DRIVING UNDER THE INFLUENCE OF DRUGS

Report from the Expert Panel on Drug Driving

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INTRODUCTION

The main challenge in establishing recommendations for driving under the influence of psychoactive drugs is the need to provide an easily-understood and justifiable scientific rationale for particular drugs being covered by the offence of drug-driving, whilst recognising that the evidence base is dynamic and will develop as our knowledge and understanding increases. The Panel aimed to establish whether there was sufficient evidence in the scientific literature to be able to determine a relationship between the use of psychoactive drugs and an effect on driving performance in average members of the general public.

INTRODUCTION (le surlignage indique les chapitres du texte anglais)

Le principal défi pour établir des recommandations concernant la conduite sous l'influence de médicaments psychoactifs est la nécessité de fournir une base rationnelle scientifique facilement compréhensible et justifiable sur les produits particuliers concernés par l'infraction de conduite sous emprise, tout en reconnaissant que cette base est dynamique et se développera au fur et à mesure que notre savoir et notre compréhension du problème augmentera. Le Panel visait à déterminer s'il y avait suffisamment de preuve dans la littérature scientifique pour pouvoir déterminer une relation entre l'utilisation de médicaments psychoactifs et un effet sur la performance de conduite chez les membres « ordinaires » de la population.

2. METHODOLOGY

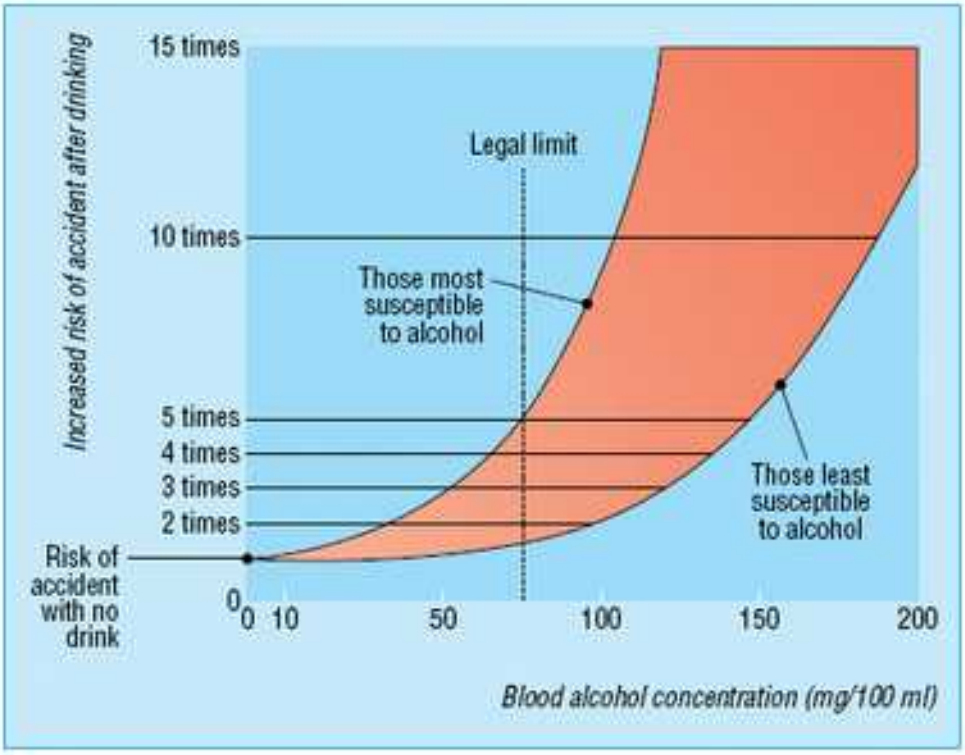
Estimating Traffic Risk
Epidemiological Evidence
Experimental studies: Meta-analysis
Reference values
Contextualisation for the British driving population
Drugs where road safety risk is apparent but data is limited
Pharmacokinetic and Pharmacodynamic considerations
Medicines
Long term prescribing (chronic dosing)
Drug manufacturers: categorisation of labelling on medicines and driving
International approaches to setting concentration thresholds for drug driving
Groups and individuals who were consulted by the Panel or who provided their opinion

Summary of Procedure for determining drug thresholds for the Panel's Recommendations

3. INITIAL FINDINGS

EPIDEMIOLOGICAL OVERVIEW

Alcohol (dans la courbe ci dessous 50= 0,5 g/l)



Effect of alcohol on behaviour

Polydrug Use

Table 3.2: DRUID risk estimates for a driver being seriously injured or killed in an accident when testing positive for a combination of drugs or a combination of drugs and alcohol.

