

SOSTANZE PSICOTROPE E IDONEITA' ALLA GUIDA

ANALISI QUALITATIVE E QUANTITATIVE



Maria Teresa Pinorini

Locarno, 24 novembre 2016

Sostanze psicoattive e circolazione stradale:

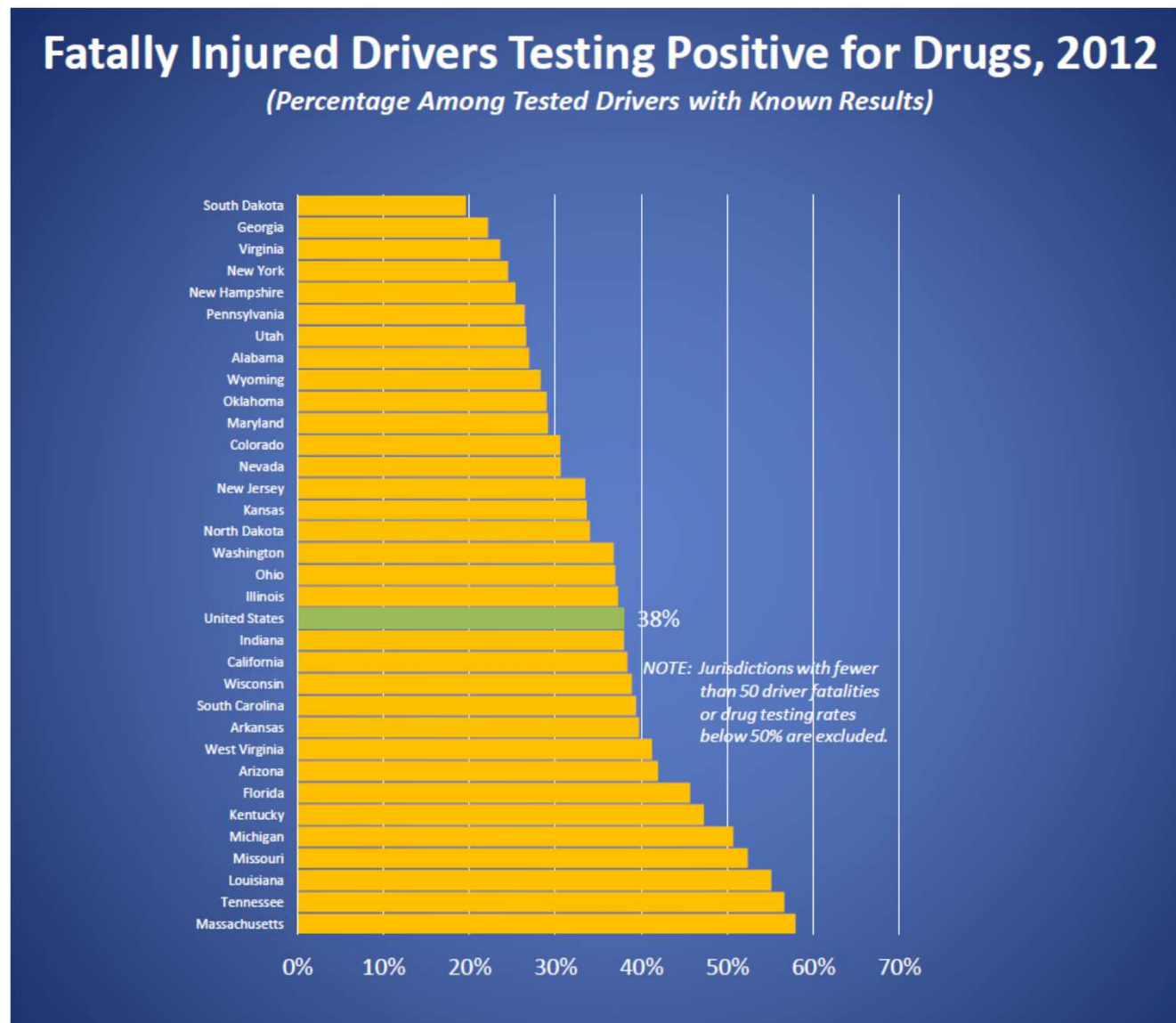
problema reale ?



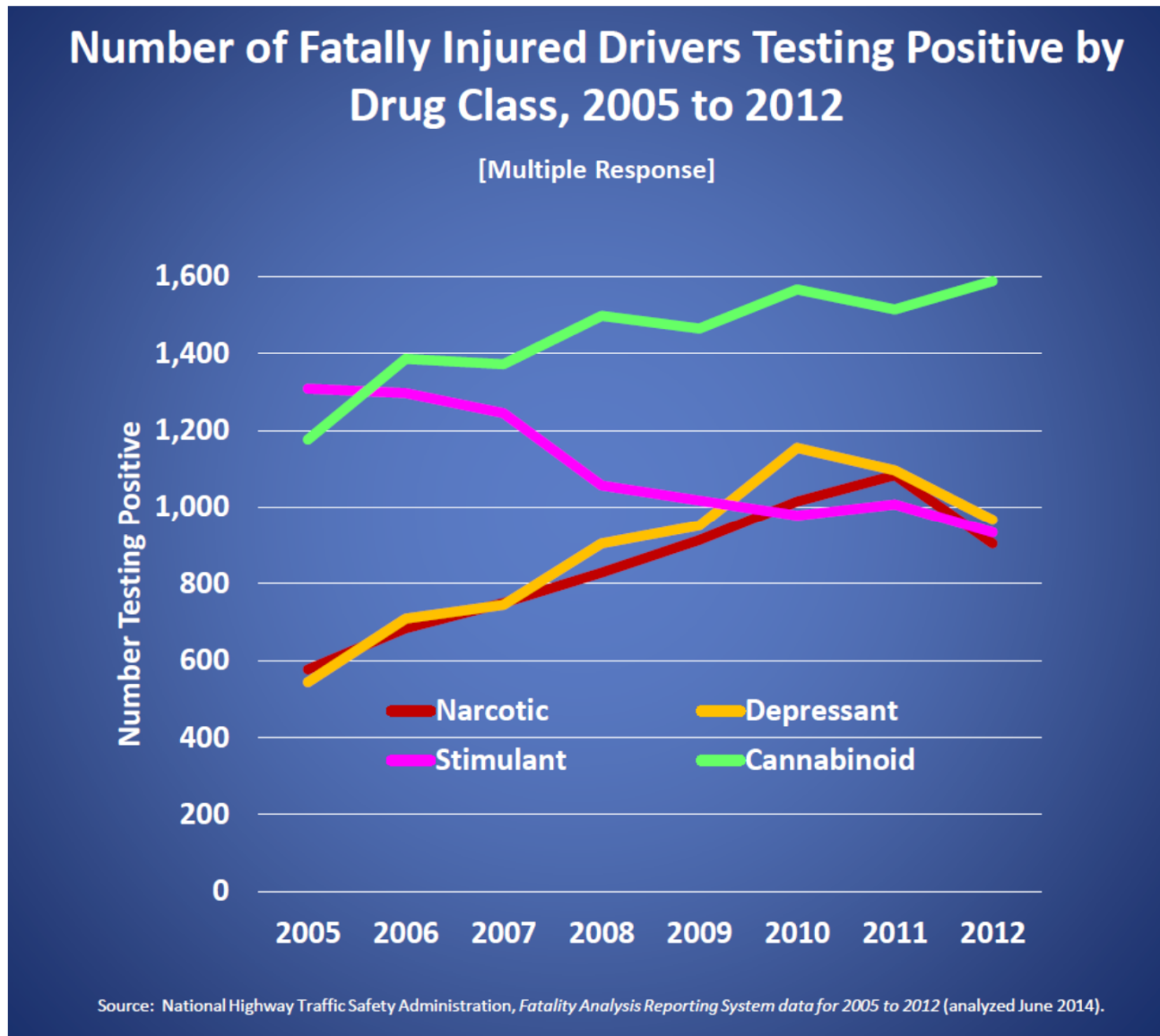
Analisi qualitative e quantitative

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USA: conducenti deceduti 2012 (positivi)

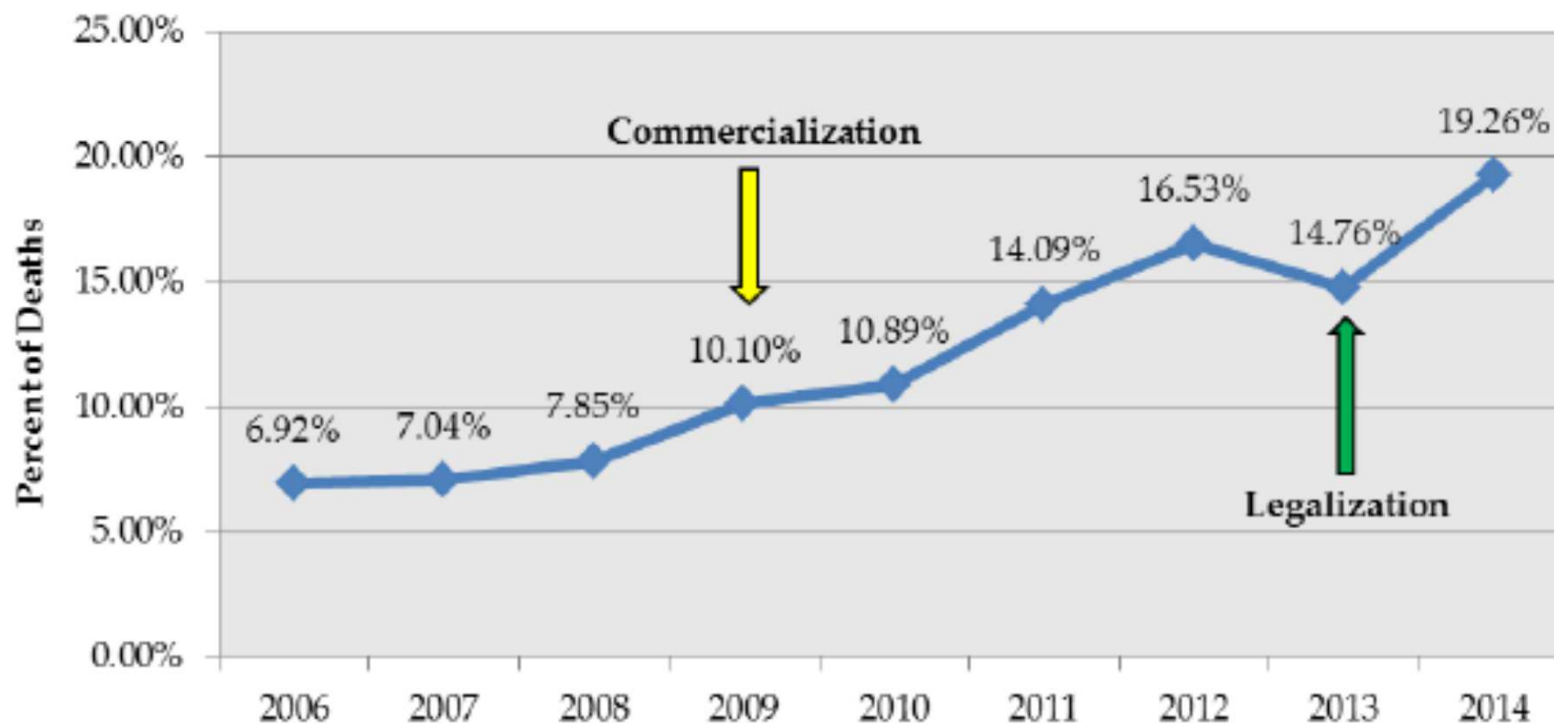


USA: conducenti deceduti 2005 – 2012 – classi di sostanze



Colorado e cannabis : conducenti deceduti 2006-2014

Percent of All Traffic Deaths That Were Marijuana Related*

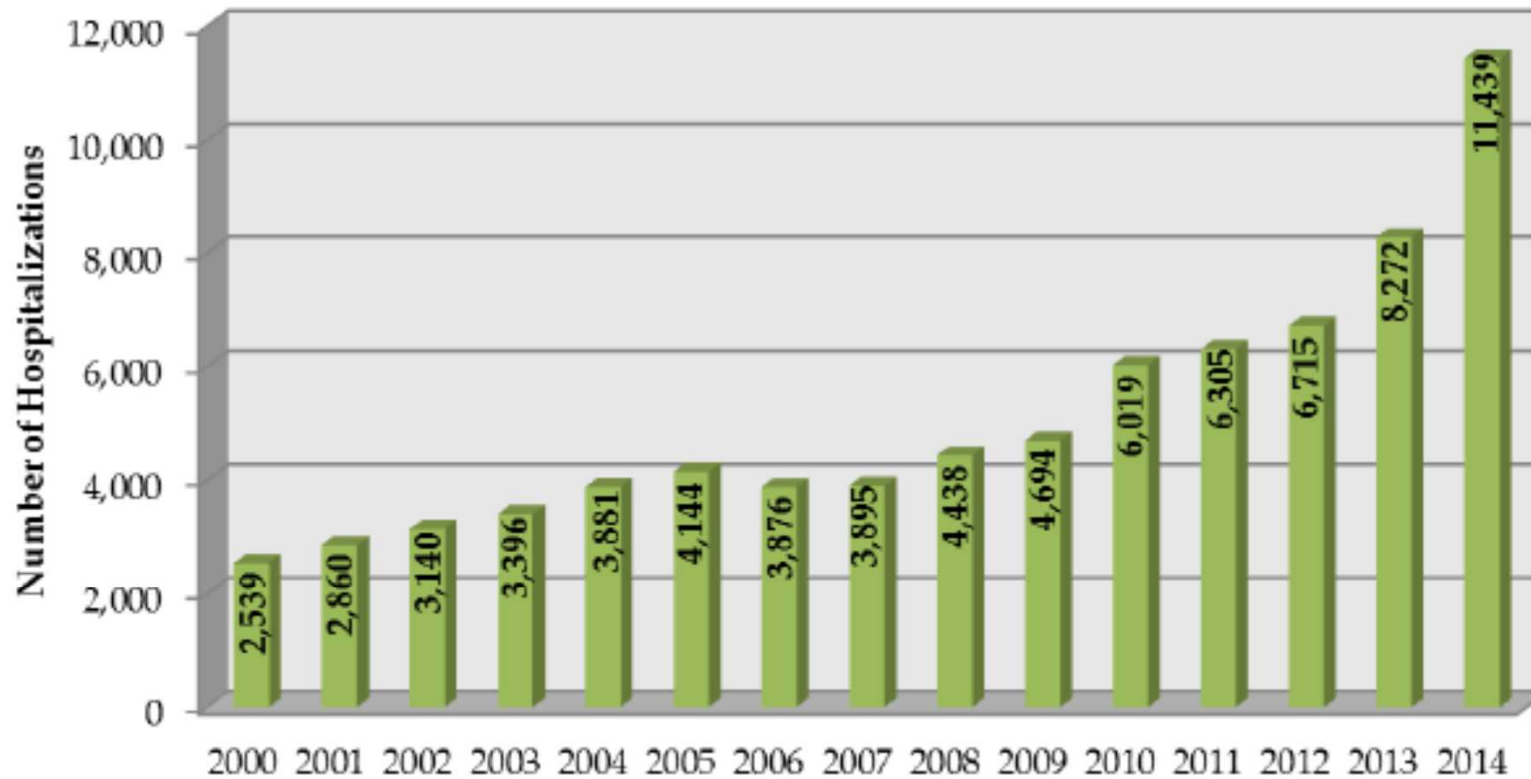


*Percent of All Fatalities Where the Operators Tested Positive for Marijuana

SOURCE: National Highway Transportation Safety Administration, Fatality Analysis Reporting System (FARS), 2006-2013 and CDOT/RMHIDTA 2014

