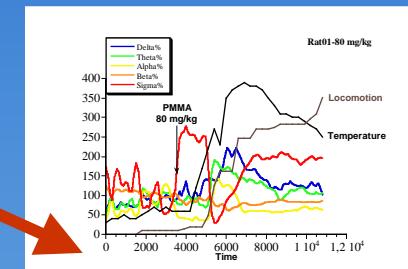




# From the clinical to the experimental data

Dependence  
Toxicology  
Evaluation



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Centre Evaluation Information Pharmacodépendance Grenoble

# Interest : Diagnosis and Prevention

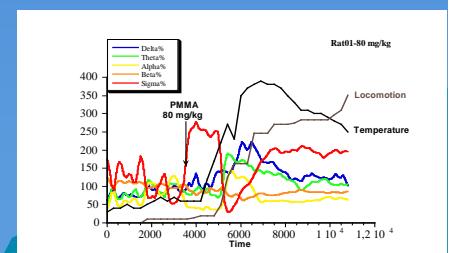
## ◆ Hyperthermia ?

- ambiant t° ?
- dance ?
- clothes ?



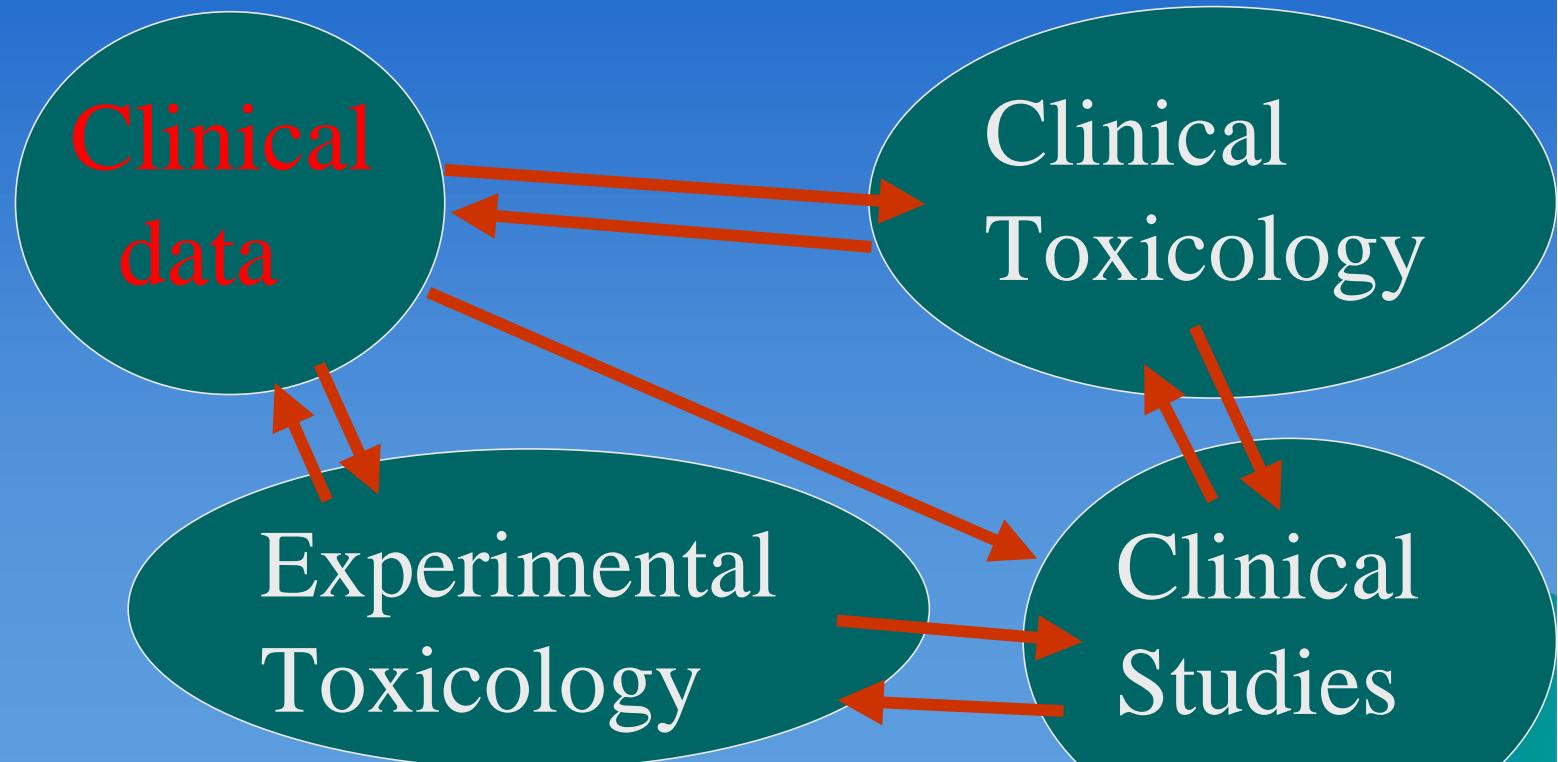
## ◆ Seizures ?

- hyperthermia ?
- hyponatraemia ?
- serotonin syndrome ?
- toxic effect ?