Populations compared	Odds ratio (OR) and 95% confidence interval (CI)	Reference
Multiple drug use compared with no drug use	OR: 6.05 (95% CI: 2.60-14)	Movig et al, 2004
Drugs + alcohol compared with no drugs	OR: 112 (95% CI: 14-893)	Movig et al, 2004

Pour l'usage simultané de plusieurs produits l'OR d'être tué ou sérieusement blessé (Odds Ratio en principe proche du Risque Relatif) est de 6 soit un risque de 600 % du risque sans produits, mais en association avec l'alcool ce risque devient 11 200 % !!!!

Illicit drugs

Medicines

EPIDEMIOLOGICAL OVERVIEW: GREAT BRITAIN

Alcohol in the context of drug-driving

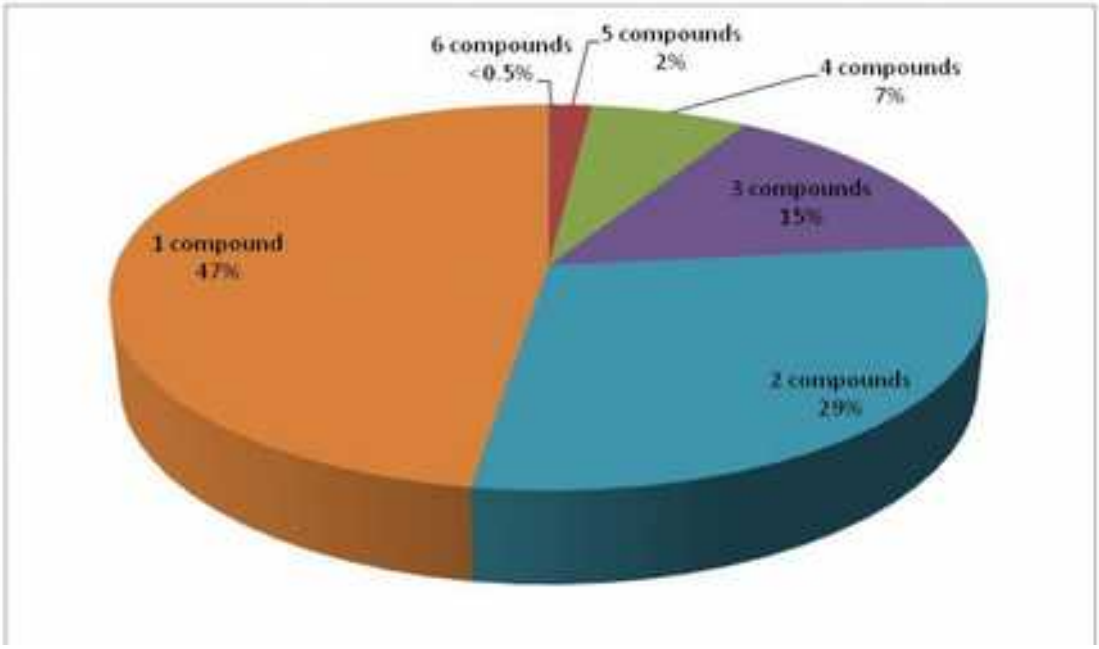
Le Panel recommande que la taux d'alcoolémie seuil, qui est de 0,8 g/l en GB soit abaissé à 0,20 en cas de prise associée d'autres psychoactifs

Illicit drug use

Prevalence of Drug Use in British Drivers

Driver fatalities aged 16 or over (Stats19)			**1,037**	-
Driver fatalities with drug data available (Stats19 matched with L407)			231	100%
Fatalities with the following drug group present	**Any illicit drug of abuse:**		**46**	**20%**
		Amphetamines, hallucinogenic amphetamines	3	1%
		Cannabinoids	26	11%
		Cocaine	10	4%
		Opiates, opioids, narcotic analgesics	15	6%
	New psychoactive substances		**1**	**0%**
		Methcathinone	1	0%
	Therapeutic drugs		**72**	**31%**
		Anti-depressants and mood stabilisers	20	9%
		Benzodiazepines, non-benzodiazepines	12	5%
		Other therapeutic drugs	60	26%

Figure 3.3: Percentage of drug positive samples containing single drugs and multiple drug combinations. Data from samples taken between January 2008 and October 2012 in cases of RTA or witnessed impairment