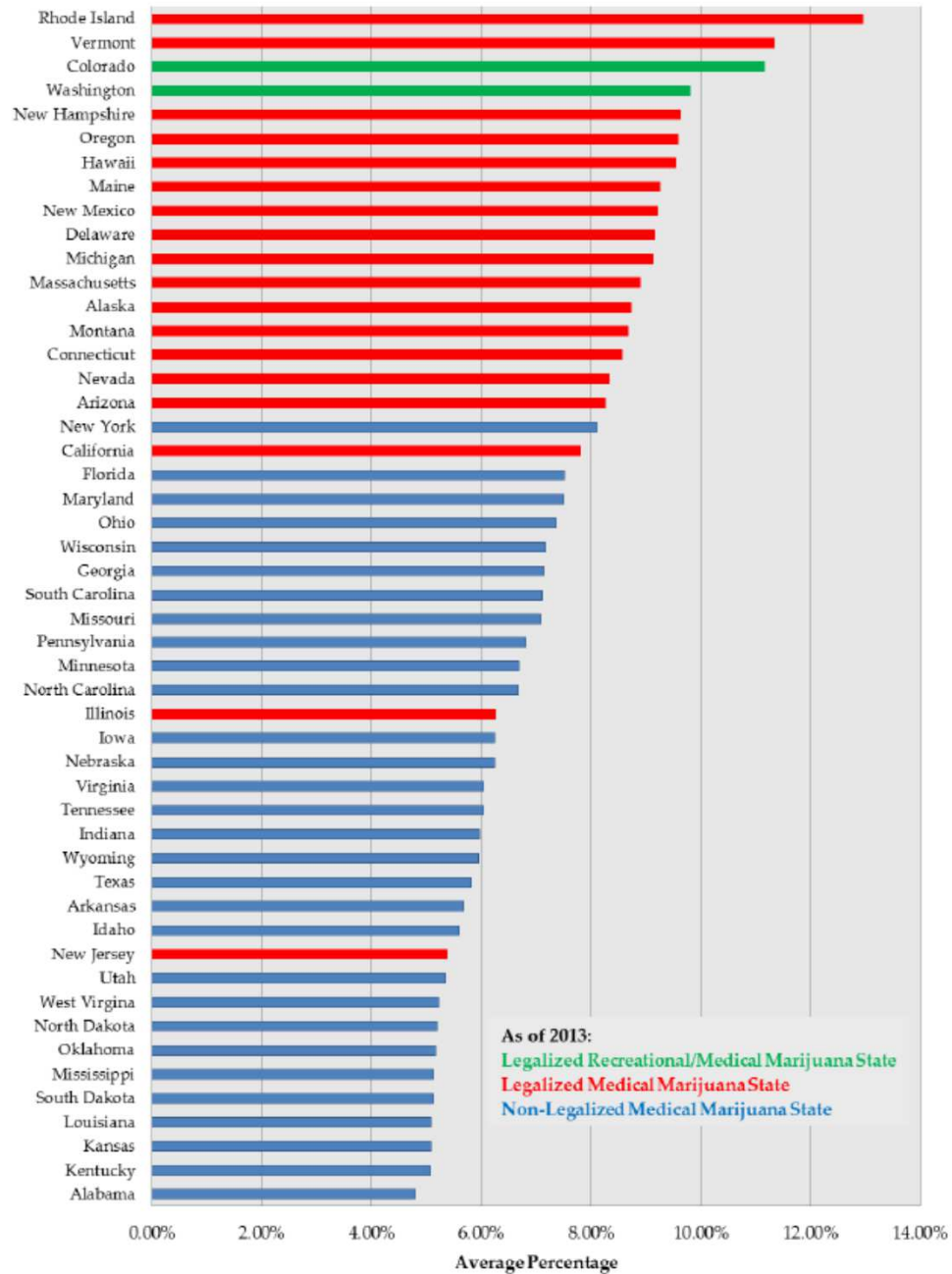
Colorado e cannabis : ricoveri

Hospitalizations Related to Marijuana

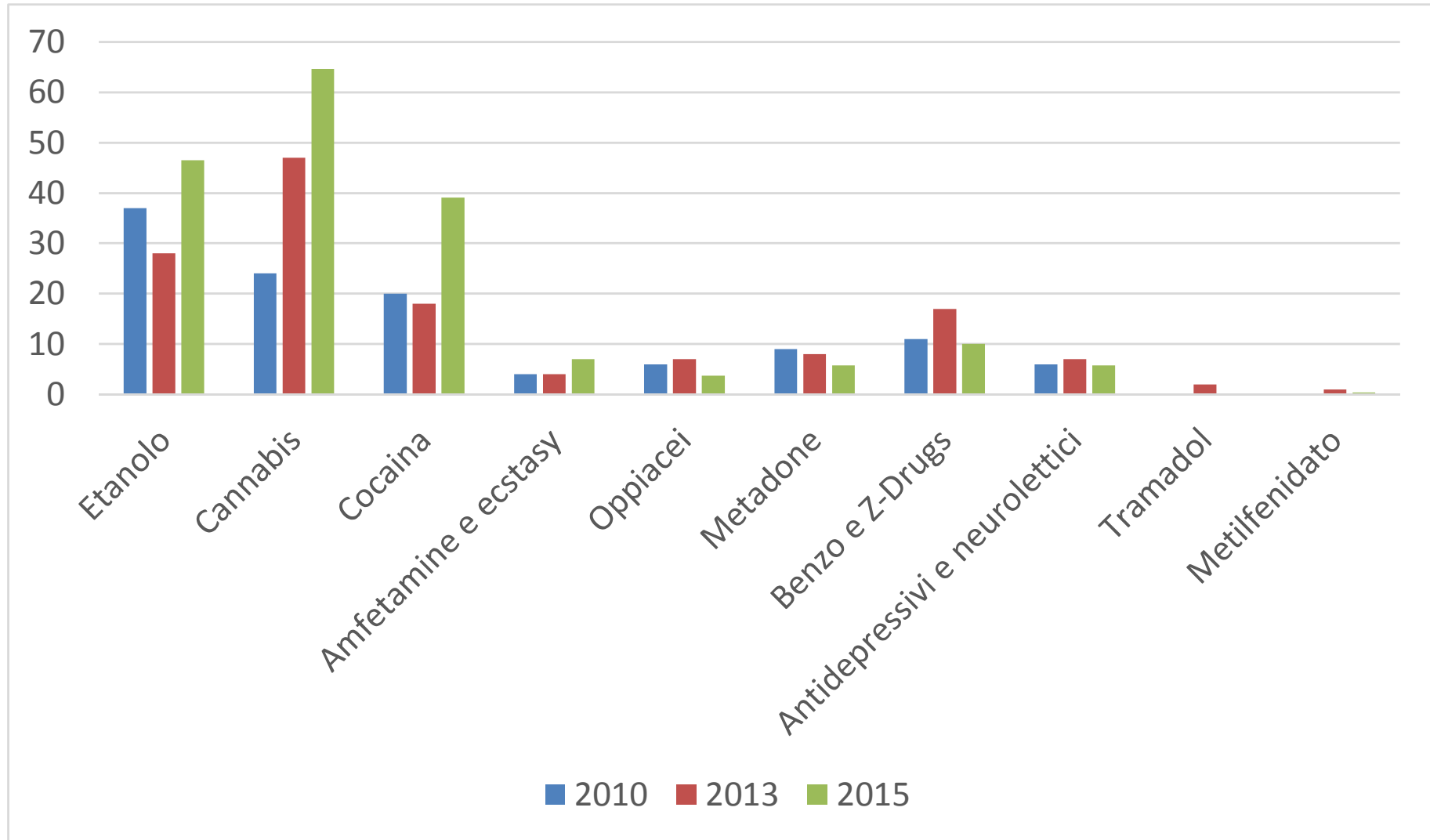


SOURCE: Colorado Hospital Association, Hospital Discharge Dataset. Statistics prepared by the Health Statistics and Evaluation Branch, Colorado Department of Public Health and Environment

State-by-State Past Month Usage by 12 to 17 Years Old, 2013

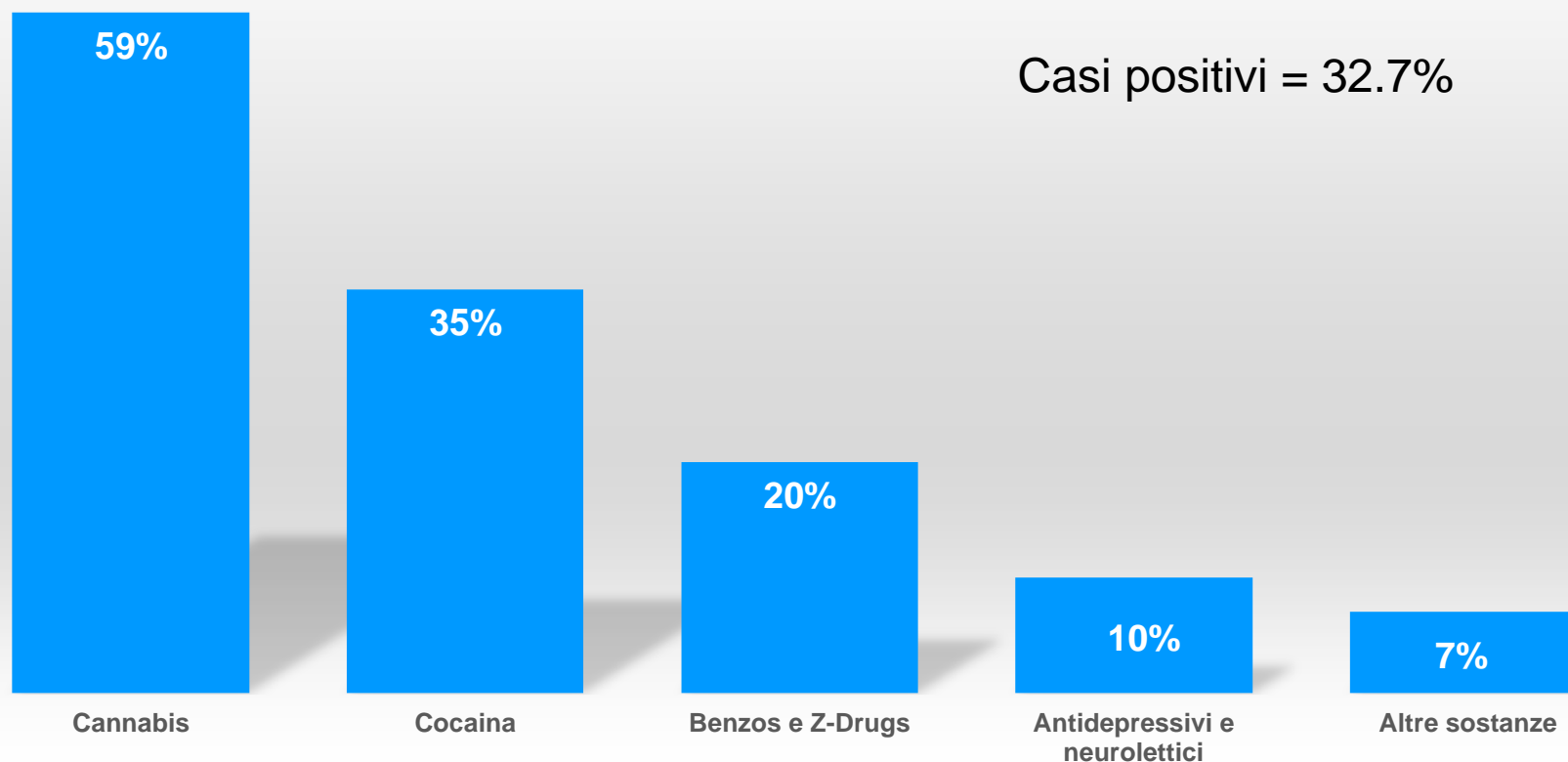


Ticino: classi di sostanze identificate in conducenti sospettati di condurre sotto l'influsso di etanolo, sostanze d'abuso e medicinali (% positività)

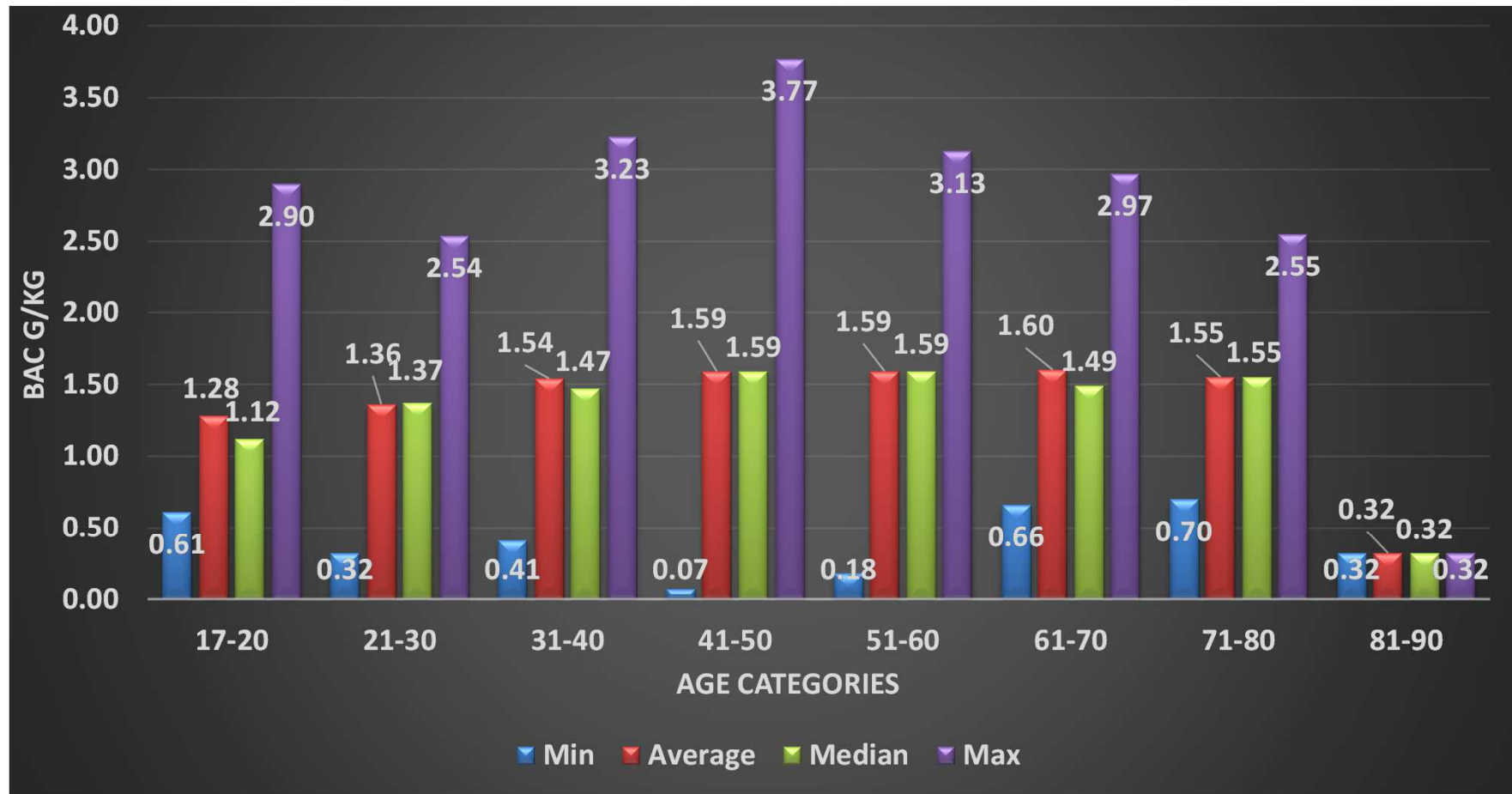


Ticino – Campioni trasmessi per verifica etanolemia analizzati per la presenza di altre sostanze ...

Guida sotto l'influsso di sostanze: % casi positivi su campioni trasmessi solo per determinazione etanolemia - 2015

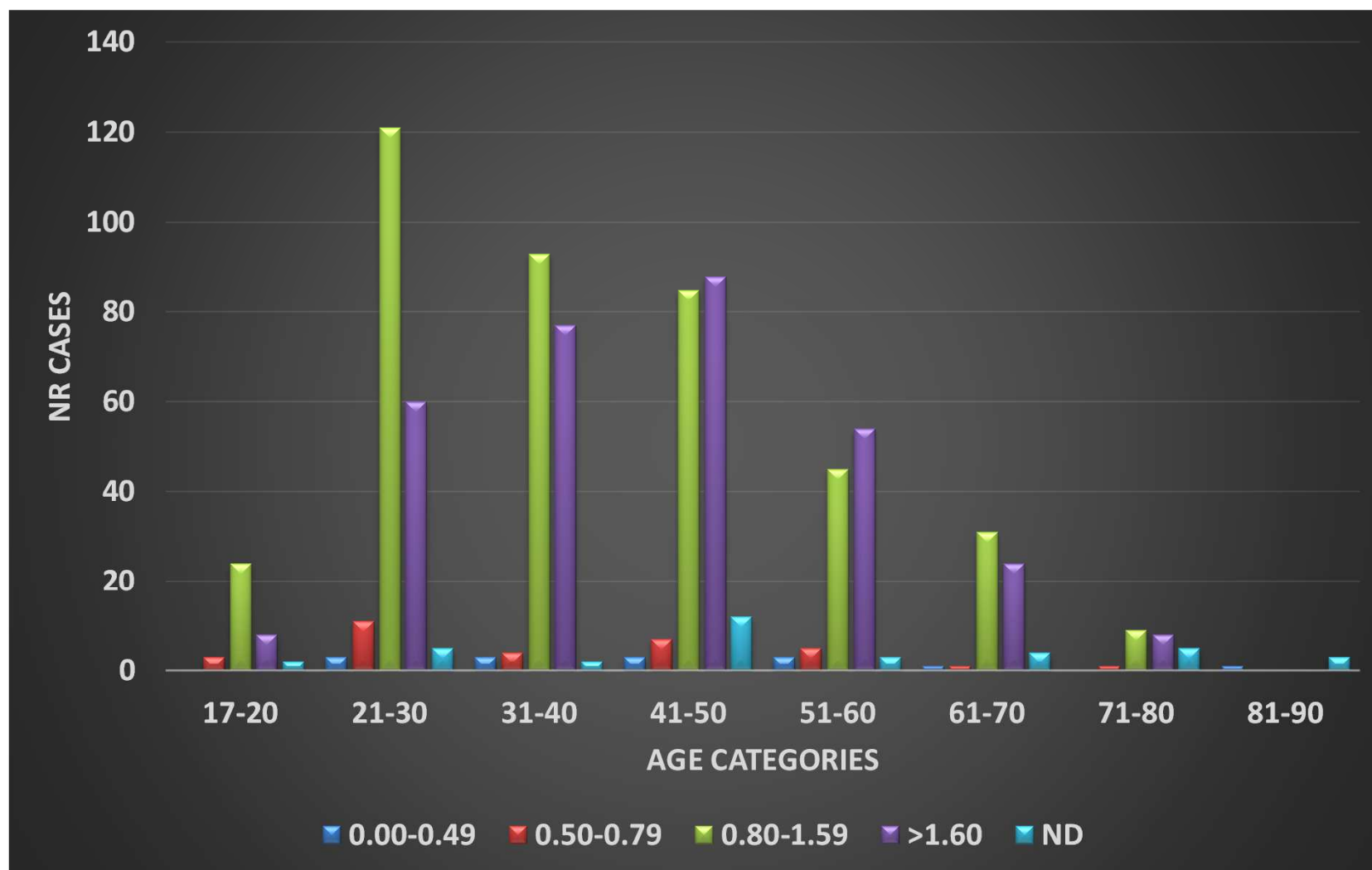


Ticino – etanolemie per categorie di età – 2015 (N=1170)



