psychotropic substances is a complex clinical and forensic subject. The present Portuguese legislation has some limitations and adjustments are needed when addressing, for example, the detection of inactive substances such as THC-COOH, for the evaluation of states of influence. The success of this will always be much greater if the collection of the blood samples is rapid, if information is available regarding the time interval between surveillance and collection [3] and if more studies aimed at clarifying blood concentrations most related to states of influence are available. Indeed, it was demonstrated a significant decrease of Δ^9-THC concentrations in samples that were taken more than 2 h after the incident [52]. The minimum concentrations reported in the literature as cut-off values when determining that an individual is effectively under

a state of influence do not take into account the phenomenon of tolerance/desensitization, concomitant consumption of other substances and possible interactions, and the genetic polymorphisms in metabolism and pharmacodynamic targets, among other factors. The zero-tolerance regime is at this stage the fairest and least susceptible to error, considering the knowledge we have. This does not invalidate that for some substances with more robust scientific data, cut-off concentration values can be established, some of which were discussed above.

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References

1. Dinis-Oliveira, R.J.; Nunes, R.; Carvalho, F.; Santos, A.; Teixeira, H.; Vieira, D.N.; Magalhães, T. Ethical, technical and legal procedures of the medical doctor responsibility to accomplish the road enforcement law about driving under the influence of alcohol and psychotropic substances. *Acta Med. Port.* **2010**, *23*, 1059–1082. [PubMed]
2. Fierro, I.; Colás, M.; González-Luque, J.C.; Álvarez, F.J. Roadside opioid testing of drivers using oral fluid: The case of a country with a zero tolerance law, Spain. *Subst. Abuse Treat. Prev. Policy* **2017**, *12*, 22. [CrossRef] [PubMed]
3. Dinis-Oliveira, R.J.; Vieira, D.N.; Magalhães, T. Guidelines for Collection of Biological Samples for Clinical and Forensic Toxicological Analysis. *Forensic Sci. Res.* **2016**, *1*, 42–51. [CrossRef] [PubMed]
4. Dinis-Oliveira, R.J.; Carvalho, F.; Duarte, J.A.; Remião, F.; Marques, A.; Santos, A.; Magalhães, T. Collection of biological samples in forensic toxicology. *Toxicol. Mech. Methods* **2010**, *20*, 363–414. [CrossRef]
5. Dinis-Oliveira, R.J. The Clinical Toxicology Perspective on the Therapeutic Use of Cannabis and Cannabinoids. *Acta Med. Port.* **2019**, *32*, 87–90. [CrossRef]
6. Ramaekers, J.G.; Kauert, G.; van Ruitenbeek, P.; Theunissen, E.L.; Schneider, E.; Moeller, M.R. High-Potency Marijuana Impairs Executive Function and Inhibitory Motor Control. *Neuropsychopharmacology* **2006**, *31*, 2296–2303. [CrossRef] [PubMed]
7. Lenné, M.G.; Dietze, P.M.; Triggs, T.J.; Walmsley, S.; Murphy, B.; Redman, J.R. The effects of cannabis and alcohol on simulated arterial driving: Influences of driving experience and task demand. *Accid. Anal. Prev.* **2010**, *42*, 859–866. [CrossRef]
8. Grotenhermen, F. Pharmacokinetics and Pharmacodynamics of Cannabinoids. *Clin. Pharmacokinet.* **2003**, *42*, 327–360. [CrossRef]