Pourcentages selon le nombre de psychotropes associés sur des prélévements faits sur des conducteurs impliqués dans un accident (de 1 à 6)

Table 3.5: Drivers' self-reported drug use as part of the DVLAs HRO scheme

Drug Type	No drugs	Cannabis	Heroin	Cocaine	Others
Weekly total	299	91	15	17	9

Déclarations de consommation par le conducteur lui même

Le tableau (page suivante) montre les taux sanguins associés à un risque au cours de la conduite selon une étude néérlandaise

Table 3.6: Active concentrations (micrograms/L, µg/L) of the most common drugs found in plasma (or serum) and blood which are known to be a hazard when driving 21 (Netherlands Advisory Committee, 2010)

Substance	Expected concentration in plasma after taking an active dose[a] (µg/L)	Blood/serum ratio[b]	Estimated concentration in blood after taking an active dose[c] (µg/L)	Median in blood NFI 1999-2008(µg/L)
Amfetamine	50-150	0.6-1.0	50-150	230
MDMA	100-350	1.2	100-400	320
MDEA	approx. 200		100-400	50
MDA	approx. 400	1.2	100-400	30[f]
THC	2-10	0.55	1-5[e]	5.8
Cocaine	50-300	1.0	50-300	60
Morphine	10-120	1.0	10-120	40
Codeine	50-250	0.87	40-250	20
GHB	[d]		> 20 mg/L	95 mg/L

21
Netherlands Advisory Committee report, 2010.

a Derived from The International Association of Forensic Toxicologists (TIAFT) supplemented by data from other scientific sources where the TIAFT list was incomplete.

b Blood/serum ratio: of the concentration in blood to the concentration in serum. Concentrations in serum are generally the same as concentrations in plasma.

c Concentrations in full blood calculated from concentrations in serum by multiplying by the blood/serum ratio.

d The literature refers to figures of 50-120 mg GHB per litre of serum during mechanical respiration.

e Grotenhermen et al. (2007) 18 put forward a limit for reduced ability to drive of 7 to 10 micrograms of THC per litre of serum (this is 3 to 5 micrograms of THC per litre of blood) which would be comparable with the limit of 0.5 grams of alcohol per litre of blood (0.5 per cent). This limit applies to occasional cannabis use and not where use is daily.

f MDA is also formed in the body through the conversion of MDMA.

Biological fluid for determining thresholds for drug driving (sang, urine, salive)
Consideration of sampling time (le moment du prélévement)

4. DRUG SPECIFIC FINDINGS: CANNABIS

Background
Epidemiological prevalence
Cannabis and driving

quelques seuils existants

Table 4.1: International drug thresholds (set in or recommended for legislation): THC[28]

Country	Approach to threshold	THC threshold in blood	Reference
Sweden	Zero tolerance	0.3 µg/L	Jones et al, 2008
Switzerland	Threshold for prosecution	1.5 µg/L	
Norway	Impairment limit	1.3 µg/L	Norwegian Institute for Public Health,
	Comparable to 0.5g/L BAC Comparable to 1.2g/L BAC	3.0 µg/L 9.0 µg/L	2012
Belgium	Analytical cut-off	1.0 µg/L	Nickel &de Gier, 2009
Portugal	Analytical cut-off	3.0 µg/L	

Patterns of use

- 5 mg to 30 mg active drug (THC) per reefer (Moffat et al, 2004)
- 10 mg to 20 mg THC intake of smoke from a pipe or joint (a hit).

Pharmacokinetics (PK) and blood drug concentrations

In heavy long term users (daily or near daily use over a number of years) variable rates of release of THC from tissue stores during abstinence have been reported. A mean THC blood concentration after 24 hours abstinence was found to be 0.7 µg/L (SD 1.4 µg/L) and after 7 days abstinence 0.3 µg/L (SD 0.7 µg/L) (Karschner, Eugene& Schwilke, 2011), whereas in regular/frequent users blood concentrations of THC were detected between 1 µg/L and 6.4 µg/L. Smoking a single cannabis cigarette (infrequent user) leads to higher concentrations of THC in the body, ranging from 3 µg/L – 12 µg/L, and maximal THC blood concentrations after oral consumption were found to be in the range of 4.4µg/L to 11.0 µg/L following a single 20 mg dose (Ohlsson, Lindgren& Wahlen, 1980; Karschner, Eugene& Schwilke, 2011)

Collection of specimens for evidential analysis (choix de sang, salive, urine)

Dans les urines la positivité est liée à la présence de métabolites, l'un actif avec une demi vie de 120 à 140 heures et l'autre inactif avec une demi vie de plusieurs jours.
La positivité dans les urines peut donc durer plusieurs semaines chez un gros fumeur.