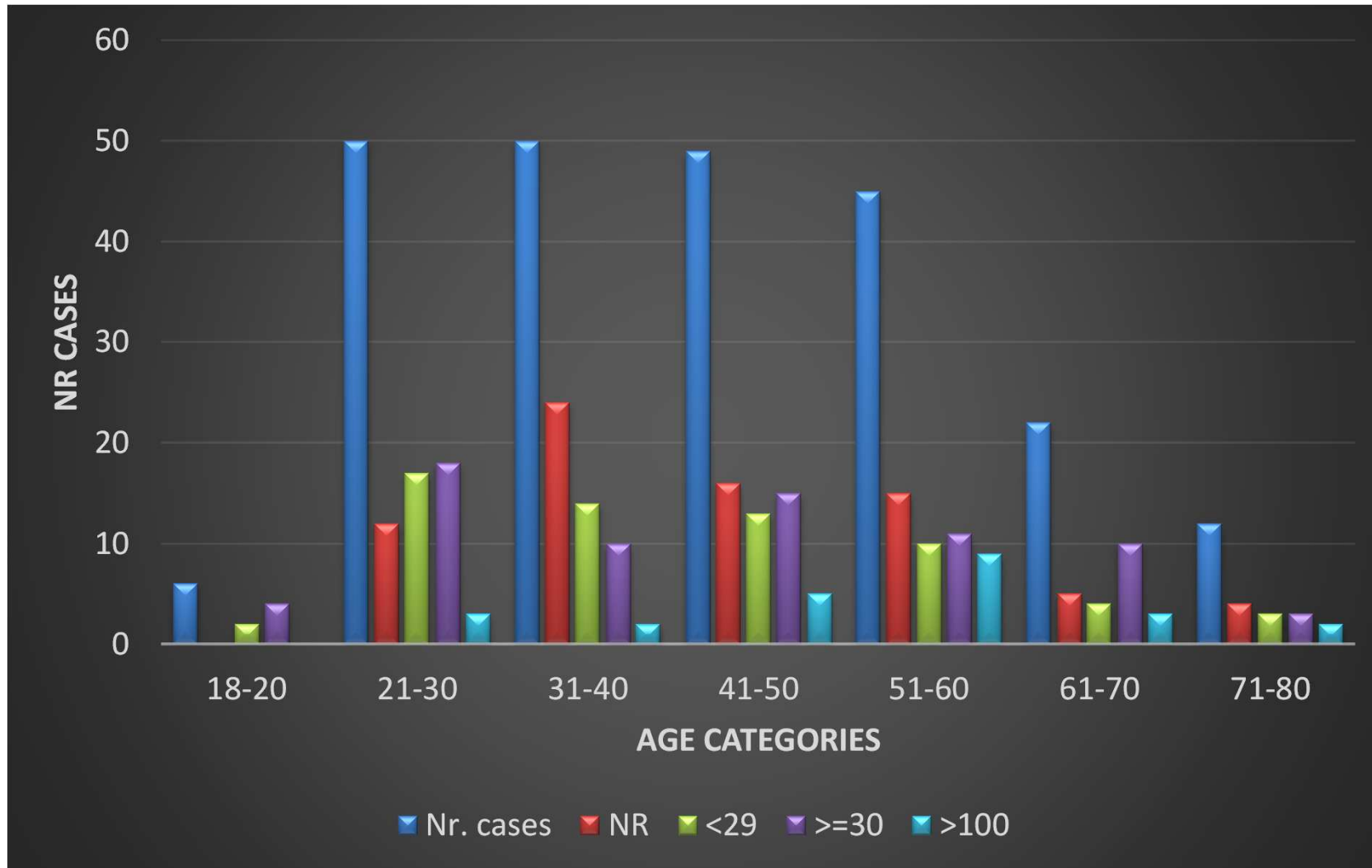
Etanolemia valore medio: 1.50 g/kg

Ticino – etanolemie – frequenza per categorie di età - 2015



Nr. casi etanolemia ≥ 1.60 g/kg (0.8 mg/l) : 319 (39.4%)

Ticino - Concentrazione EtG per categorie di età



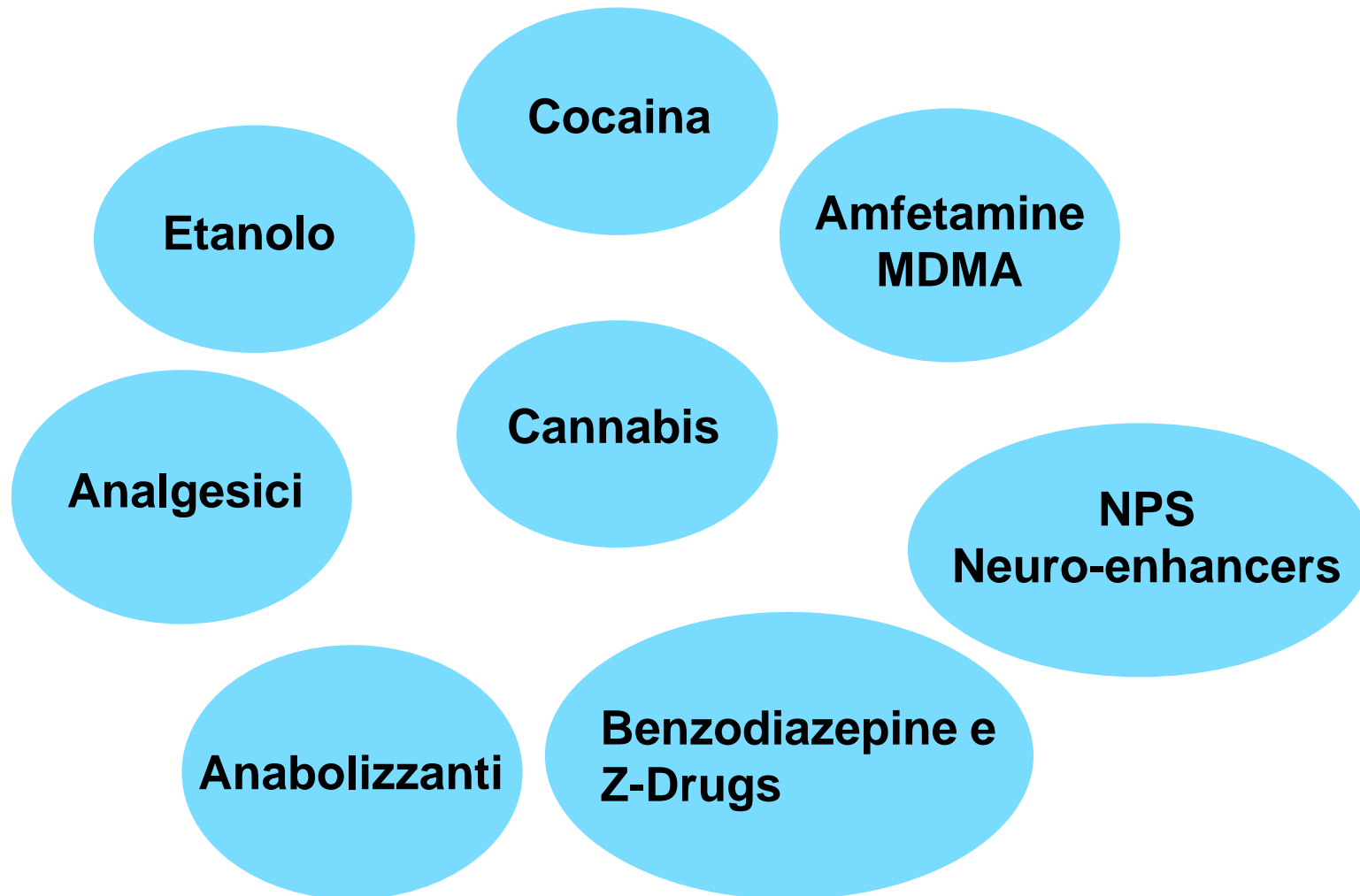
**Prima visita presso CMT dopo l'evento
234 casi ; 57% idonei alla guida**

2015 – POLICONSUMO – MDV (N=272)

1 sostanza 53%	2 sostanze 24%	3 sostanze 12%	4 sostanze 5.0 %	5 o + sostanze 6.0%
---------------------------------	---------------------------------	---------------------------------	-----------------------------------	--------------------------------------

- ✓ **etanolo + cannabis**
- ✓ **etanolo + cocaina**
- ✓ **etanolo + cannabis + cocaina**
- ✓ **etanolo + cannabis + benzodiazepine**
- ✓ **oppiacei + metadone + cocaina + benzo**
- ✓ **etanolo + cocaina + amfetamine/MDMA**
- ✓ **etanolo + benzodiazepine + antidepressivi**

GIOVANI E GUIDA – SOSTANZE RILEVATE



GIOVANI – Caso 1 – Incidente

Uomo, 18 anni, automobilista – patente in prova

Risultati analisi quantitative (sangue)	
Analita	Concentrazione
Cocaina	4.2 µg/l (2.9 -5.5) µg/l
Benzoilecgonina	200 µg/l
Ecgoninametilestere	13 µg/l
Etilcocaina	Non rilevato
THC	15 µg/l (10 – 20) µg/l
OH-THC	9.3 µg/l
THC-COOH	54 µg/l

GIOVANI – Caso 2 – Incidente

Uomo, 24 anni, automobilista

Risultati analisi quantitative (sangue)	
Analita	Concentrazione
Cocaina	55 µg/l (38 -72) µg/l
4-FA (4-fluoroamfetamina)	22 µg/l
THC	2.3 µg/l (1.6 – 3.0) µg/l
Etanolo	1.43 g/kg (1.36 – 1.50) g/kg

GIOVANI E CANNABIS – ALTRE MODALITA' DI ASSUNZIONE



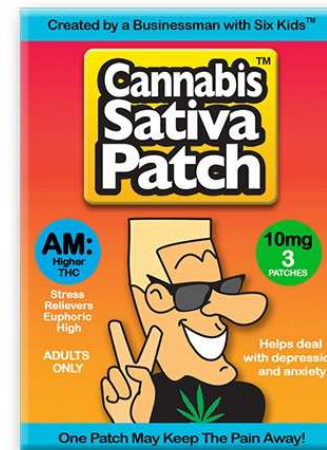
Dabs (BHO)



Transdermal THC patches



Puppy chow



Warnung: NBOMe verkauft als LSD

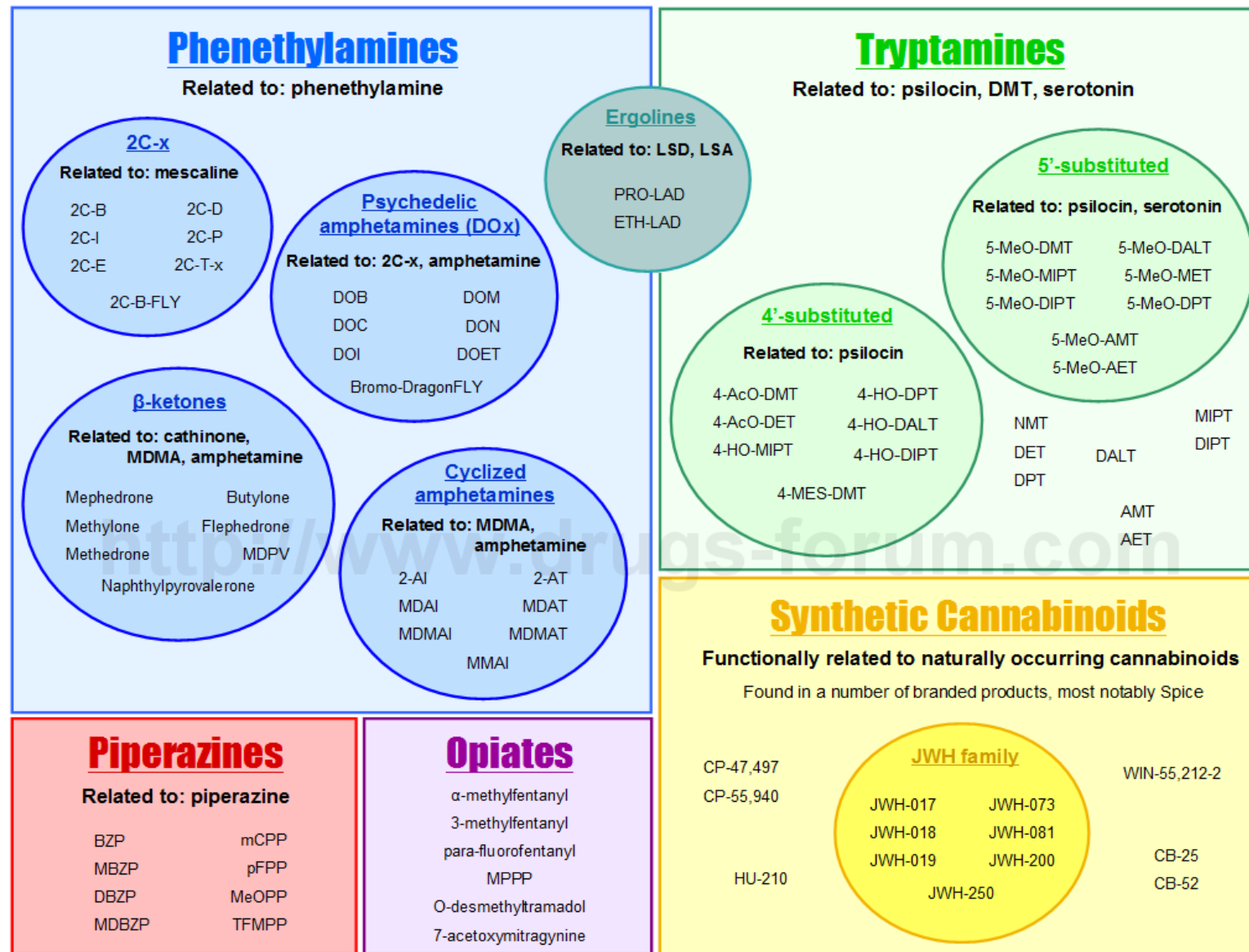
Name	Unbekannt
Gewicht	14.4 mg
Grösse	8.0 x 7.0 mm
Farbe	Weiss/Rot/Blau
Inhaltsstoffe	25C-NBOMe*HCl: 436.3 µg 25B-NBOMe*HCl: 580.5 µg div. Syntheseverunreinigungen
Bemerkungen	Bitterer Geschmack im Unterschied zu LSD!
Getestet in	Zürich (DIZ), 03. August 2016



Risikoeinschätzung

Dieser Filz enthält kein LSD, sondern **25C-NBOMe** und **25B-NBOMe**! Die beiden Substanzen können zu peripheren Blutgefässverengungen führen und stehen im Zusammenhang mit einigen Todesfällen in Europa. Besonders bedenklich ist, dass die Aufnahme und der Abbau dieser Substanzen von Person zu Person sehr unterschiedlich ausfallen können. Beide Substanzen wirken direkter und schneller, wenn sie sublingual (unter der Zunge) über die Schleimhäute aufgenommen werden. Wenn die Substanzen oral eingenommen werden, kann es zu einer schwächeren und/oder zeitlich verzögerten Wirkung kommen. Dadurch besteht die Gefahr, dass nachdosiert und ungewollt überdosiert wird. Aufgrund der schwierigen Handhabung und auch da die Substanzen kaum erforscht sind, raten wir vom Konsum ab!

NUOVE SOSTANZE PSICOATTIVE (NPS)

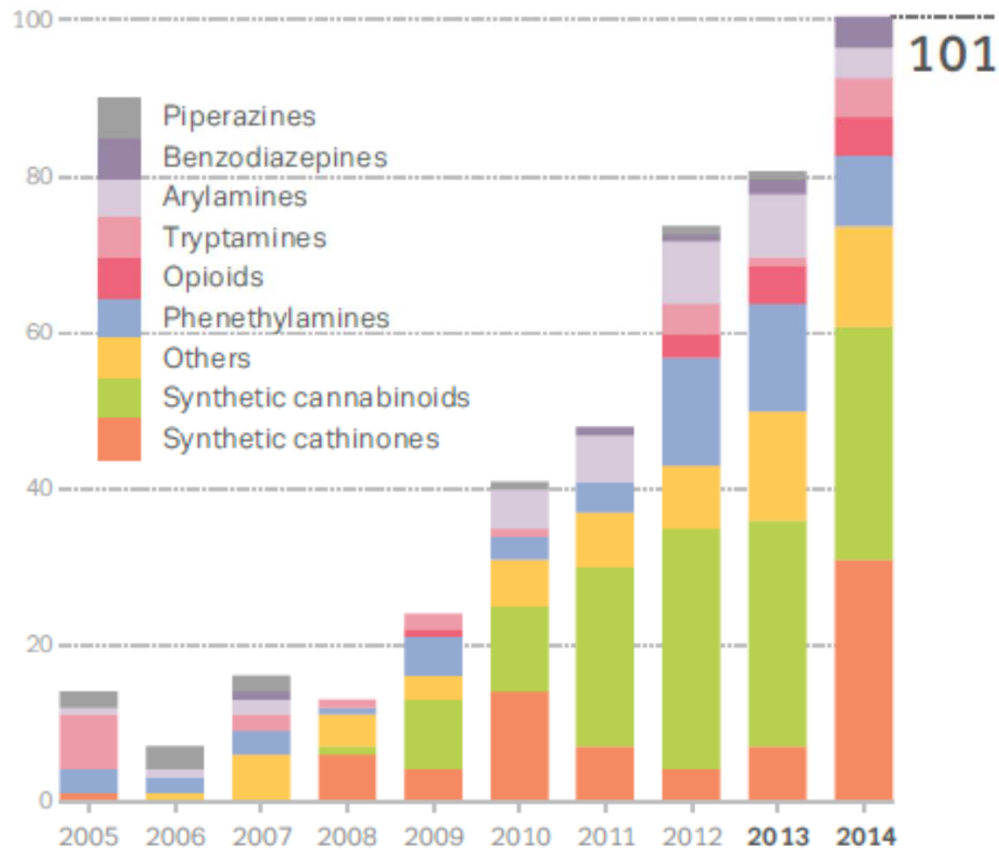


Analisi qualitative e quantitative

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NPS - DIFFUSIONE

FIGURE 1
Number of new psychoactive substances reported to the EU Early Warning System, 2005–14