9. Huestis, M.A.; Henningfield, J.E.; Cone, E.J. Blood Cannabinoids. I. Absorption of THC and Formation of 11-OH-THC and THCCOOH During and After Smoking Marijuana. *J. Anal. Toxicol.* **1992**, *16*, 276–282. [CrossRef]
10. Dinis-Oliveira, R.J. Metabolomics of Δ9-tetrahydrocannabinol: Implications in toxicity. *Drug Metab. Rev.* **2016**, *48*, 80–87. [CrossRef]
11. Khiabani, H.Z.; Bramness, J.G.; BjøRneboe, A.; MøRland, J. Relationship between THC Concentration in Blood and Impairment in Apprehended Drivers. *Traffic Inj. Prev.* **2006**, *7*, 111–116. [CrossRef] [PubMed]
12. Ramaekers, J.; Berghaus, G.; van Laar, M.; Drummer, O. Dose related risk of motor vehicle crashes after cannabis use. *Drug Alcohol Depend.* **2004**, *73*, 109–119. [CrossRef] [PubMed]
13. Cone, E.J.; Huestis, M.A. Relating Blood Concentrations of Tetrahydrocannabinol and Metabolites to Pharmacologic Effects and Time of Marijuana Usage. *Ther. Drug Monit.* **1993**, *15*, 527–532. [CrossRef]
14. Ramaekers, J.; Moeller, M.; Van Ruitenbeek, P.; Theunissen, E.; Schneider, E.; Kauert, G. Cognition and motor control as a function of Δ9-THC concentration in serum and oral fluid: Limits of impairment. *Drug Alcohol Depend.* **2006**, *85*, 114–122. [CrossRef] [PubMed]
15. Hartman, R.L.; Huestis, M.A. Cannabis Effects on Driving Skills. *Clin. Chem.* **2013**, *59*, 478–492. [CrossRef]
16. Drummer, O.H.; Gerostamoulos, J.; Batziris, H.; Chu, M.; Caplehorn, J.; Robertson, M.D.; Swann, P. The involvement of drugs in drivers of motor vehicles killed in Australian road traffic crashes. *Accid. Anal. Prev.* **2003**, *36*, 239–248. [CrossRef]
17. Grotenhermen, F.; Leson, G.; Berghaus, G.; Drummer, O.; Krüger, H.-P.; Longo, M.; Moskowitz, H.; Perrine, B.; Ramaekers, J.G.; Smiley, A.; et al. Developing limits for driving under cannabis. *Addiction* **2007**, *102*, 1910–1917. [CrossRef]
18. Macdonald, S.; Anglin-Bodrug, K.; Mann, R.E.; Erickson, P.; Hathaway, A.; Chipman, M.; Rylett, M. Injury risk associated with cannabis and cocaine use. *Drug Alcohol Depend.* **2003**, *72*, 99–115. [CrossRef]

19. Herrera-Gómez, F.; Gutiérrez-Abejón, E.; García-Mingo, M.; Álvarez, F. Positivity to Cocaine and/or Benzoylecgonine in Confirmation Analyses for On-Road Tests in Spain. *Int. J. Environ. Res. Public Health* **2021**, *18*, 5371. [CrossRef]
20. Elvik, R. Risk of road accident associated with the use of drugs: A systematic review and meta-analysis of evidence from epidemiological studies. *Accid. Anal. Prev.* **2013**, *60*, 254–267. [CrossRef]
21. Dinis-Oliveira, R.J. Metabolomics of cocaine: Implications in toxicity. *Toxicol. Mech. Methods* **2015**, *25*, 494–500.
22. Jufer, R.A.; Walsh, S.L.; Cone, E.J. Cocaine and metabolite concentrations in plasma during repeated oral administration: Development of a human laboratory model of chronic cocaine use. *J. Anal. Toxicol.* **1998**, *22*, 435–444. [CrossRef] [PubMed]
23. Jones, A.; Holmgren, A.; Kugelberg, F. Concentrations of cocaine and its major metabolite benzoylecgonine in blood samples from apprehended drivers in Sweden. *Forensic Sci. Int.* **2008**, *177*, 133–139. [CrossRef] [PubMed]