Dans le sang la demi vie est assez courte (1,5 heures)

For instance, 5 µg/L of THC will be expected to decrease to 1.25 µg/L after 3 hours. It is therefore recommended that blood sampling occur as quickly as possible after the road traffic incident for prosecution to occur.

(Par exemple un taux de 5 microgrammes par litre peut s'abaisser à 1,25 après 3 heures)

Rappelons (bas de la page précédente)

A mean THC blood concentration after 24 hours abstinence was found to be 0.7 µg/L (SD 1.4 µg/L) and after 7 days abstinence 0.3 µg/L (SD 0.7 µg/L) (Karschner, Eugene& Schwilke, 2011), whereas in regular/frequent users blood concentrations of THC were detected between 1 µg/L and 6.4 µg/L

(chez un usager habituel le taux sanguin après 24 heures d'abstinence est d'environ 0,7 microgrammes/litre et après 7 jours d'abstinence 0,7 alors que chez un usager régulier un taux sanguin de 1 à 6,4 microgramme/L est habituel.
Nb= variabilité importante +++)

Pharmacodynamics (PD)

Cannabis and driving: the scientific evidence

In those given doses (often experimentally) to duplicate a single cannabis cigarette (18 mg THC or less), maximal psychotropic effect was found 20-40 minutes after smoking, but effects had largely disappeared 2.5 hours later (Berghaus et al, 2002).

(Chez des sujets à qui on a donné l'équivalent d'un seul joint (18 mg de THC ou moins) l'effet psychotrope a été maximal à 20-40 minutes et a pratiquement disparu après 2,5 heures)

A further meta-analysis of 21 studies investigating cannabis ingestion and driving performance revealed that a blood concentration of 3.7 µg/L THC (3.1 µg/L to 4.5 µg/L) impairs drivers to a concentration equivalent to a BAC of 50mg/100 ml (Berghaus et al, 2010) and another meta-analysis of 78 studies investigating smoking cannabis revealed a blood concentration of 3.8 µg/L THC (range 3.3 µg/L to 4.5 µg/L) impairing drivers to a concentration equivalent to BAC of 0.5mg/100 ml for smoked administration (DRUID D1.1.2b).

(Une concentration sanguine après ingestion de cannabis de 3,7 microgrammes par litre (3,1 à 4,5) correspond à 0,5 G/L d'alcool (nb= le seuil français) et pour le cannabis fumé c'est 3,8 (3,3 à 4,5))

Table 4.2: Overview of the risks for involvement in, responsibility for or injury as the result of a traffic accident (as an odds ratio (OR)) for driving under the influence of cannabis or specific THC concentrations

Substances	Odds ratio (OR)	Reference
Cannabinoids	OR: 1.22 (95% CI: 0.55-2.73)	Movig et al 2004
	OR: 2.79 (95% CI 1.23-6.33; P =0.01)	Asbridge et al, 2005
	Collision*	Asbridge et al, 2005
	0R : 2.10 (95% CI 2.10-3.36; P =0.002)	Bernard et al, 2007
	Fatal collisions**	Laumon et al, 2005
-THC < 1 µg/L blood	OR: 1.29 (99% CI: 1.11-1.50)	Laumon et al, 2005
-THC 1-2 µg/L blood	OR:1.57 (95% CI: 0.84-2.95)	Laumon et al, 2005
-THC 3-4 µg/L blood	OR:1.54 (95% CI: 1.09-2.18)	Laumon et al, 2005
-THC ≥ 5 µg/L blood	OR: 2.13 (95% CI: 1.22-3.73	
	OR: 2.12 (95% CI: 1.32-3.38)	Mura et al, 2003
-THC < 1 µg/L blood	OR: 2.50 (95% CI:1.5-4.2)	Drummer et al, 2004
	OR: 2.70 (95% CI:1.02-7.0)	Drummer et al, 2004
-THC ≥ 5 µg/L blood	OR: 6.60 (95% CI:1.5-28)	Blows et al, 2004
	0R: 9.50, (95% CI: 2.8 – 32.3	DRUID (D2.3.5)*
Habitual cannabis use	OR: 1.38 (95% CI: 0.88 – 2.17	DRUID (D2.3.5)**
THC or THCCOOH + THC	OR: 1.33 (95% CI: 0.48 – 3.67	

*Seriously injured based on aggregated data, ** fatally injured based aggregated data

Conclusion

For this reason and based on the evidence (summarised above) available to the Panel, the threshold recommended in whole blood for THC is 5 µg/L. At this concentration, the risks for involvement in, responsibility for, or injury as the result of a traffic accident when driving under the influence of cannabis are significant compared to a driver who has not consumed cannabis.