New psychoactive substances in Europe

An update from the EU Early Warning System
March 2015



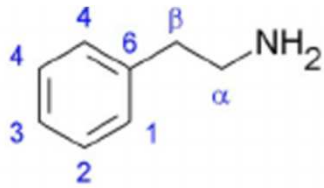
SALI DA BAGNO, ODORIZZANTI PER AMBIENTE, FERTILIZZANTI



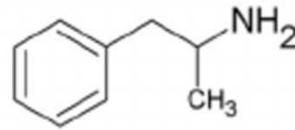
Analisi qualitative e quantitative

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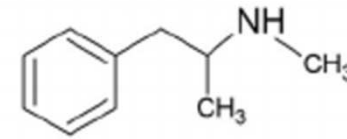
FENETILAMMINE – STIMOLANTI / ALLUCINOGENI



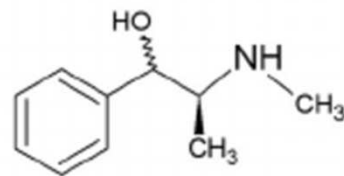
Phenylethylamine



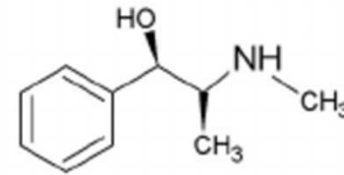
Amphetamine



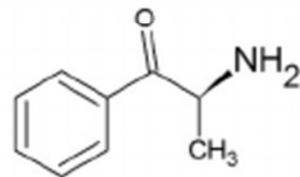
Methamphetamine



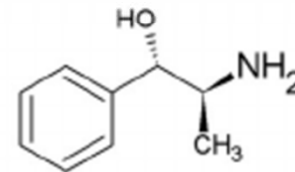
Pseudoephedrine



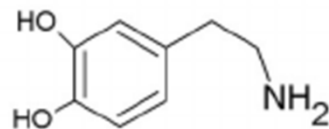
Ephedrine



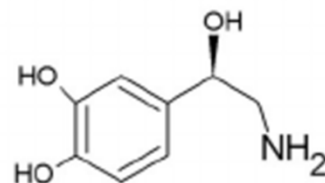
Cathinone



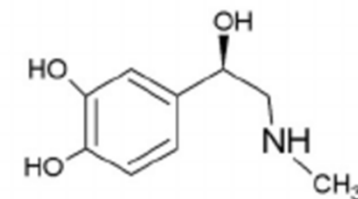
Cathine (norpseudoephedrine)



Dopamine



Norepinephrine

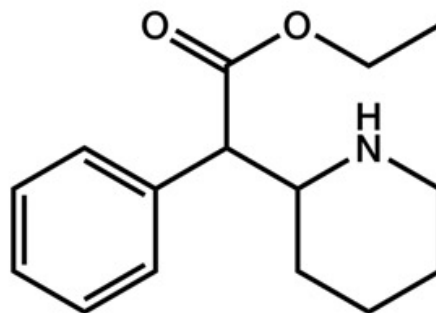


Epinephrine (adrenaline)

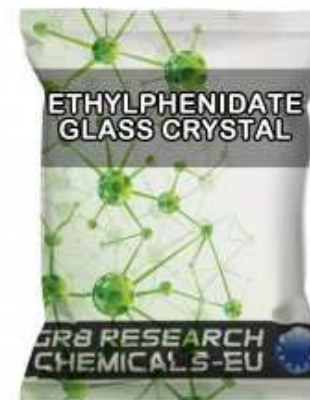
DERIVATI DEL METILFENIDATO – NPS – Neuro-enhancers



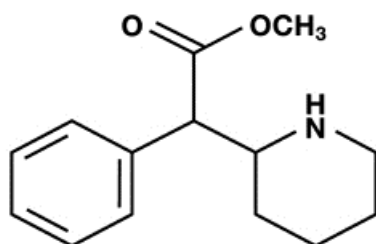
© HCl Solutions AG



Ethylphenidate (C₁₅H₂₁NO₂)
Image by Erowid, © 2012 Erowid.org



Metilfenidato



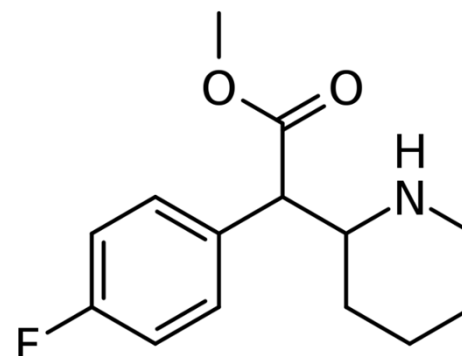
Methylphenidate Hydrochloride

C₁₄H₁₉NO₂ • HCl

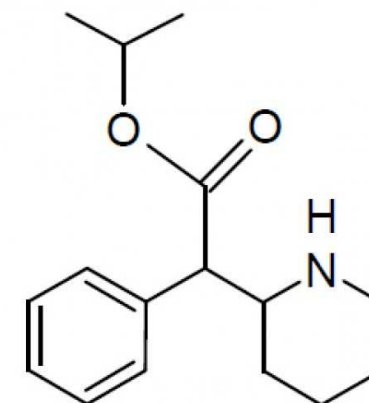
• HCl

MW = 269.77

Etilfenidato



4-fluoro-metilfenidato

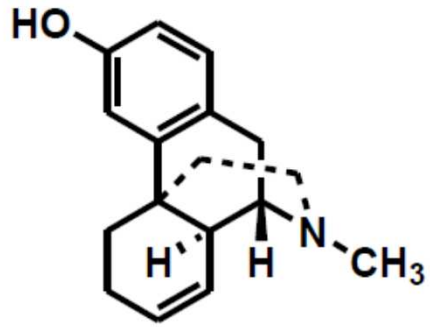


Isopropilfenidato

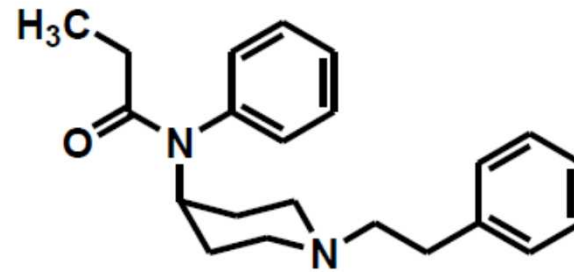
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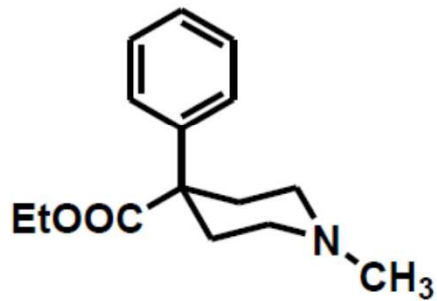
OPPIOIDI SINTETICI



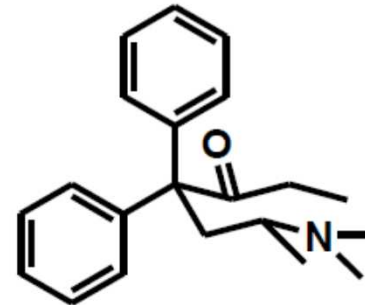
DESTROMETORFANO



FENTANILE



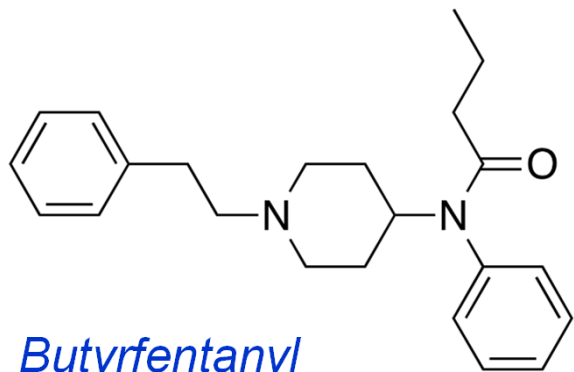
**PETIDINA
(MEPERIDINA)**



METADONE



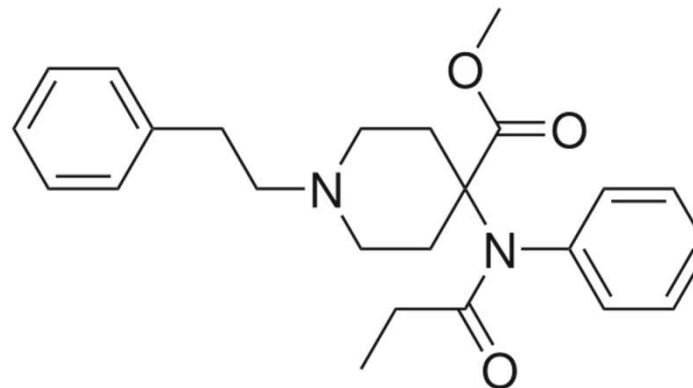
DERIVATI FENTANILICI - NPS



Butyrfentanyl

Dose: 2-4 mg

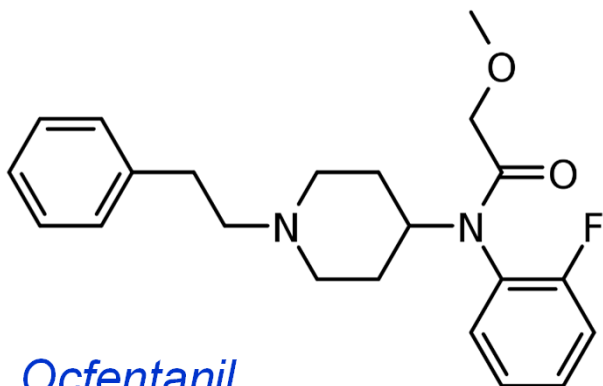
Potenza analgesica: 40



Carfentanyl

Dose: 1-2 µg

Potenza analgesica: 7500



Ocfentanil

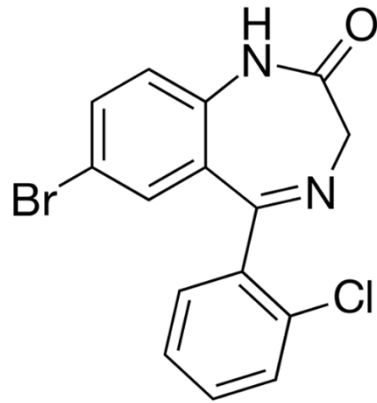
Dose: ?

Potenza analgesica: 160

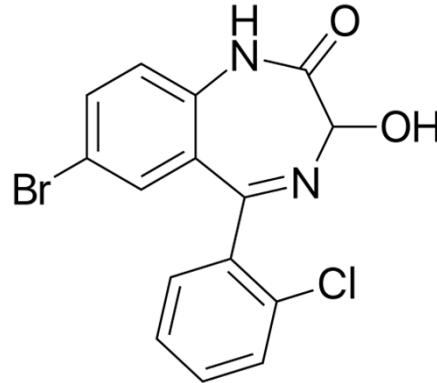
DEA Sounds Alarm on Elephant Tranquilizer Carfentanil (23.09.2016)

The US Drug Enforcement Agency (DEA) is warning the public and police nationwide about the risks of carfentanil, an analogue of the synthetic opioid analgesic fentanyl, which is 100 times more potent than fentanyl.

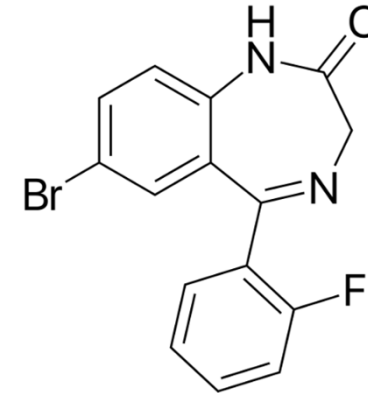
NEW BENZOS- NPS



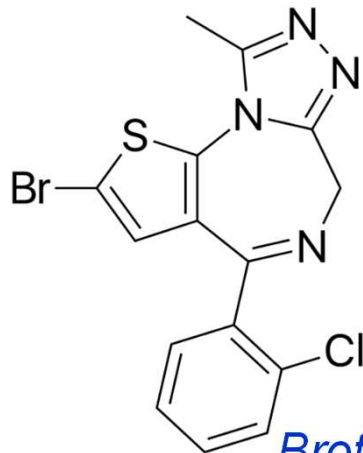
Phenazepam



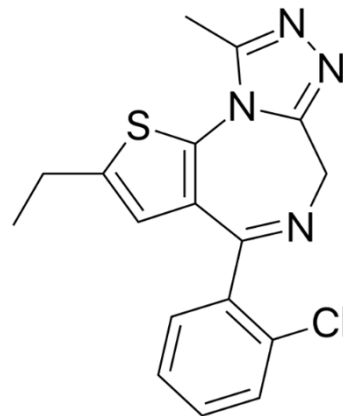
3-OH-Phenazepam



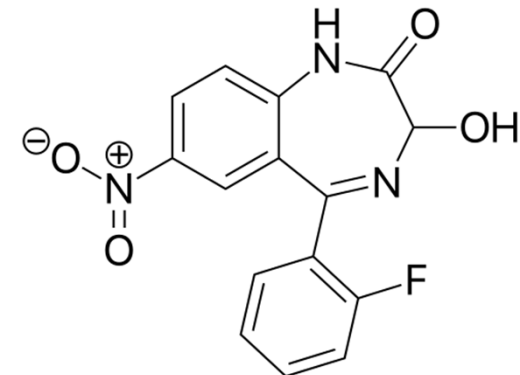
Flubromazepam



*Brotizolam
(Lendormin)*



*Etizolam
(Etilaam)*



*Nifoxipam
3-idrossi-desmetil-
flunitrazepam*

CANNABINOIDI SINTETICI

I cannabinoidi sintetici rappresentano una vasta famiglia di **molecole strutturalmente non correlate tra di loro ma funzionalmente simili al THC**, principio attivo della cannabis.

Individuati in diverse miscele di erbe da fumare o in incensi profumatori ambientali



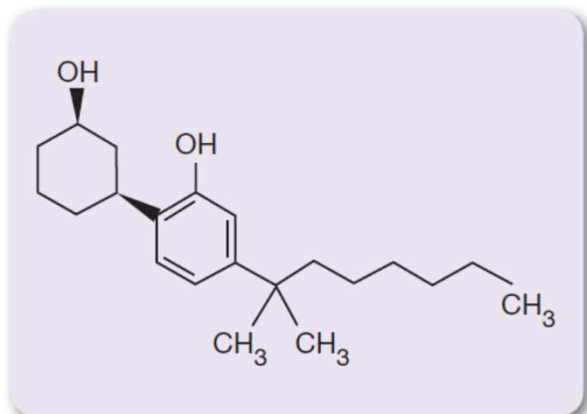
CANNABINOIDI SINTETICI

	Δ-9-THC	HU-210	CP 47, 497	JWH-018	JWH-073	JWH-398	JWH-250
Famiglia/ gruppo	Dibenzopirano naturale	Dibenzopirano (Cannabinoidi "classico")	Cicloesilfenolo	Naftoilindolo	Naftoilindolo	Naftoilindolo	Fenilacetilindolo/ benzoilindolo
Sottogruppo		Analogo del Δ9-THC		1-alchil-3- (1-naftoil) indolo	1-alchil-3- (1-naftoil) indolo	3-(4-alo-1- naftoil)indolo	1-pentil-3- fenilacetilindolo
Potenza e selettività	Riferimento. Agonista parziale del CB1	Agonista non-selettivo dei recettori CB1/CB2	Potente agonista selettivo dei recettori CB1	Agonista selettivo estremamente potente dei recettori CB2 (potente agonista anche dei CB1)	Potente agonista dei recettori CB1 (più debole agonista dei CB2)	Agonista non selettivo molto potente dei recettori CB1/CB2	Agonista selettivo dei recettori CB1 molto potente (agonista più debole dei recettori CB2)
Affinità di legame per CB1_Ki (nM)	10,2	0,06	9,54	9	8,9	2,3	11
Sintetizzato da	Origine naturale	R. Mechoulam	Industria farmaceutica	JW Huffman	JW Huffman	JW Huffman	JW Huffman

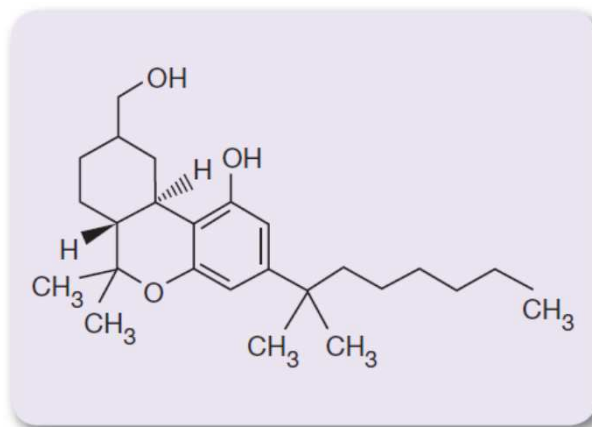
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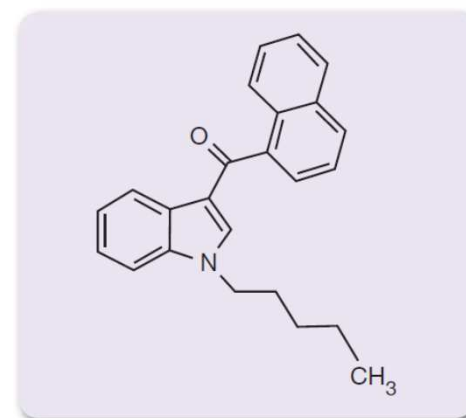
CANNABINOIDI SINTETICI CON ELEVATA AFFINITA` PER IL RECETTORE CB1



CP-47, 497



HU-210



JWH-18

GIOVANI – Caso 3 – Incidente

Uomo, 28 anni, automobilista

Risultati analisi quantitative (sangue)	
Analita	Concentrazione
Etilfenidato (II*)	51 µg/l (ter)
Alprazolam (II) OH-Alprazolam	25 µg/l (ter) 9.7 µg/l
Steroidi anabolizzanti (LAD Losanna)	Boldenone Nandrolone
Etanolo	1.10 g/l

The risk or severity of adverse effects can be increased when Ethanol is combined with Benzos and Methylphenidate.*



GIOVANI – Caso 4 - antibiotici

Donna, 22 anni, automobilista

Risultati analisi quantitative (sangue)

Analita	Concentrazione
THC	1.8 µg/l (1.2 -2.4) µg/l
OH-THC	0.73 µg/l
THC-COOH	5.0 µg/l
Sulfametossazolo, trimetoprim e paracetamolo	Conc. terapeutiche

GIOVANI – Caso 3 – Interazioni e farmacogenomica

SuperCYP

> Home
Results

Drug

- > Drug search
- > Drug-drug interaction
- > Chemotherapy
- > Neuro diseases
- > ATC tree

CYP

- > CYP-drug interaction
- > Polymorphism
- > Alignments
- > 3D structures
- > Browse

> Upload

- > Statistics
- > FAQs
- > Links
- > Contact

In this table you can see all cyps that are involved in the metabolism of your drug-cocktail. If two or more drugs are metabolized by the same CYP, the column is coloured yellow (2 drugs), orange (3 drugs) or red (4 and more drugs). The table gives alternatives for all chosen drugs and their metabolism based on their ATC-groups.