24. Augsburger, M.; Donzé, N.; Ménétrey, A.; Brossard, C.; Sporkert, F.; Giroud, C.; Mangin, P. Concentration of drugs in blood of suspected impaired drivers. *Forensic Sci. Int.* **2005**, *153*, 11–15. [CrossRef] [PubMed]
25. Ambre, J.; Ruo, T.I.; Nelson, J.; Belknap, S. Urinary Excretion of Cocaine, Benzoylecgonine, and Ecgonine Methyl Ester in Humans. *J. Anal. Toxicol.* **1988**, *12*, 301–306. [CrossRef]
26. Moolchan, E.T.; Cone, E.J.; Wstadik, A.; Huestis, M.A.; Preston, K.L. Cocaine and metabolite elimination patterns in chronic cocaine users during cessation: Plasma and saliva analysis. *J. Anal. Toxicol.* **2000**, *24*, 458–466. [CrossRef]
27. Pergolizzi, J.J.V.; Taylor, J.R.; Bisney, M.J.; LeQuang, B.J.A.; Raffa, R.B.; Pergolizzi, J.F.; Colucci, D.; Batastini, J.L. Driving under the influence of opioids: What prescribers should know. *J. Opioid Manag.* **2018**, *14*, 415–427. [CrossRef]
28. Nagpal, A.; Xu, R.; Pangarkar, S.; Dworkin, I.; Singh, J.R. Driving Under the Influence of Opioids. *PM&R* **2016**, *8*, 698–705. [CrossRef]
29. Cameron-Burr, K.T.; Conicella, A.; Neavyn, M.J.; Cameron-Burr, K.T.; Conicella, A.; Neavyn, M.J. Opioid Use and Driving Performance. *J. Med. Toxicol.* **2021**, *17*, 289–308. [CrossRef]
30. Freye, E.; Levy, J.V. (Eds.) *Opioids in Medicine: A Comprehensive Review on the Mode of Action and the Use of Analgesics in Different Clinical Pain States*; Springer: Dordrecht, The Netherlands, 2008.
31. Dinis-Oliveira, R.J. Metabolism and metabolomics of opiates: A long way of forensic implications to unravel. *J. Forensic Leg. Med.* **2018**, *61*, 128–140. [CrossRef]
32. Dinis-Oliveira, R.J.; Carvalho, F.; Moreira, R.F.; Duarte, J.A.; Proença, J.; Santos, A.; Magalhães, T. Clinical and Forensic Signs Related to Opioids Abuse. *Curr. Drug Abuse Rev.* **2012**, *5*, 273–290. [CrossRef] [PubMed]
33. Krenn, L.; Glantschnig, S.; Sorgner, U. Determination of the five major opium alkaloids by reversed-phase high-performance liquid chromatography on a base-deactivated stationary phase. *Chromatographia* **1998**, *47*, 21–24. [CrossRef]
34. Frick, S.; Kramell, R.; Schmidt, J.; Fist, A.A.J.; Kutchan, T.M. Comparative Qualitative and Quantitative Determination of Alkaloids in Narcotic and Condiment Papaver somniferum Cultivars. *J. Nat. Prod.* **2005**, *68*, 666–673. [CrossRef] [PubMed]
35. Bogusz, M.J.; Maier, R.-D.; Driessen, S. Morphine, Morphine-3-Glucuronide, Morphine-6-Glucuronide, and 6-Monoacetylmorphine Determined by Means of Atmospheric Pressure Chemical Ionization-Mass Spectrometry-Liquid Chromatography in Body Fluids of Heroin Victims. *J. Anal. Toxicol.* **1997**, *21*, 346–355. [CrossRef]
36. Bogusz, M.J.; Maier, R.-D.; Erkens, M.; Driessen, S. Determination of morphine and its 3- and 6-glucuronides, codeine, codeine-glucuronide and 6-monoacetylmorphine in body fluids by liquid chromatography atmospheric pressure chemical ionization mass spectrometry. *J. Chromatogr. B Biomed. Sci. Appl.* **1997**, *703*, 115–127. [CrossRef]
37. Fehn, J.; Megges, G. Detection of O6-Monoacetylmorphine in Urine Samples by GC/MS as Evidence for Heroin Use. *J. Anal. Toxicol.* **1985**, *9*, 134–138. [CrossRef]