(Le Panel recommande donc le taux seuil de 5 microgrammes par litre. A cette concentration les risques d'accident, de responsabilité dans l'accident ou de blessures sont significativement élevés)

Cannabis and alcohol in relation to driving

The threshold recommended in whole blood for THC when detected in combination with alcohol is 3 µg/L.
The threshold recommended in whole blood for alcohol when detected in combination with THC is 20 mg alcohol per 100 mL of blood.

(quand le cannabis est associé à l'alcool les taux doivent être abaissés à 3 microgramme/L pour le cannabis et 0,20 mg/L pour l'alcool.)

5. DRUG SPECIFIC FINDINGS: COCAINE

Background
Epidemiological prevalence
Cocaine and driving

Table 5.1: International drug thresholds (set in or recommended for legislation):

Country	Approach to threshold	Cocaine	BZE*	Reference
Portugal	Zero tolerance	5 µg/L (B)	5 µg/L (B)	Belgian Official Gazette 15.09.2009 Ed. 2
Germany	Zero tolerance	10 µg/L (Se)	75 µg/L (Se)	Nickel & de Gier, 2009
Finland	Zero tolerance	15 µg/L (Se)	10 µg/L (Se)	Belgian Official Gazette 15.09.2009 Ed. 2
Norway	Impairment limit Comparable to 0.5g/L BAC Comparable to 1.2g/L BAC	24 µg/L (B) *legal limits for graded sanctions not defined*	*no limits*	Norwegian Institute for Public Health, 2012
Netherlands	Threshold	50 µg/L (B)		Netherlands Advisory Committee

Key: Biological fluids: B – blood; Se – serum; OF – oral fluid; *BZE (benzoylecgonine) is the main metabolite of cocaine,

Patterns of use

Pharmacokinetics (PK) and blood drug concentrations

Table 5.2: Plasma/serum concentration data after consumption of cocaine under different circumstances in human volunteers*

Route of administration	Cocaine plasma conc (µg/L)	Time (h) between dose administration and sampling	BZE plasma conc (µg/L)	Time (h) between dose administration and sampling
25 mg Intravenous dose	775	3.9	15,611	5.6
32 mg Intranasal dose	412	5.1	13,681	7.8
42 mg Smoked cocaine base	707	2.6	9,395	4.1

*As the concentration ratio for cocaine in blood:plasma/serum is one, these results can be compared to other findings in whole blood.

Collection of specimens for evidential analysis
Pharmacodynamics (PD)
Cocaine and Driving: the scientific evidence

Based on the concentrations of cocaine as measured in the blood of individuals suspected of or proven to have been driving under its influence the Panel recommends that a threshold concentration of cocaine in blood might be usefully set at 80 µg/L

(Le Panel recommande un taux dans le sang de 80 microgrammes par Litre)

A threshold of BZE 36 in whole blood was therefore recommended at 500 µg/L because this concentration of BZE in blood was deemed to be indicative of continued cocaine effect

(Le panel recommande un taux sanguin de 500 microgrammes/L por la BZE (le metabolite de la cocaine) car ce taux indique un effet de la cocaine encore présent.

Cocaine and alcohol in relation to driving

the Panel to recommend halving the cocaine threshold when detected in blood in the presence of alcohol to 40 µg/L cocaine and setting a threshold for blood alcohol concentration at 20 mg/100 ml blood.

(Avec l'alcool taux de 40 microgrammes/l pour la cocaine et 20 mg/L pour l'alcool)

6. DRUG SPECIFIC FINDINGS: AMFETAMINE-TYPE DRUGS

Background
Epidemiological prevalence
European data: amfetamines and driving

Table 6.2: International drug thresholds (set in or recommended for legislation): amphetamine and metamfetamine

Country	Approach to threshold	Amfetamine (in blood)	Metamfetamine (in blood)	Reference
Netherlands	Threshold	50 µg/L *	50 µg/L *	NAC, 2010
France	Threshold	50 µg/L *	50 µg/L *	Mura et al, 2003
Sweden	Zero-tolerance			Jones et al, 2006
Norway	Impairment limit Comparable to 50 mg/100 ml BAC Comparable to 120 mg/100 ml BAC	41 µg/L *legal limits for graded sanctions not defined*	45 µg/L *legal limits for graded sanctions not defined*	Norwegian Institute of Public Health, 2012