Legend

s = substrate, inh = inhibitor, ind = inducer

By clicking on the the drug you get information about it.

By clicking on the cyp you get information about it.

By clicking on a relation (s, inh or ind) you get the source.

Name	1A1	1A2	2A6	2A13	2C8	2C9	2C19	2D6	2E1	3A4	3A5	3A7	46A	excretion
Paracetamol	S	S	S		S	S		Ind S	S Ind	S Ind Inh	S Ind			
Sulphamethox					Inh	Inh S				Inh S				
Tetrahydroca	S		S			S	S							
Trimetoprim					S Inh	S Inh				S				
alternative drugs for Paracetamol	1A1	1A2	2A6	2A13	2C8	2C9	2C19	2D6	2E1	3A4	3A5	3A7	46A	excretion
Phenacetin	S	S	S	S		S	S	S	S	S			S	
alternative drugs for Sulphamethoxazole	1A1	1A2	2A6	2A13	2C8	2C9	2C19	2D6	2E1	3A4	3A5	3A7	46A	excretion
Sulfadiazine					S	Inh S			S	S				
Sulfamoxole						Inh								

Vi sono possibili interazioni metaboliche in grado di modificare le concentrazioni sanguigne e la durata di permanenza nell'organismo di queste sostanze.

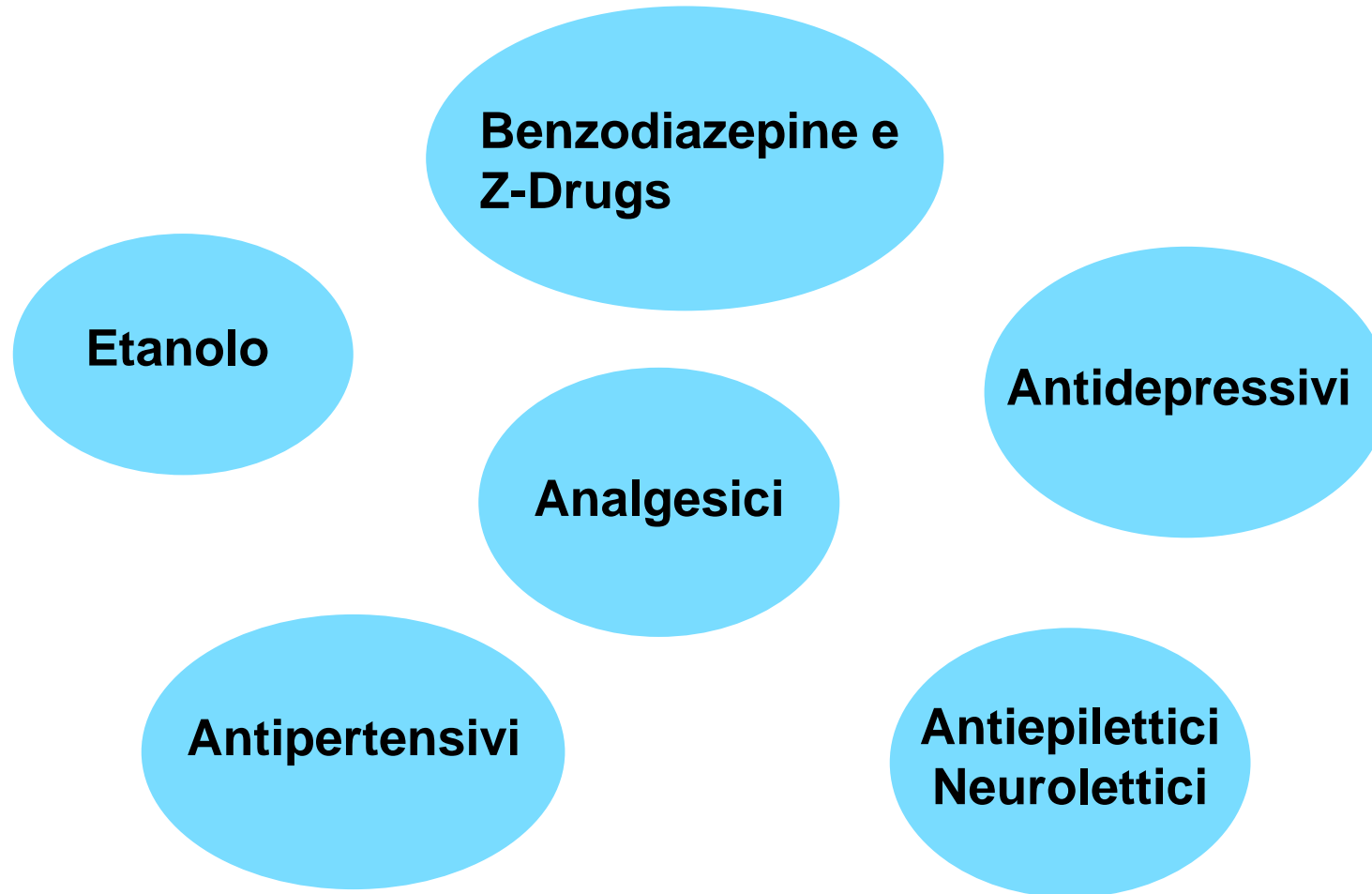
The serum concentration of THC can be increased when it is combined with Trimethoprim.

http://bioinformatics.charite.de/supercyp/index.php?site=get_drug_interaction

Analisi qualitative e quantitative

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MENO GIOVANI E GUIDA – SOSTANZE RILEVATE



MENO GIOVANI – Caso 1

Uomo, 44 anni, automobilista

Risultati analisi quantitative (sangue)	
Analita	Concentrazione
Cocaina	32 µg/l (22 -42) µg/l
THC	3.5 µg/l (2.4 – 4.6) µg/l
Lorazepam (II)	50 µg/l (ter.)
Sildenafil (I)	276 µg/l (ter.)

MENO GIOVANI – INTERAZIONI – Caso 1

SuperCYP

Results

In this table you can see all cyps that are involved in the metabolism of your drug-cocktail. If two or more drugs are metabolized by the same CYP, the column is coloured yellow (2 drugs), orange (3 drugs) or red (4 and more drugs). The table gives alternatives for all chosen drugs and their metabolism based on their ATC-groups.

Legend

s = substrate, inh = inhibitor, ind = inducer
 By clicking on the the drug you get information about it.
 By clicking on the cyp you get information about it.
 By clicking on a relation (s, inh or ind) you get the source.

Name	1A1	1A2	2A6	2A13	2B6	2C8	2C9	2C18	2C19	2D6	2E1	2J2	3A4	3A5	3A7	3A43	excretion	metabolism	P450
Cocaina	Ind	Ind	Ind	Ind		Inh	Inh		S	S Inh		Ind	Inh S Ind	Ind S	S				
Lorazepam																		X	
Sildenafil	Inh						S		S Inh	S Inh	Inh		Inh S	S	S				
Tetrahydroca	S		S				S		S										
alternative drugs for Cocaina	1A1	1A2	2A6	2A13	2B6	2C8	2C9	2C18	2C19	2D6	2E1	2J2	3A4	3A5	3A7	3A43	excretion	metabolism	P450
Lidocaine		Inh S	S		S	S	S	S		S Inh			S Inh	S	S				
Ambroxol													S Inh						
Benzocaine											Inh		Inh						
Lidocaine		Inh S	S		S	S	S	S		S Inh			S Inh	S	S				
Tetracaine																		X	
Procaine																	X		
Phenazone		S	S		S Inh	S	S	S	S Inh	S Inh	S		S Inh						

The serum concentration of THC can be increased when it is combined with Sildenafil

http://bioinformatics.charite.de/supercyp/index.php?site=get_drug_interaction

Analisi qualitative e quantitative

Istituto Alpino di Chimica e di Tossicologia

MENO GIOVANI – Caso 2

Uomo, 32 anni, automobilista

Risultati analisi quantitative (sangue)	
Analita	Concentrazione
Fluoxetina (II)	120 µg/l (ter.)
Alprazolam (II)	25 µg/l (ter.)
Etanolo	1.43 g/kg (1.36 – 1.50) g/kg

MENO GIOVANI – INTERAZIONI – Caso 2

Name	1A1	1A2	1B1	2A6	2B6	2C8	2C9	2C18	2C19	2D6	2E1	3A4	3A5	3A7	3A43	4A11	11A	19A	e
Alcohol (eth	Inh	S			Inh		Inh		Inh		Ind S Inh	Ind S Inh				Ind		Ind	
Alprazolam												S	S	S					
Fluoxetine		S Inh			S Inh	S Inh	S Inh		S Inh	S Inh	S	S Inh							
alternative																			

The risk or severity of adverse effects can be increased when Alprazolam is combined with Fluoxetine or Alcohol.

Effet sur l'aptitude à la conduite et l'utilisation de machines

Comme une somnolence et des vertiges ont été rapportés sous Fluctine, il convient d'être prudent lors de la conduite de véhicules ou lors de l'utilisation de machines jusqu'à ce que la réaction individuelle au médicament soit manifeste. La consommation simultanée d'alcool ou d'autres médicaments (voir «Interactions») entraîne une perturbation supplémentaire des capacités de réaction et des capacités psychomotrices. Il convient de rendre les patients attentifs à ce danger.

http://bioinformatics.charite.de/supercyp/index.php?site=get_drug_interaction

Analisi qualitative e quantitative

Istituto Alpino di Chimica e di Tossicologia

MENO GIOVANI – Caso 3

Uomo, 51 anni, ciclista

Risultati analisi quantitative (sangue)	
Analita	Concentrazione
Morfina	Intervento medico
Tramadolo (II)	280 µg/l (ter.)
Oxazepam (II)	460 µg/l (ter.)
Etanolo	1.21 g/kg (1.15 – 1.27) g/kg
Bisoprololo (I)	pos

MENO GIOVANI – INTERAZIONI – Caso 3

by clicking on a relation (s, inh or ind) you get the source.

Name	1A1	1A2	1B1	2A6	2B6	2C8	2C9	2C18	2C19	2D6	2E1	3A4	3A5	3A7	3A43	4A11	11A	19A	excretion	typ	P450
Alcohol	Inh	S			Inh		Inh		Inh		Ind S Inh	Ind S Inh				Ind		Ind			
Bisoprolol										S		S									
Oxazepam												S	S	S	S						
Tramadol					S					S Inh		Inh S									
alternative																					

Effet sur l'aptitude à la conduite et l'utilisation de machines

Même pris en respectant les recommandations, **Tramadol** Helvepharm peut diminuer les réactions (par ex. par somnolence et vertiges) des conducteurs de véhicules et des utilisateurs de machines. Cette considération s'applique en particulier en cas d'association avec d'alcool ou d'autres psychotropes.

Effet sur l'aptitude à la conduite et l'utilisation de machines

L'aptitude à la conduite ou à l'utilisation de machines peut être affectée par des réactions individuelles aux antihypertenseurs. **C'est tout particulièrement le cas en début de traitement ou lors d'un changement de médication, ainsi qu'avec l'action conjuguée de l'alcool.** Cependant, des recherches menées dans ce contexte ont montré qu'il n'y a pas lieu de redouter d'effet direct du β_1 -bloquant sélectif bisoprolol sur les capacités de réaction.

MENO GIOVANI – Caso 4

Donna, 35 anni, automobilista

Risultati analisi qualitative (screening di conferma)

Metadone e EDDP

Bromazepam

Risultati analisi quantitative (sangue)

Analita	Concentrazione
Metadone (II)	230 µg/l (ter.)
EDDP	36 µg/l
Bromazepam (II)	130 µg/l (ter.)
Etanolo	1.52 g/kg (1.44 – 1.60) g/kg

MENO GIOVANI – INTERAZIONI – Caso 4

Name	1A1	1A2	1B1	2A6	2B6	2C8	2C9	2C18	2C19	2D6	2E1	3A4	3A5	3A7	3A43	4A11	11A	19A	excretion	metab	P450
(+)-Methado		S			S	S	S	S	S	S Inh		S Inh Ind	S	S				S			
Alcohol	Inh	S			Inh		Inh		Inh		Ind S Inh	Ind S Inh				Ind		Ind			
Bromazepam		S							S		Inh	S									
alternative																					

Effet sur l'aptitude à la conduite et l'utilisation de machines

Kétalgine possède une influence marquée sur la capacité de conduire et le maniement de machines.

Les patients qui utilisent des machines et/ou qui conduisent un véhicule doivent être avisés du fait que la méthadone peut compromettre la vitesse de réaction.

MENO GIOVANI – Caso 5

Donna, 45 anni, automobilista

Risultati analisi quantitative (sangue)	
Analita	Concentrazione
THC	5.1 µg/l
Nordiazepam (II)	530 µg/l (ter.)
Oxazepam (II)	55 µg/l (ter.)
Escitalopram (II)	32 µg/l (ter.)
Trazodone	620 µg/l (ter.)
Metoclopramide (II)	pos
Ledipasvir, sofosbuvir	pos

MENO GIOVANI – INTERAZIONI – Caso 5

Name	1A1	1A2	1B1	2A6	2B6	2C8	2C9	2C18	2C19	2D6	2E1	3A4	3A5	3A7	3A43	11B1	11B2	17A	excl
Escitalopram									S	S Inh		S							
Metocloprami										S Inh						Inh	Ind	Inh	
Nordiazepam									S			S							
Oxazepam												S	S	S	S				
Tetrahydroca	S			S			S		S										
Trazodone										S		S	S	S					

Escitalopram may increase the serotonergic activities of Trazodone.

The risk or severity of adverse effects can be increased when nordiazepam, oxazepam, escitalopram, trazodone, metoclopramide are combined.

ANZIANI E GUIDA – SOSTANZE RILEVATE

Etanolo

**Benzodiazepine e
Z-Drugs**

Antidepressivi

Analgesici

**Antipertensivi
Antiarritmici**

Antiaggreganti

Antidiabetici

ANZIANI – Caso 1 – Incidente con esito fatale

Uomo, 75 anni, automobilista

Risultati analisi quantitative (sangue)	
Analita	Concentrazione
Tramadolo (II)	2100 µg/l (tox/let.)
N-desmetil-tramadolo	460 µg/l
O-desmetil-tramadolo	670 µg/l
MAA*	9 mg/l (ter.)
Lorazepam	1.5 µg/l (< ter.)

*active metabolite of metamizole: 4-methyl-amino-antipyrine

Effet sur l'aptitude à la conduite et l'utilisation de machines
Ce médicament (Novalgin) peut affecter les réactions, l'aptitude à la conduite et l'aptitude à utiliser des outils ou des machines!

ANZIANI – Caso 2 – Incidente con esito fatale

Uomo, 67 anni, automobilista

Risultati analisi quantitative (sangue)	
Analita	Concentrazione
Metformina	17 mg/L (ter. sup.)
Nordiazepam (II)	710 µg/l (ter sup.)
Oxazepam (II)	76 µg/l (< ter.)
Zolpidem (III)	7.4 µg/l (< ter.)
Acido salicilico	pos

ANZIANI – Caso 2 – Incidente con esito fatale

Name	1A1	1A2	1B1	2B6	2C8	2C9	2C18	2C19	2D6	2E1	3A4	3A5	3A7	3A43	excre
Acetylsalicy					S	S		Ind							
Metformin											Inh				
Nordazepam								S			S				
Oxazepam											S	S	S	S	
Zolpidem		S Inh				S Inh		S	Inh S		S	S	S		

L'acido acetilsalicilico può incrementare le attività ipoglicemiche della metformina.

Il rischio o la severità degli effetti indesiderati possono essere aumentati quando lo zolpidem è associato a nordiazepam e oxazepam.