38. Cone, E.J.; Welch, P.; Mitchell, J.M.; Paul, B.D. Forensic Drug Testing for Opiates: I. Detection of 6-Acetylmorphine in Urine as an Indicator of Recent Heroin Exposure; Drug and Assay Considerations and Detection Times. *J. Anal. Toxicol.* **1991**, *15*, 1–7. [CrossRef]
39. Cone, E.J.; Welch, P.; Paul, B.D.; Mitchell, J.M. Forensic Drug Testing for Opiates, III. Urinary Excretion Rates of Morphine and Codeine Following Codeine Administration. *J. Anal. Toxicol.* **1991**, *15*, 161–166. [CrossRef]
40. Mitchell, J.M.; Paul, B.D.; Welch, P.; Cone, E.J. Forensic Drug Testing for Opiates. II. Metabolism and Excretion Rate of Morphine In Humans After Morphine Administration. *J. Anal. Toxicol.* **1991**, *15*, 49–53. [CrossRef]
41. Goldberger, B.A.; Darwin, W.D.; Grant, T.M.; Allen, A.C.; Caplan, Y.H.; Cone, E.J. Measurement of heroin and its metabolites by isotope-dilution electron-impact mass spectrometry. *Clin. Chem.* **1993**, *39*, 670–675. [CrossRef]
42. Rooney, B.; Gouveia, G.J.; Isles, N.; Lawrence, L.; Brodie, T.; Grahovac, Z.; Chamberlain, M.; Trotter, G. Drugged Drivers Blood Concentrations in England and Wales Prior to the Introduction ofPer SeLimits. *J. Anal. Toxicol.* **2016**, *41*, 140–145. [CrossRef] [PubMed]
43. Musshoff, F.; Madea, B. Driving Under the Influence of Amphetamine-Like Drugs. *J. Forensic Sci.* **2012**, *57*, 413–419. [CrossRef] [PubMed]
44. Kuypers, K.P.C.; Bosker, W.M.; Ramaekers, J.G. Ecstasy, driving and traffic safety. In *Drugs, Driving and Traffic Safety*; Verster, J.C., Pandi-Perumal, S.R., Ramaekers, J.G., de Gier, J.J., Eds.; Birkhäuser: Basel, Switzerland, 2009; pp. 501–518. [CrossRef]
45. Meyer, M.R.; Peters, F.T.; Maurer, H.H. The Role of Human Hepatic Cytochrome P450 Isozymes in the Metabolism of Racemic 3,4-Methylenedioxyethylamphetamine and Its Single Enantiomers. *Drug Metab. Dispos.* **2009**, *37*, 1152–1156. [CrossRef]
46. Hegadoren, K.; Baker, G.; Bourin, M. 3,4-Methylenedioxy analogues of amphetamine: Defining the risks to humans. *Neurosci. Biobehav. Rev.* **1999**, *23*, 539–553. [CrossRef]

47. Meyer, M.R.; Peters, F.T.; Maurer, H.H. Stereoselective differences in the cytochrome P450-dependent dealkylation and demethylenation of N-methyl-benzodioxolyl-butanamine (MBDB, Eden) enantiomers. *Biochem. Pharmacol.* **2009**, *77*, 1725–1734. [CrossRef]
48. Busardò, F.P.; Pichini, S.; Pacifici, R. Driving Under the Influence of Drugs: Looking for Reasonable Blood Cutoffs and Realistic Analytical Values. *Clin. Chem.* **2017**, *63*, 781–783. [CrossRef]
49. Busardo, F.P.; Pichini, S.; Pellegrini, M.; Montana, A.; Faro, A.F.F.L.; Zaami, S.; Graziano, S. Correlation between Blood and Oral Fluid Psychoactive Drug Concentrations and Cognitive Impairment in Driving under the Influence of Drugs. *Curr. Neuropharmacol.* **2017**, *16*, 84–96. [CrossRef]
50. Dinis-Oliveira, R.J. Licit and ilicit uses of medicines. *Acta Med. Port.* **2014**, *27*, 755–766. [CrossRef]
51. Dinis-Oliveira, R.J. The Genesis of a New Open-Access Journal Focused on the Latest Scientific Advances in Psychoactive Substances. *Psychoactives* **2022**, *1*, 1–6. [CrossRef]
52. Urfer, S.; Morton, J.; Beall, V.; Feldmann, J.; Gunesch, J. Analysis of Δ9-tetrahydrocannabinol Driving Under the Influence of Drugs Cases in Colorado from January 2011 to February 2014. *J. Anal. Toxicol.* **2014**, *38*, 575–581. [CrossRef]