* The sum of the concentration of amfetamine, plus metamfetamine, plus MDMA, plus MDEA, plus MDA must not exceed 50 µg/L.Key: NAC Netherlands Advisory Committee

Patterns of use
Pharmacokinetics (PK) and blood drug concentrations
Collection of specimens for evidential analysis
Pharmacodynamics (PD)
Amfetamines and driving: the scientific evidence

the recommended threshold in whole blood for amfetamine was 600 µg/L. the recommended threshold for metamfetamine was set at 200 µg/L.

(recommandations de seuils de 600 microgrammes par litre pour l'amphatamine et de 200 microgramme par litre pour la methamphatamine)

Amfetamine and alcohol in relation to driving

The threshold recommended in whole blood for amfetamine when detected in combination with alcohol is 300 µg/L and the threshold recommended in whole blood for metamfetamine when detected in combination with alcohol is 100 µg/L

(en combinaison avec l'alcool les taux seuils deviennent 300 microgrammes/L pour l'amphetamine et 100 pour la methamphétamine. Nb= et toujours 0,20 g/L pour l'alcool)

7. Drug-Specific Findings: MDMA ('Ecstasy')

Background
Epidemiological prevalence
European data: MDMA and driving
Patterns of use
Pharmacokinetics (PK) and blood drug concentrations
Pharmacodynamics (PD)
MDMA and Driving: the scientific evidence

Table 7.5: Active concentrations of the most common drugs found in plasma (or serum) and blood) which are known to be a hazard when driving (NFI, 2010) [40]

Substance	Expected concentration in plasma after taking an active dose (µg/L)	Blood/serum ratio [2]	Estimated concentration in blood after taking an active dose[3] (µg/L)	Median in blood NFI 1999-2008 (µg/L)
MDMA	100-350	1.26	100-400	320
MDEA	approx. 200		100-400	50
MDA	up to approx. 400	1.2	100-400	30[41]

Based on the evidence available to the Panel (summarised above), the threshold recommended in whole blood for MDMA is 300 µg/L because at this concentration the drug is not compatible with the skills required for driving.

(Un seuil de 300 microgrammes par litre est recommandé)

MDMA and alcohol in relation to driving

The threshold recommended in whole blood for MDMA when detected in combination with alcohol is 150 µg/L

(En combinaison avec l'alcool un taux de 150 microgrammes/L et alccol 0,2 mg/L)
nb= la demi vie de l'Xta est assez longue plus de 7 heures !

Il insiste aussi sur l'information qui doit être donnée par les prescripteurs d'opioides, de BZD ou d'amphétamines.

8. DRUG SPECIFIC FINDINGS: KETAMINE

Background
Epidemiological prevalence
European data: ketamine and driving
Patterns of use
Pharmacokinetics (PK) and blood drug concentrations
Collection of specimens for evidential analysis
Pharmacodynamics (PD)
Ketamine and Driving: the scientific evidence

Based on the evidence available to the Panel (summarised above) the threshold recommended in whole blood for ketamine is 200 µg/L because at this concentration the drug is not conceivably compatible with the skills required for driving. A concentration of 200 µg/L ketamine would capture 70% of those drivers tested positive for ketamine in the UK data presented above.

(Un taux de 200 microgramme/L est recommandé. Dans le travail utilisé par le panel ce taux est atteint par 70 % des conducteurs testés positifs à la ketamine)

Ketamine and alcohol in relation to driving

The threshold recommended in whole blood for ketamine when detected in combination with alcohol is 100 µg/L and the threshold recommended in whole blood for alcohol when detected in combination with ketamine is 20 mg alcohol per 100 mL blood.

(avec l'alccol le taux recommandé s'abaisse à 100 microgrammes/L et alcool 0,2 mg/L)

9. DRUG SPECIFIC FINDINGS: OPIOIDS

Background
Epidemiological prevalence
Opioids and driving
Patterns of use
Pharmacokinetics (PK) and blood drug concentrations
Collection of specimens for evidential analysis

Table 9.1: Expected and estimated blood concentration data for morphine and codeine as compiled by the Netherlands Forensic Institute (NFI 1999-2008)

Substance	Expected concentration in plasma after taking an active dose[a] (µg/L)	Blood/serum ratio [b]	Estimated concentration in blood after taking an active dose(µg/L)	Median in blood (µg/L)
Morphine	10-120	1.0	10-120	40
Codeine	50-250	0.87	40-250	20