ANZIANI – Caso 3 – Incidente ore 08:30

Donna, 78 anni, automobilista

Risultati analisi quantitative (sangue)

Analita	Concentrazione
Zolpidem (III)	95 µg/l (ter inf.)
Lorazepam (II)	22 µg/l (ter inf.)
Ondansetron	pos

ANZIANI – Caso 3 – Esempio tratto da NHTSA Report

Multiple Medications and Vehicle Crashes: Analysis of Databases

Patient ID: 5702AAAAAACBMGK,

Date	Type	Code	D
01/06/2001	DIAG	25000	D
01/06/2001	DIAG	27800	O
01/06/2001	DIAG	4019	U
01/06/2001	DIAG	41090	A
01/06/2001	DIAG	4111	I
01/06/2001	DIAG	78650	U
01/06/2001	DIAG	78651	P
01/06/2001	DIAG	78701	N
01/22/2001	DRUG	00378020801	
01/22/2001	DRUG	59762372704	
01/23/2001	DRUG	00005321943	
01/29/2001	DRUG	00378034505	
01/29/2001	DRUG	00378104901	
01/30/2001	DIAG	25000	D
01/30/2001	DIAG	78050	U
02/01/2001	DRUG	00087607005	
02/03/2001	DRUG	00069306075	
02/03/2001	DRUG	00258365401	
02/06/2001	DRUG	00002314460	
02/08/2001	DIAG	4660	A
02/08/2001	CPT4	99213	
02/09/2001	DRUG	00026851251	
02/10/2001	DRUG	61570007201	
02/17/2001	DRUG	00085045803	
02/19/2001	DRUG	61570007201	

66 YO FEMALE WITH A HX OF DM I
 GLYBURIDE, DOXEPIN, FUROSEMIDE
 THE DOXEPIN AND FUROSEMIDE AFF
 BENZONATATE, AND DOXEPIN INTER
 MAY CAUSE EXCESSIVE HYPOGLYCEM
 DIABETIC PATIENTS. DOXEPIN HAS
 PATIENTS. DIAZEPAM IS A LONG-A
 AND INCREASE THE RISK OF FALLS

02/20/2001	DIAG	E8199	M
02/20/2001	DIAG	7231	C
02/20/2001	DIAG	8470	S
02/20/2001	DIAG	8470	S
02/20/2001	DRUG	00406035705	
02/20/2001	DRUG	52544080601	

Final Report



Rx	Days Supply
FUROSEMIDE	
GLYBURIDE	
ATENOLOL	
DIAZEPAM	
DOXEPIN HCL	
METFORMIN HCL	
AZITHROMYCIN	
BENZONATATE	
NIZATIDINE	
CIPROFLOXACIN HCL	
ESTROGENS, ESTERIFIED	
LORATADINE	
ESTROGENS, ESTERIFIED	
OROCODONE BIT/ACETAMINOPHEN	
METHOCARBAMOL	

TEST RAPIDI SU URINA



Analisi qualitative e quantitative

Istituto Alpino di Chimica e di Tossicologia

SCREENING URINARIO

Test	Vantaggi	Svantaggi
POCT	Tempo di risposta rapido	Sensibilità limitata
	Risultato immediato per una classe di sostanze	Specificità limitata Non identifica sostanze e metaboliti specifici Lettura soggettiva Falsi positivi / negativi
	Portatili	Costo elevato
Test immunologici in laboratorio	Automatici >numero test disponibili Rapidi «Poco costosi»	Sensibilità e specificità limitate Falsi positivi / negativi
Laboratorio Tecniche cromatografiche GC-MS LC-MS/MS LC-QTOF-MS	Specifici e sensibili Grande numero di sostanze e metaboliti rilevati	Più costoso Risultati non immediati Operatori specializzati Disponibilità limitata

TEST RAPIDI E TEST IMMUNOLOGICI – LIMITI – FALSI NEGATIVI

Test negativo : significato ?

Il paziente non ha assunto il farmaco/sostanza

Il paziente non ha assunto il farmaco/sostanza in modo corretto
(↓ frequenza; ↓ dose)

Variabili farmacocinetiche alterate

✓ farmaco/sostanza non assorbita

✓ metabolismo/eliminazione alterati

Urina diluita / alterata / sostituita

Il test non è adeguato (cross-reactivity) per il farmaco/sostanza di interesse

Errore di laboratorio

La sostanza/farmaco è presente ma sotto il valore soglia (cut-off)
→ **falso negativo**

TEST RAPIDI E TEST IMMUNOLOGICI – VALORI CUT-OFF

Classe/sostanza	Cut-off Test immunologici	Cut-off LC-MS/MS
Amfetamine	300/500/1000 ng eq d-amfetamina/ml	200 ng/ml
Metamfetamina	300/500/1000 ng eq d-metamfetamina/ml	200 ng/ml
MDMA	500 eq d,l-MDMA/ml	200 ng/ml
Barbiturici	300 ng eq secobarbital/ml	300 ng/ml
Benzodiazepine	100/200/300 eq oxazepam/ml	50 ng/ml
Buprenorfina	10 eq buprenorfina/ml	5 ng/ml
Cocaina	150/300 ng eq benzoilecgonina/ml	100 ng/ml
Metadone	300 ng eq metadone	100 ng/ml
Oppiacei	300/2000 ng eq morfina/ml	50 ng/ml
6-MAM	10 ng eq 6-MAM/ml	10 ng/ml
THC	50/150 ng eq THC-COOH/ml	15 ng/ml
Tramadol	100 ng eq cis-tramadol/ml	50 ng/ml
ETG	100/200/300/500 eq ETG/ml	100 ng/ml

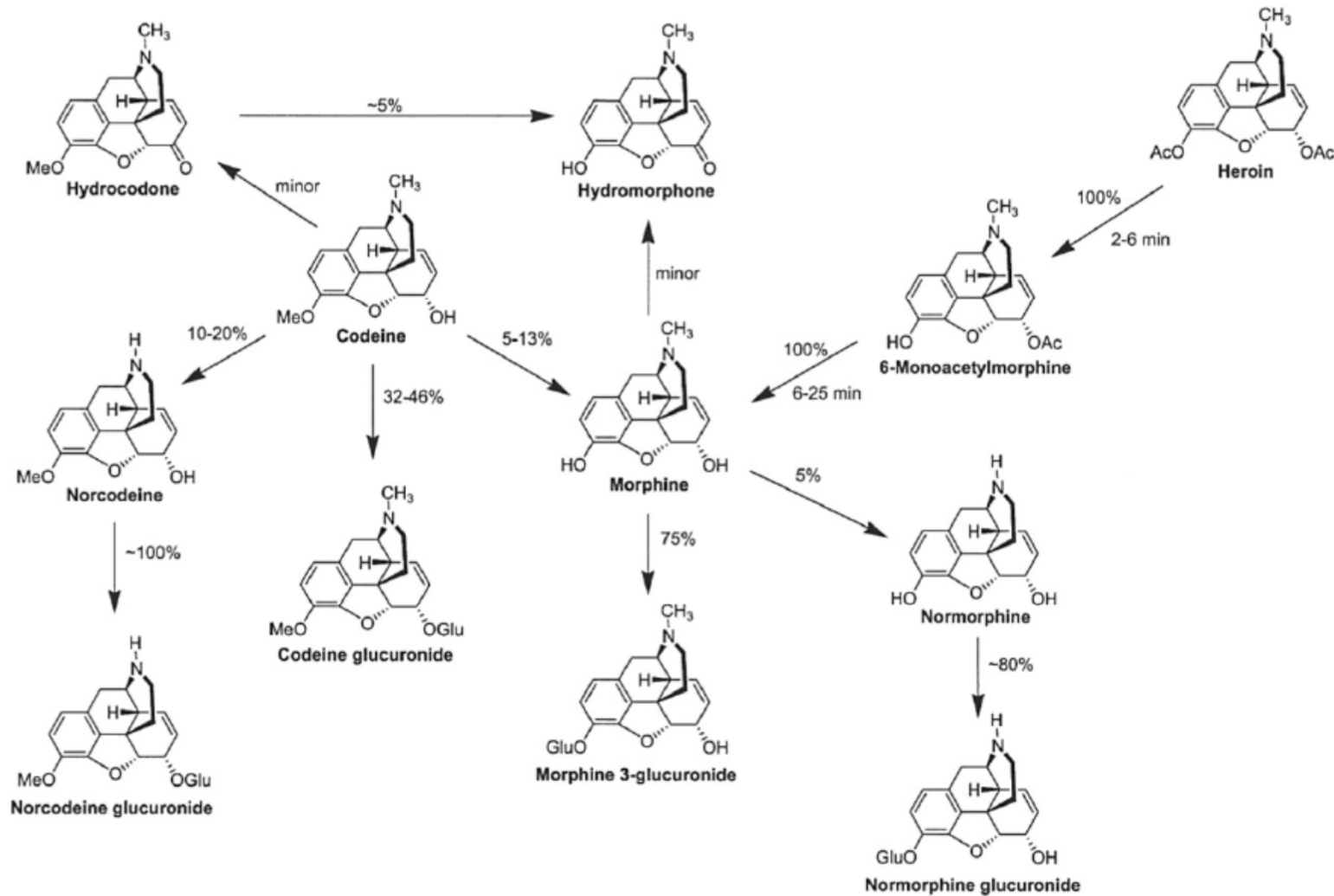
TEST RAPIDI E TEST IMMUNOLOGICI – ES OPPIACEI

Limitations of Immunoassays

Drug	Immunoassay	Immunoassay cutoff	LC-MS/MS cutoff	Samples missed
Codeine	Opiates	300 ng/mL	50 ng/mL	~30%
Hydrocodone				~23%
Hydromorphone				~69%
Morphine				~12%
Oxycodone	Oxycodone	100 ng/mL	50 ng/mL	~5%
Oxymorphone				~10%
Alprazolam (alpha-hydroxyalprazolam)	Benzodiazepine	200 ng/mL	20 ng/mL	~53%
Lorazepam			40 ng/mL	~18%

Mikel C et al., LC-MS/MS Extends the Range of Drug Analysis in Pain Patients, *Ther Drug Monit* 2009; 31(6) 746-748

OPPIACEI - METABOLISMO



Pesce A. et al. Interpretation of Urine Drug Testing in Pain Patients, Pain Medicine 2012;13:868-885

FINESTRA DI RILEVABILITÀ NELL'URINA – LEGATA AL VALORE SOGLIA (CUT-OFF)

Sostanze/Famiglia di sostanze	Finestra di rilevabilità nell'urina
Anfetamina	2-4 g
Metanfetamina	2 g
MDMA (ecstasy, XTC)	1,5-2 g
Barbiturici	1g / 2-3 g / 7 + g
Benzodiazepine	12h / 1g / 2-3 g / 7 o + g
Cannabinoidi	3 g / 30 g / 80 g
Cocaina	6-8h / 2-4 g / fino a 8 g
Metadone	7-9 g
Oppiacei	1-3 g
6-monoacetilmorfina	2-4 h
Morfina/eroina	2-3 g
Codeina	2-3 g

TEST RAPIDI E TEST IMMUNOLOGICI – LIMITI – FALSI POSITIVI

Test positivo : significato ?

Il paziente ha assunto il farmaco/sostanza come prescritto

Il paziente ha aggiunto il farmaco/sostanza nell'urina

Il paziente ha assunto una dose prima della raccolta
(compliance parziale)

Il paziente ha assunto un'altra sostanza che ha una reazione
crociata (cross-reaction) con il test

Errore di laboratorio

Risultato **falso-positivo**

TEST RAPIDI E TEST IMMUNOLOGICI – LIMITI – FALSI POSITIVI 1

Classe	Sostanze interferenti (cross-reacting drugs)
Amfetamine	Amantadina, bupropione, clorpromazina, ranitidina, desipramina, fluoxetina, labetalolo, metilfenidato, fentermina, fenilefedrina, fenilpropanolamina, metformina, ofloxacina, prometazina, pseudoefedrina, trazodone (m-CPP), trimipramina
Antidepressivi triciclici	Carbamazepina, difenidramina, idrossizina, quetiapina, ibuprofene
Barbiturici	Ibuprofene, naprossene
Benzodiazepine	Sertralina, EFV
Cannabinoidi	Dronabinol, EFV, ibuprofene, naprossene, inibitori pompa protoni
Cocaina	Foglie di coca, anestetici topici contenenti cocaina
LSD	Ambroxol, amitriptilina, bupropione, buspirone, clopromazina, desipramina, fluoxetina, aloperidolo, imipramina, labetalolo, metoclopramide, risperidone, sertralina, trazodone, verapamil, ergotamina, metilfenidato, fentanyl

TEST RAPIDI E TEST IMMUNOLOGICI – LIMITI – FALSI POSITIVI 2

Classe	Sostanze interferenti (cross-reacting drugs)
Metadone	Clorpromazina, clomipramina, difenidramina, ibuprofene, quetiapina, verapamil
Oppiacei	Amisulpride, destrometorfano, difenidramina, fluoroquinoloni, levofloxacin, oxfloxacin, naloxone, olio/semi di papavero, quetiapina, chinino, rifampicina, tapentadolo, tramadolo, verapamil

Moeller et al., Urine Drug Screening: Practical Guide for Clinicians, Mayo Clin Proc 2008; 83(1): 66-76

Saitman A et al., False-Positive Interferences of Common Urine Drug Screen Immunoassays: A Review, Journal of Analytical Toxicology 2014;38:387-396

Pawlowski J et al., Urine drug screens: When might a test result be false-positive? Current Psychiatry 2015;14(10):17-24

Brahm NC et al., Commonly prescribed medications and potential false-positive urine drug screens, Am J Health Syst Pharm 2010; 67:1344-1350

Zanjani BR, False positive and False negative Results in Urine drug screening tests: tampering methods and specimen integrity tests, PharmacologyOnline 2014;1:102-108.

LABORATORIO DI CHIMICA E TOSSICOLOGIA (2007)



Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

USTRA
dal 2010/2012



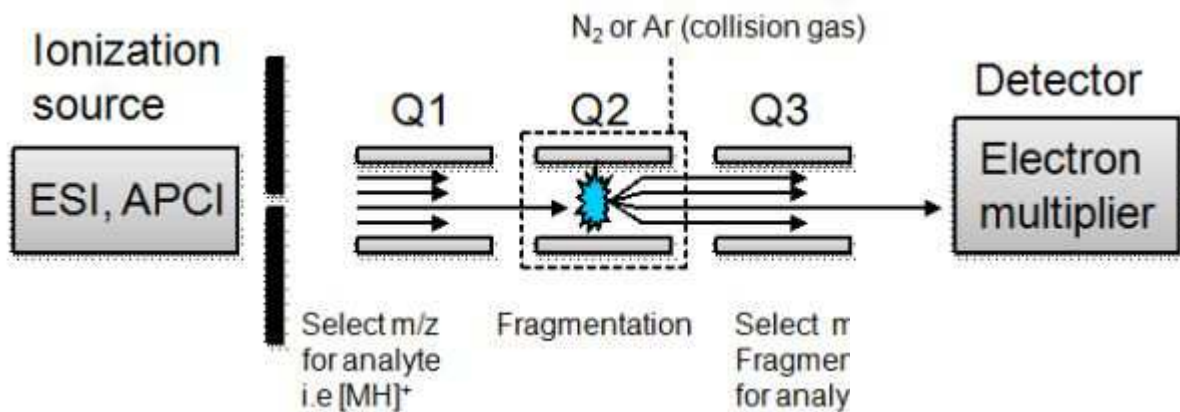
ISO/IEC 17025
STS 563
dal 2011

Analisi qualitative e quantitative

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TECNICHE CROMATOGRAFICHE ULTIMA GENERAZIONE

HPLC-MS/MS



Analisi qualitative e quantitative

$\mu\text{g/l}$; \rightarrow fg

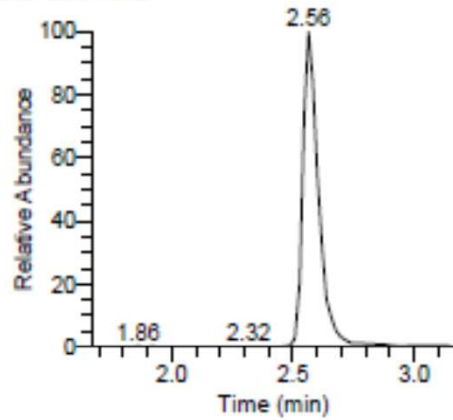


Analisi qualitative e quantitative

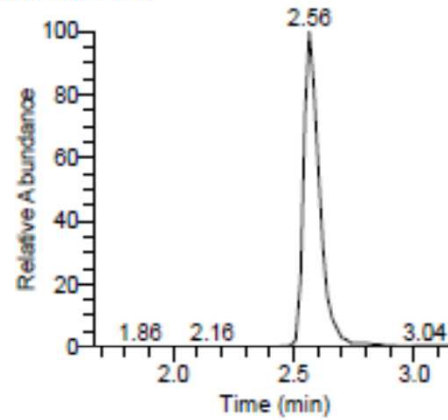
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HPLC-MS/MS: esempio cocaina e metaboliti

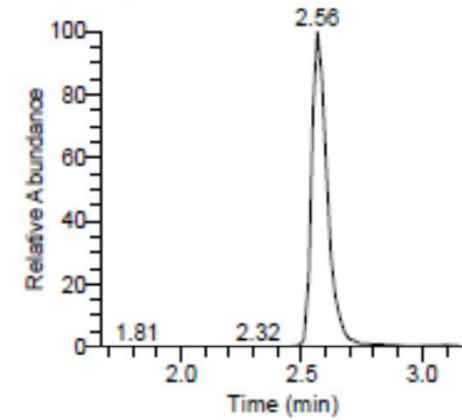
RT: 1.67 - 3.17



RT: 1.67 - 3.17

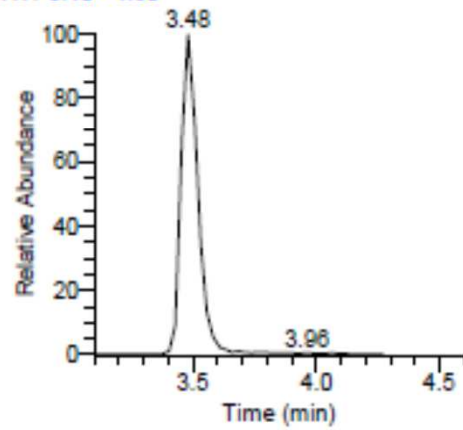


RT: 1.67 - 3.17

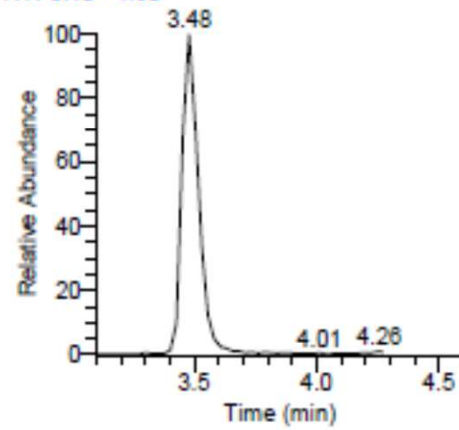


Benzoyllecgonine

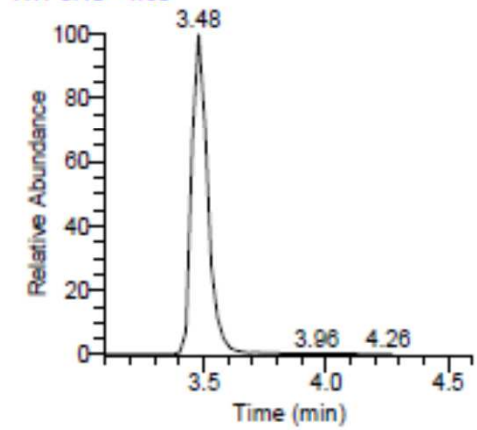
RT: 3.10 - 4.60



RT: 3.10 - 4.60



RT: 3.10 - 4.60



Cocaethylene

TECNICHE CROMATOGRAFICHE ULTIMA GENERAZIONE

LC-Q-TOF MS/MS

Analisi di massa ad alta risoluzione

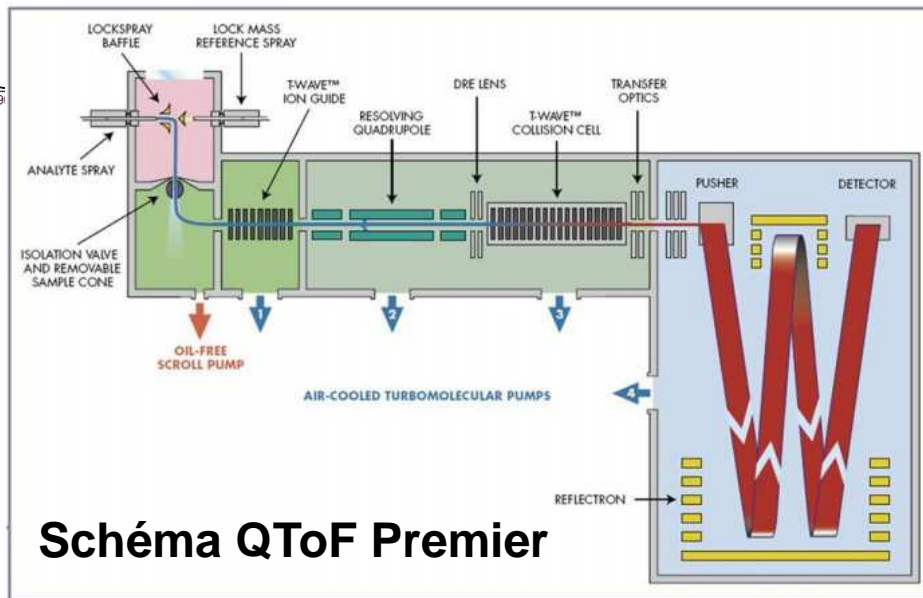
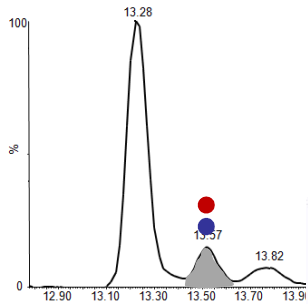
Analisi qualitative e quantitative

NPS & Neuroenhancers

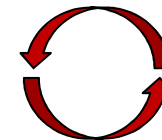
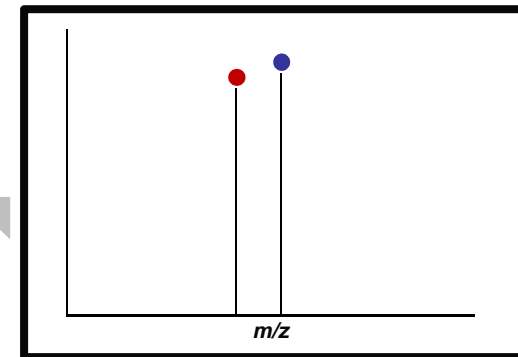
Nuove sostanze / nuovi metaboliti



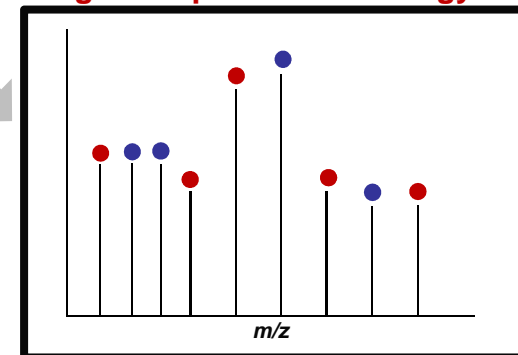
Analisi UHPLC-QTOF-MS^E



Low Collision Energy



High/Ramp Collision Energy

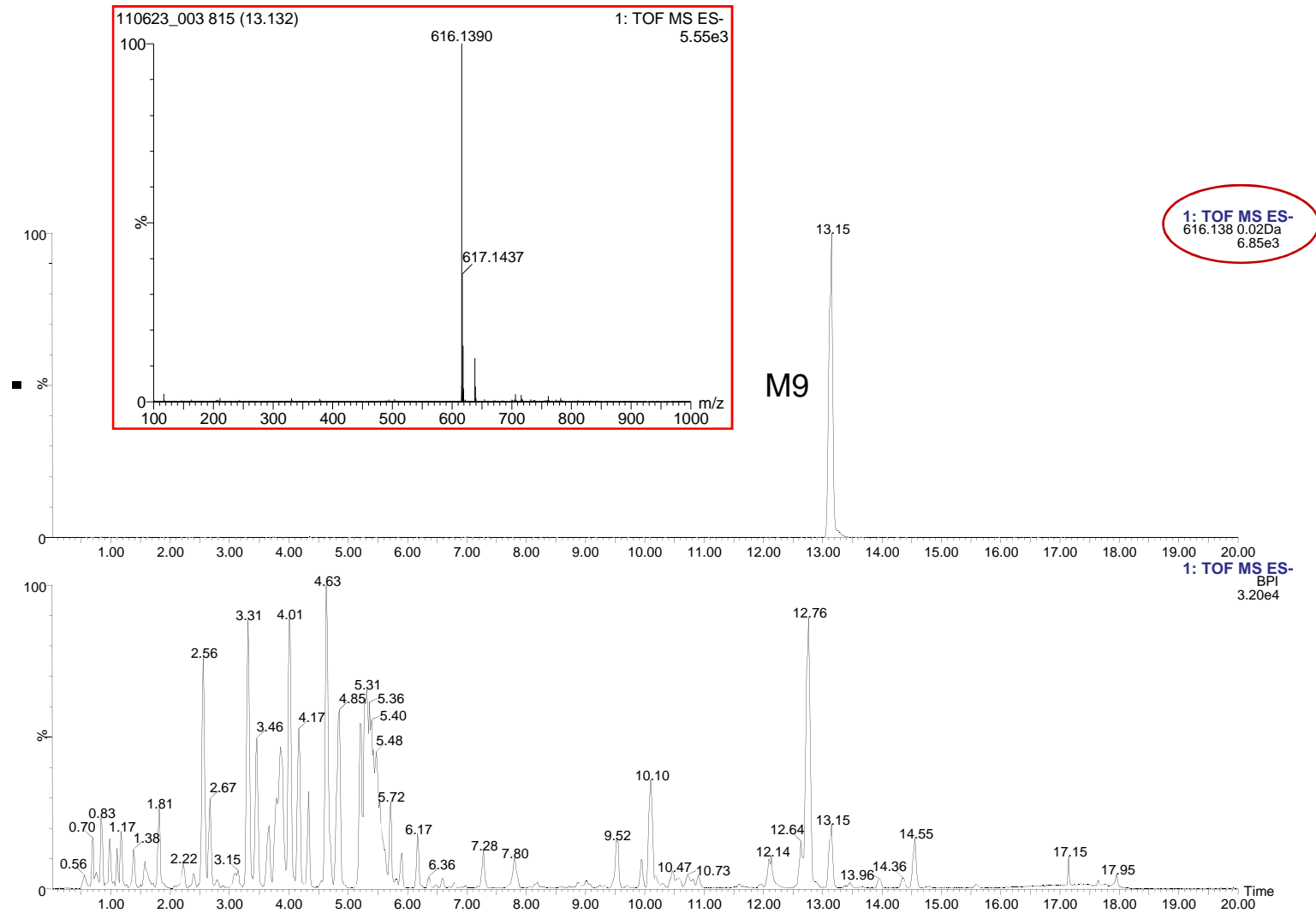


Plumb et al., *Rapid Commun. Mass Spectrom.*, 2006, 20:1989-1994

Analisi qualitative e quantitative

Istituto Alpino di Chimica e di Tossicologia

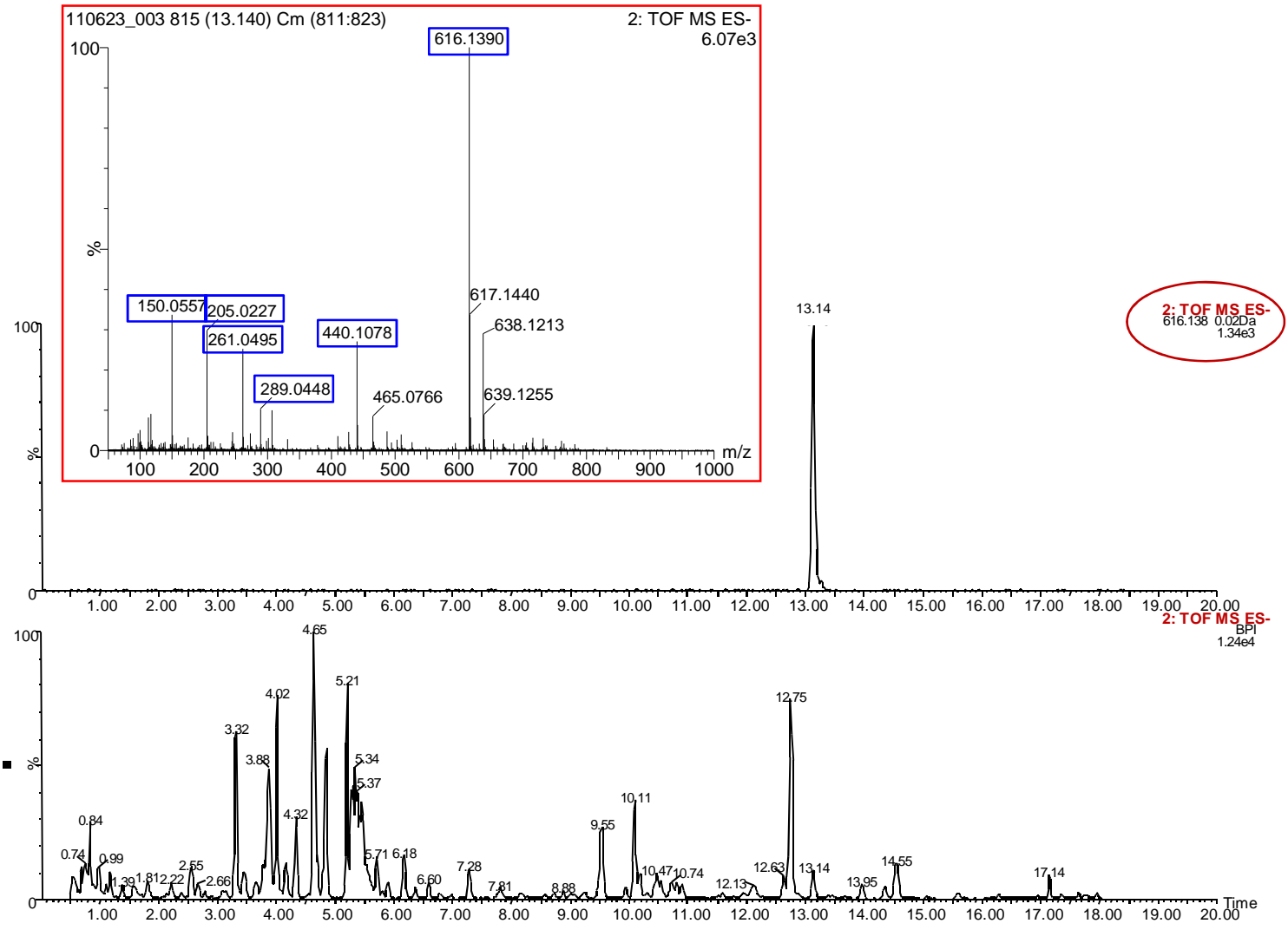
Esempio M9: Funzione 1 (5eV)



Analisi qualitative e quantitative

Istituto Alpino di Chimica e di Tossicologia

Esempio M9: Funzione 2 (ramp 5-40eV)



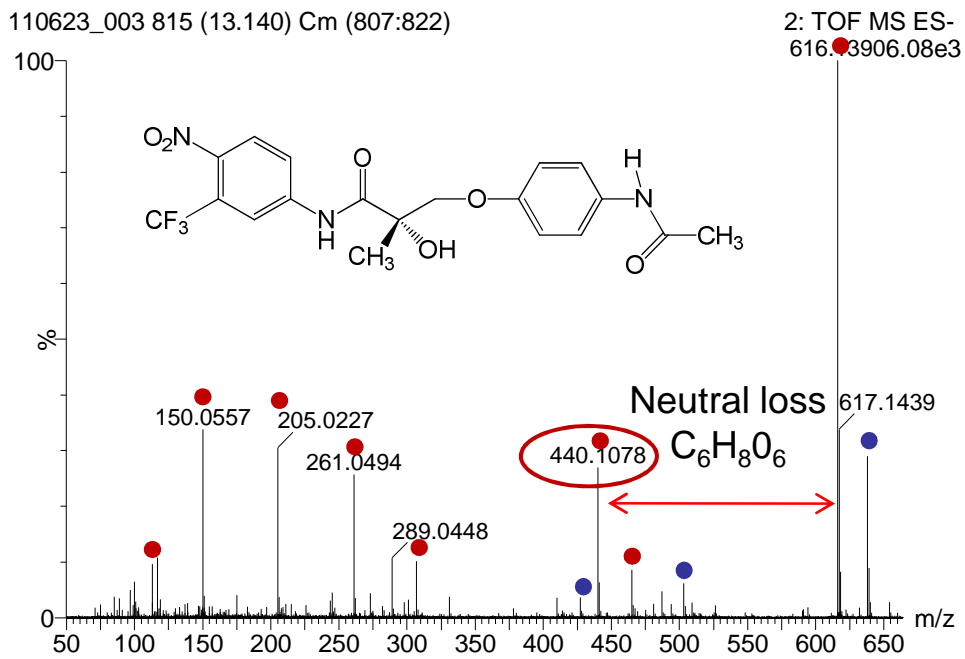
Analisi qualitative e quantitative

Istituto Alpino di Chimica e di Tossicologia

Spettri di frammentazione

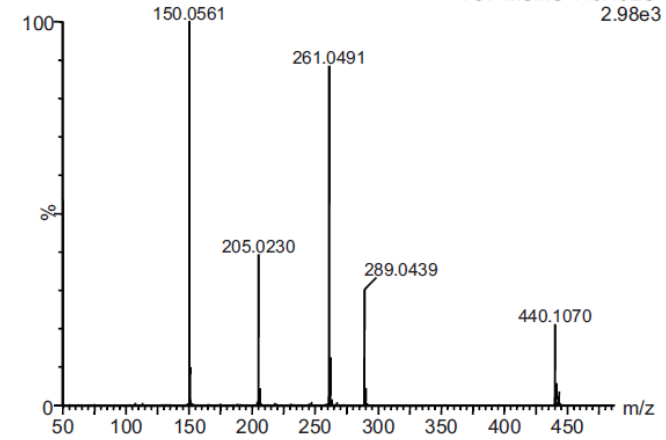
Spettrale MS^E

110623_003 815 (13.140) Cm (807:822)