Taux sanguin après une dose thérapeutique

Pharmacodynamics (PD)
Opioids and driving: the scientific evidence

Table 9.2: European overview of OR for getting seriously injured or killed based on aggregated data (DRUID, summary of main findings)

Substances	Odds ratio (OR)	CI (95%)	Reference and basis for ORs
Medicinal opioids	**Seriously injured**		
	Crude OR:7.99	5.73 – 11.15	DRUID (D2.3.5)
	Adjusted OR: 9.06	6.40 – 12.83	Greenland et al, 2000
	Killed		
	Crude OR: 4.82	2.61 – 8.88	Countries providing data for Seriously injured OR: BE, DK, FL, IT, LT, NL
	Adjusted OR: 4.82	2.60 – 8.93	
	Seriously injured		
Illicit opiates	Crude OR: 4.03	1.32 - 12.32	Countries providing data for Killed OR: FL, NO, PT, SE, NL
	Adjusted OR:2.47	0.50 – 12.10	
	Killed		
	Crude OR: 10.04	2.04 – 49.32*	Bernhoft, 2011 DRUID Deliverable 2.4.1)
	Adjusted OR n/a		

Note= l'usage des opiacés prescrits semblent ici plus dangereux que celui des opiacés illégaux

Méthadone
The use of methadone obtained illicitly to supplement prescribing is also commonplace. For these reasons and in consideration of the epidemiological evidence, the Panel recommended a threshold should be set at 500 µg/L methadone in whole blood, indicative of high dose consumption:

(Compte tenu de la fréquence de prise de méthadone de rue ou de « suppléments de dsoe » non prescrits un seuil de 500 microgramme/L est recommandé pour la méthadonémie)
nb= la zone thérapeutique est environ 400 microgrammes/L seuil divisé par 2 avec présence d'alcool

Table 9.3: Overview of the risk estimates as an odds ratio (OR) for involvement in, responsibility for or injury as the result of a traffic accident when driving under the influence of opioid drugs (based on a report by Clockwork Research Ltd. to the Panel).

Substances	OR	CI (95%)
Opioids	Incident rate ratio	
Opioids (all) first 4 weeks	1.70	1.39 – 2.08
Extended use	1.29	1.08 – 1.54
Codeine first 4 weeks	1.61	1.11 – 2.32
Codeine extended use	1.33	0.88 – 2.00
Morphine first 4 weeks	1.16	0.39 – 3.45
Morphine extended use	0.87	0.43 – 1.75
DHC** first 4 weeks	1.60	1.14 – 2.25
DHC extended use	1.05	0.78 – 1.42
Tramadol first 4 weeks	1.46	1.02 – 2.11
Tramadol extended use	1.34	1.02 – 1.76
Opioids	2.35	0.87 – 6.32

Donc des mises en garde doivent être données à TOUS les utilisateurs d'opiacés, qu'ils soient prescrits ou non !!!!

Morphine
In recognition of the blood concentration values found in drivers and the epidemiological evidence discussed above the Panel recommended a threshold of 80 µg/L morphine in whole blood
(Pour la morphine un seuil de 80 microgrammes/L est recommandé)

Opioids and alcohol in relation to driving
The Panel recommended that a threshold for morphine at 40 µg/L could be recommended where alcohol was detected in the body above 20 mg/100ml blood

(avec alcool seuil de 40 microgrammes/L et alcool 0,2 g/L)

10. DRUG SPECIFIC FINDINGS: BENZODIAZEPINES

Background
Epidemiological prevalence
European data: benzodiazepines and driving
Patterns of use
Pharmacokinetics (PK) and blood-drug concentrations
Pharmacodynamics (PD)
Benzodiazepines and driving: the scientific evidence

Reviews estimate that the increased risk of a RTA in those consuming benzodiazepines compared to non-users ranged from 61% (Rapoport et al, 2009) to 290% (Engeland, Skurtveit, & Morland, 2007)

(Le risque d'accident sous BZD est augmenté de 61 à 290%) en fait bien plus chez les personnes âgées (voir tableaux ci dessous)

Table 10.5: BZ medication and risk estimate (as an OR) of a RTA requiring hospitalisation (n = 616) in drivers aged ≥60 years (adapted from Meuleners et al, 2011)