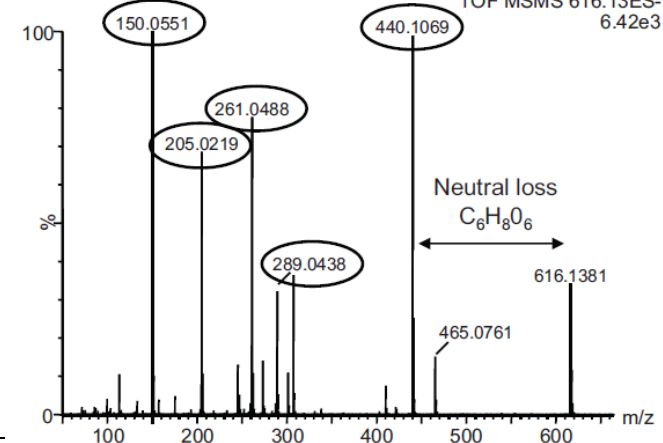
Spettrale MS/MS SARM-S4

TOF MSMS 440.10ES-2.98e3

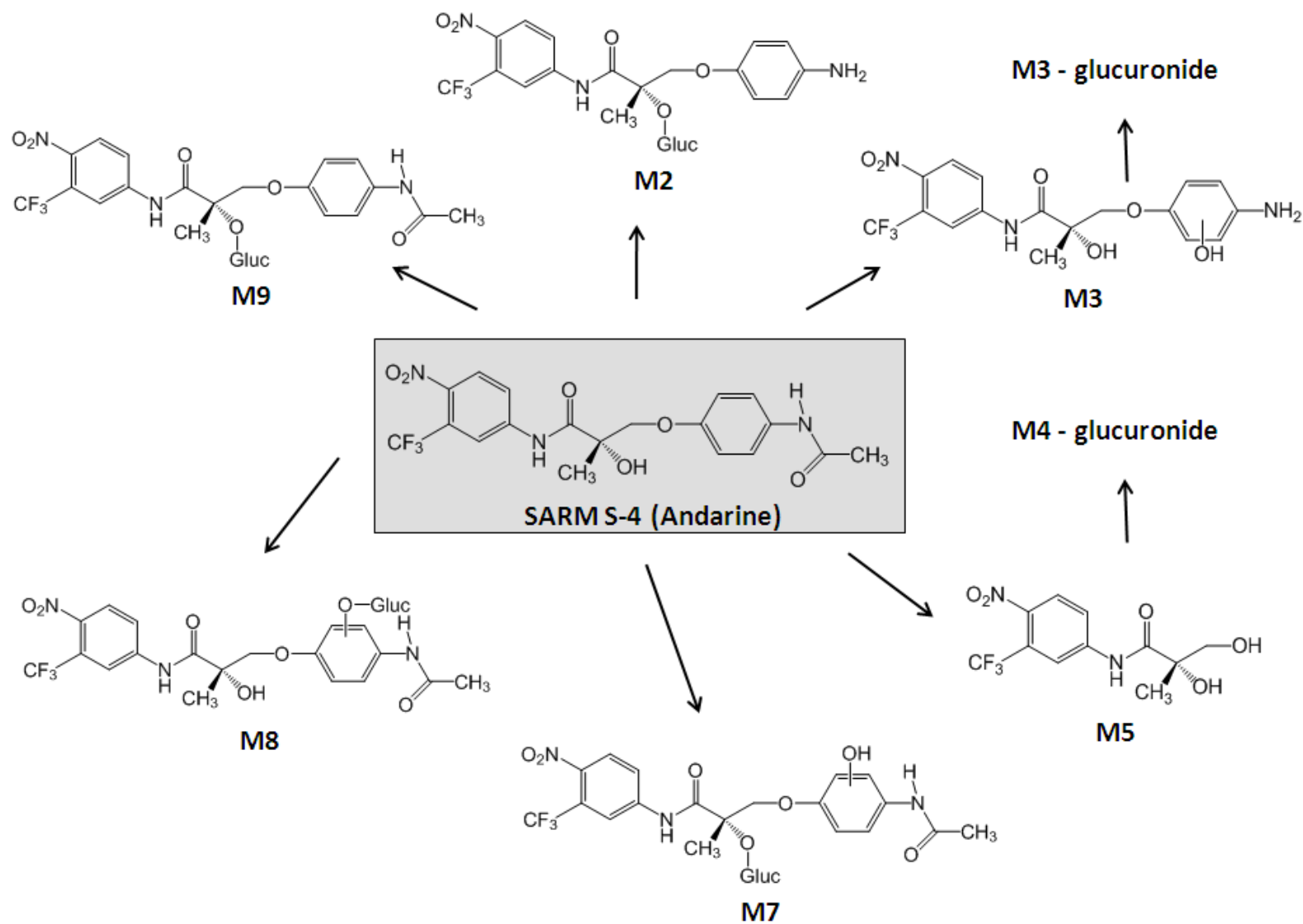


Spettrale MS/MS M9

TOF MSMS 616.13ES-6.42e3



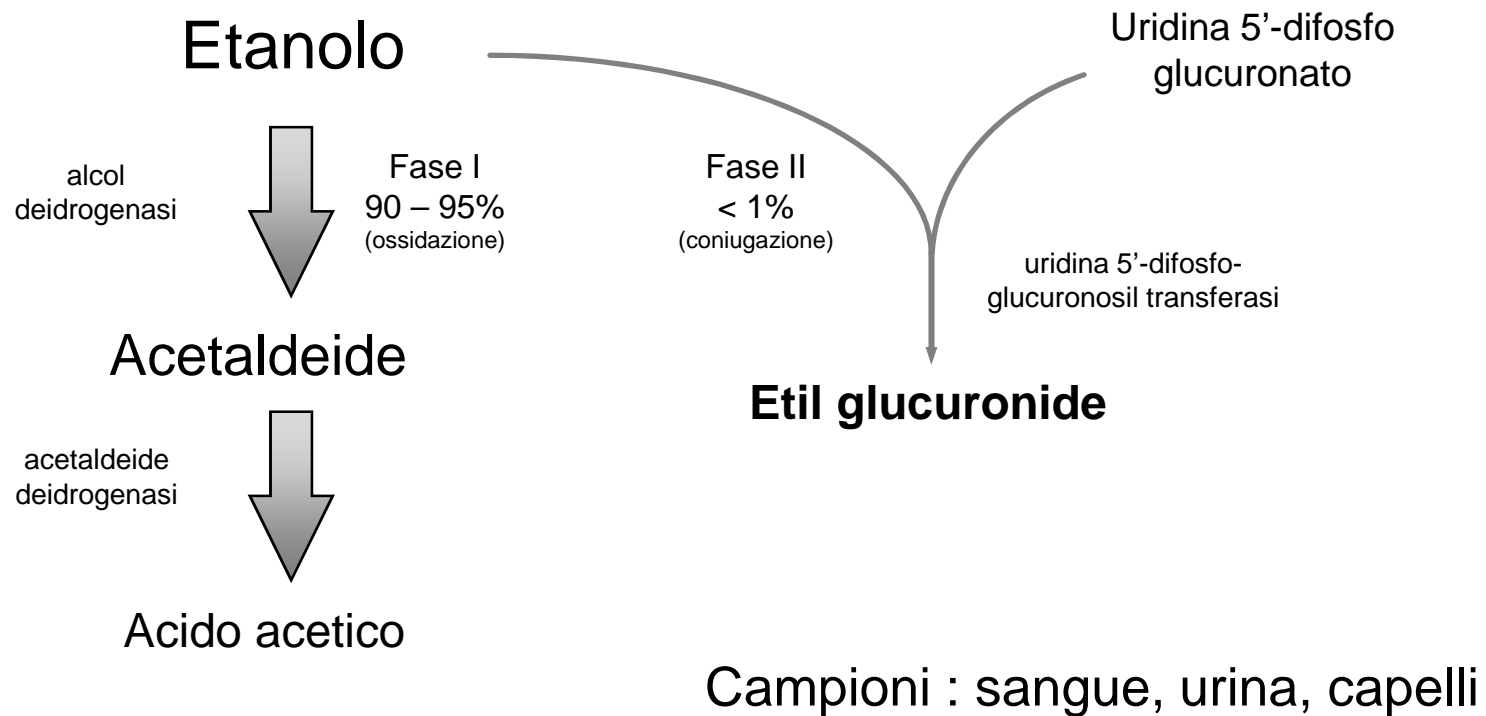
Metaboliti messi in evidenza



Grata E. et al., SARM-S4 and metabolites detection in sports drug testing: A case report, Forensic Science International 213(2011)104-108.

ETILGLUCURONIDE - ETG

L'etilglucuronide (EtG) come marcatore dell'abuso di alcol

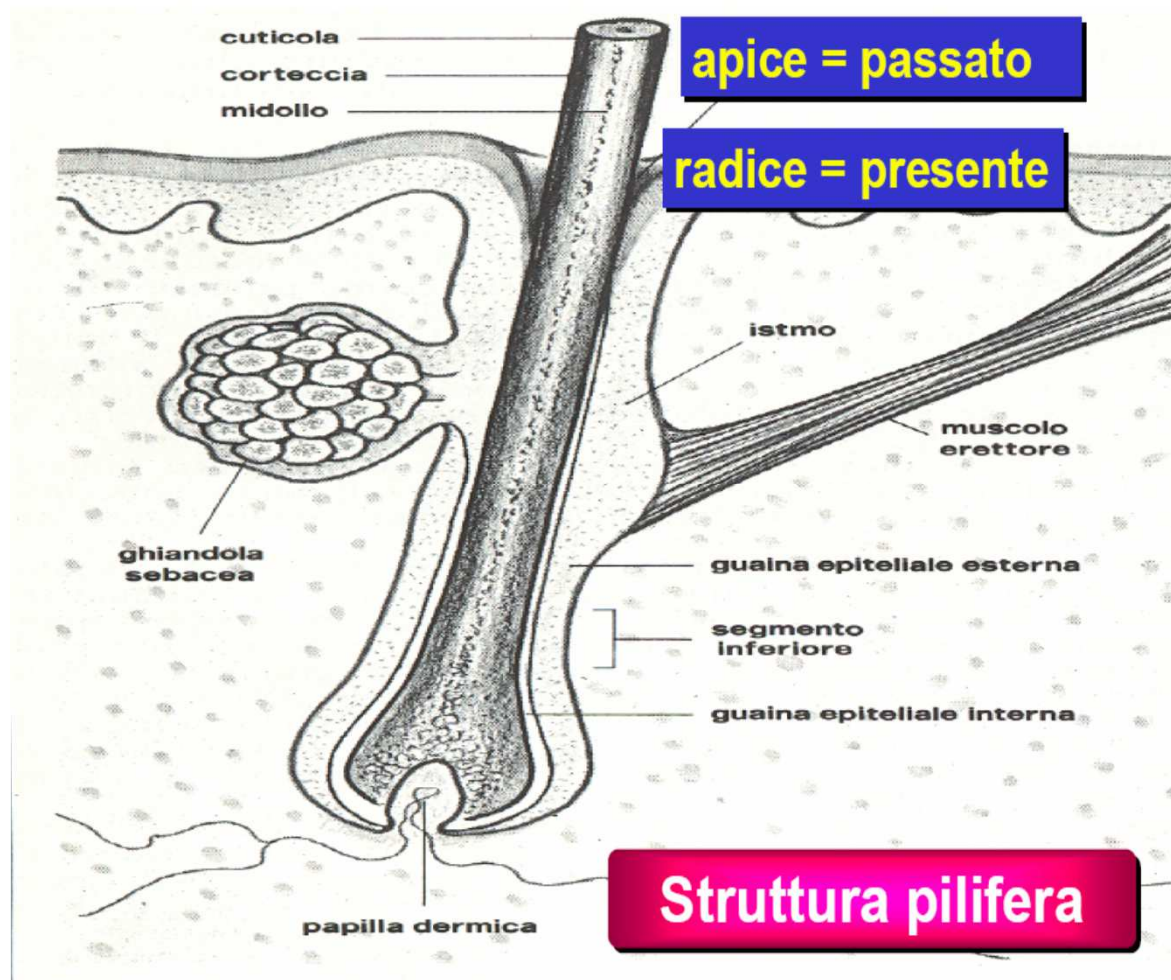


ANALISI DELLA MATRICE CHERATINICA

- **Morti correlate all'uso di farmaci, sostanze d'abuso o sostanze tossiche**
- **Valutazione dell'idoneità alla guida**
- **Verifica dell'astinenza da etanolo, sostanze d'abuso o farmaci (es: trapianto)**
- **Responsabilità criminale**
- **Affidamento, custodia di minori**
- **Esposizione prenatale a farmaci, sostanze d'abuso o sostanze tossiche**

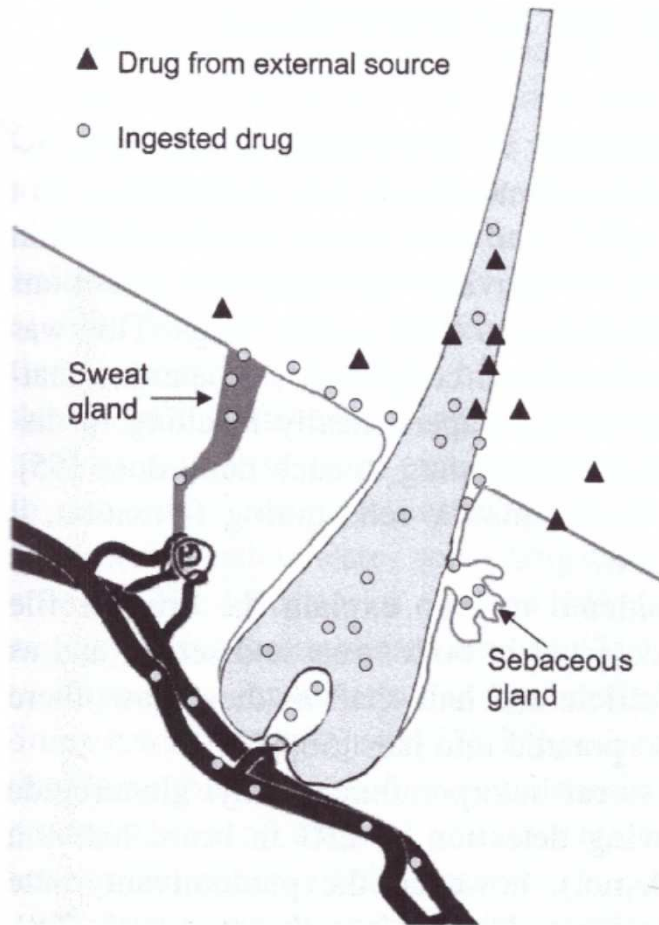


STRUTTURA DEL FOLLICOLO PILIFERO



Struttura pilifera

INCORPORAZIONE SOSTANZE NEL CAPELLO/PELO



Etilglucuronide

**Valore soglia per un
consumo eccessivo di
etanolo: 30 pg/mg**

[1] Schweizerische Gesellschaft für Rechtsmedizin (SGRM), Bestimmung von Ethylglucuronid (EtG) in Haarproben, Arbeitsgruppe Haaranalytik, 01.09.2014.

[2] Schweizerische Gesellschaft für Rechtsmedizin (SGRM), Bestimmung von Drogen und Medikamenten in Haarproben, Arbeitsgruppe Haaranalytik, 27.01.2010.

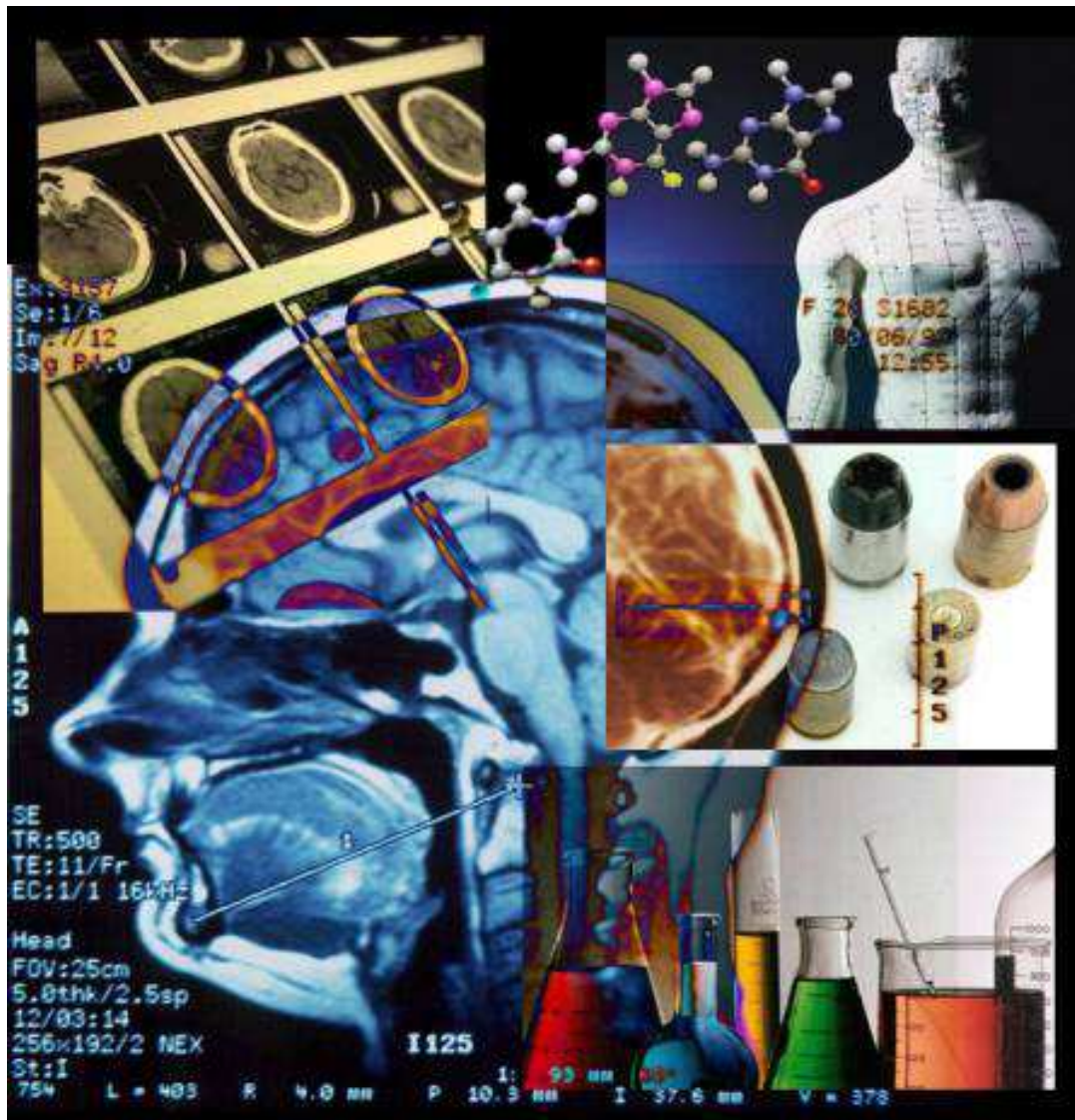
RIASSUMENDO...

- **Giovanissimi: cannabis (+ etanolo)**
- **Giovani: etanolo, cannabis, cocaina**
- **Policonsumo (benzodiazepine, antidepressivi)**
- **Nuove tendenze : NPS e neuro-enhancer e nuove forme di assunzione (es: THC patches; preparazioni orali)**
- **Etanolo in combinazione con numerose altre sostanze psicoattive (sostanze stupefacenti o farmaci): a tutte le età**
- **Interazione fra sostanze / farmacogenomica**
- **Foglietto illustrativo ? Avviso di cautela da parte del medico ?**

RIASSUMENDO...

- **Test urinari rapidi: risultato immediato per alcune classi di sostanze; valore indicativo**
- **Falsi negativi / falsi positivi**
- **Test di conferma (screening LC-MS/MS): specifici e sensibili; grande numero di sostanze e metaboliti rilevati; risposta non immediata; più costosi**
- **Analisi del capello: utile per la messa in evidenza del consumo/abuso di etanolo; del consumo di sostanze stupefacenti/farmaci**

Grazie per l'attenzione !



Istituto alpino di chimica
e di tossicologia (IACT)
CH-6718 Olivone
Tel. 091 872 21 68
Fax 091 872 21 69
iact@fasv.ch
maria.teresa.pinorini@fasv.ch

Analisi qualitative e quantitative

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