Benzodiazepine	Odds-Ratio (95% Confidence interval) *P*-value
All exposed subjects	OR: 5.3 (3.6 – 7.8) p<.001
Male	OR: 6.2 (3.2 – 12.2) p<.001
Female	OR: 4.9 (3.1 – 7.8) p<.001
Chronic condition: No	OR: 6.0 (3.8 – 9.5) p<.001
Chronic condition: Yes	OR: 4.0 (2.9 – 8.1) p<.001

Table 10.6: An overview of the relative risks as an odds ratio (OR) for involvement in, responsibility for, or injury as the result of a traffic accident when driving under the influence of benzodiazepines

Substance	Odds Ratios (OR)	Reference and basis for OR
Diazepam	OR: 1.61 (N=411; p<0.001)	Bramness 2002
Oxazepam	OR: 3.65 (N=73; P<0.05)	Impairment in apprehended
Flunitrazepam	OR: 4.11 (N=211;p<0.05)	drivers in Norway
Different BZ combined*		
Mildly >Therapeutic Range-TR	OR: 1.60 (0.84 - 3.05)	*Adjusted for all background
Moderately > TR	OR: 3.71 (1.34 - 10.27)	variables
Highly elevated>TR	OR: 3.75 (1.46 – 9.63)	
Long half-life (diazepam)	OR: 1.45 (1.04-2.03)	Hemmelgarn 1997
Continued use up to 1 yr	OR: 1.26 (1.09-1.45)	Drivers in injurious accidents
Short half-life (oxazepam)	OR: 1.04 (0.81-1.34)	Age 67-84 yrs
Continued use up to 1 yr	OR: 0.91 (0.82-1.01)	
Hypnotics (2-4 weeks)	OR: 6.5 (1.9-22.4)	Neutel 1995
Flurazepam/Triazolam	OR: 3.9 (1.9-8.3)	Saskatchewan study
Anxiolytics (2-4 weeks)	OR: 5.6 (1.7-18.4)	Accidents severe enough to
Diazepam, Lorazepam, Oxazepam	OR: 2.5 (1.2-5.2)	require hospitalisation
BZ + positive breath test	OR; 8.15 (2.06-32.34)	Barbone 1998
Anxiolytics (long half-life)	OR: 2.22 (1.47 – 3.37)	UK Tayside police19,386 drivers
Hypnotic (long half-life)	OR: 0.88 (0.41-1.87)	first RTA: 1731 used drugs

Benzodiazepines, drug concentrations and driving

the threshold recommended in whole blood for diazepam is 550 µg/L. At this concentration, impairment in driving and RTAs have been found to occur compared to drivers who had not consumed the drug. Recommendations are also made for oxazepam (recommended threshold is 300 µg/L); flunitrazepam (recommended threshold is 300 µg/L); lorazepam (recommended threshold is 100 µg/L); clonazepam (recommended threshold is 50 µg/L); and temazepam (recommended threshold is 1,000 µg/L) since these compounds have also been shown to increase the risk of a RTA in a concentration-dependent fashion: risk is significantly higher when blood concentrations are above the normal therapeutic range.

(Seuil recommandé 550 microgrammes/L pour le diazepam, 300 pour l'oxazepam et le flunitazepam, 100 pour le lorazepam, 50 pour le clonazepam et 1000 pour le temazepam
Le risque est particulièrement élevé quand le taux sanguin est supérieur aux taux thérapeutiques)

Benzodiazepines and alcohol in relation to driving

In the presence of alcohol fordiazepam is 275µg/L; for oxazepam is 150 µg/L; for flunitrazepam is 150 µg/L; clonazepam is 25 µg/L; lorazepam is 50 µg/L and for temazepam is 500 µg/L. (taux divisés par deux avec l'alcool)
Le Panel insiste aussi sur l'information qui doit être donnée par les prescripteurs d'opioides, de BZD ou d'amphétamines.

11. DRUG SPECIFIC FINDINGS: MISCELLANEOUS DRUGS

Mephedrone
Gamma-hydroxybutyrate (GHB) and Gamma-butyrolactone (GBL)
Lysergic Acid Diethylamide (LSD)

The use of LSD is not likely to be compatible with the skills required for driving due to its severe psychomotor, cognitive and residual effects.

(L'usage du LSD est incompatible avec la conduite)

12. SUMMARY AND CONCLUSIONS

Le Panel rajoute l'Imovane (Zopiclone) qui n'était pas compris dans les produits à examiner mais qui présente un sur-risque probable.

Il insiste aussi sur l'information qui doit être donnée par les prescripteurs d'opioides, de BZD ou d'amphétamines.

REFERENCES