# New clinical facts need some more Toxicology in case of drug dependence

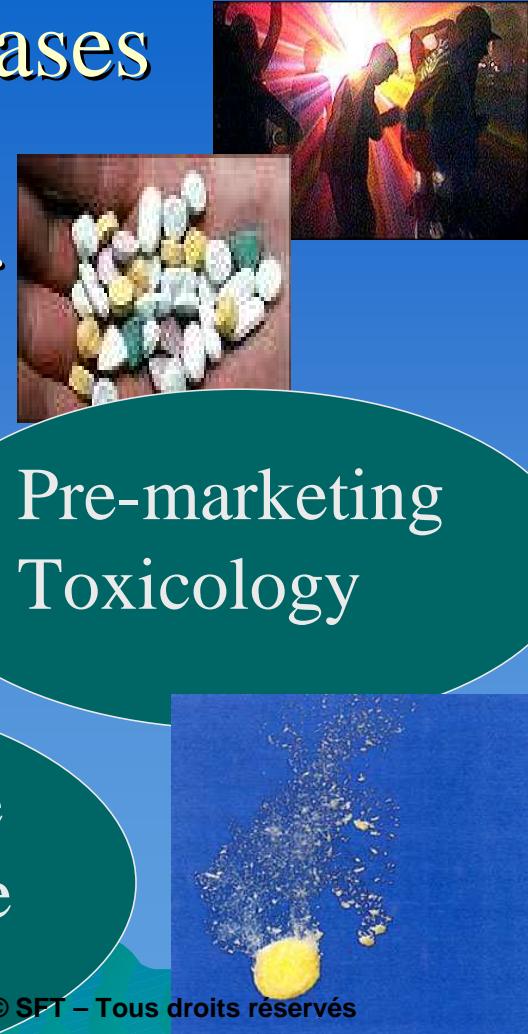


# Interests of toxicology before and after abuse / dependence cases

- ◆ New «syndromes» or behaviours : chemical submission, « raves »,..
- ◆ Consequences of toxic effects
- ◆ Drug dependence
- ◆ Specific aspects of abuse
- ◆ Risk management plans  
(minimisation)

Illicit drug use consequences

Medicine abuse and dependence consequences



Pre-marketing Toxicology

# 1 Analysis and synthesis of substance

## ◆ Abuse, toxic case reports



AFRICAPHYTO INTERNATIONAL



Tabernanthe  
Iboga

prix au détail : 4 euros/gramme	Pas de minimum
prix en gros : Nous contacter	Minimum de 1 kg

## ◆ Analysis of the «responsible» substance :

ibogaine, ketamine, cannabis and sand..

Cristallography ?

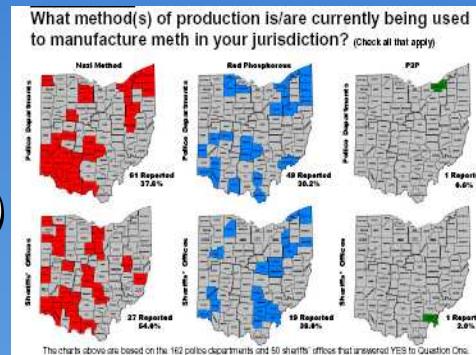
SINTES  
(OFDT, CEIP,...)

# 1 Analysis and synthesis of substance

- ◆ Synthesis of a pure substance (time consuming) :

Ex. : 2 – CI in CEIP Grenoble

- ◆ Which synthesis ?  
Which precursors ?  
(ex.: methamphetamine)



- ◆ There is a great need of synthesis of pure substances with cooperation of European authorised laboratories

## 2 Samples of new «designer» drugs

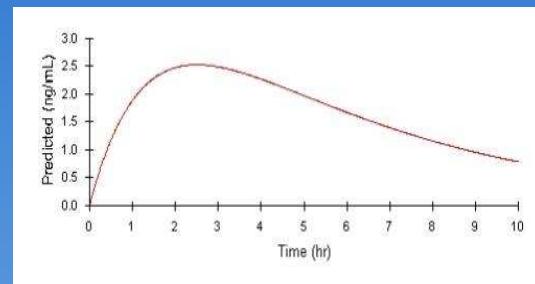
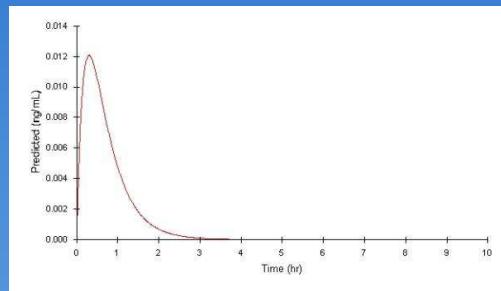
- ◆ «We can't find things we don't know ! »
- ◆ Do all the analytical toxicological laboratories have the necessary drug samples ?
- ◆ There is a need of samples of pure «designer» drugs in European authorised laboratories



### 3. Kinetics and dynamics of drugs



- ◆ Diversion of long acting drugs ?  
Intravenous injection of long acting oral morphine ?



- ◆ Synthesis of high risk drugs from marketed drugs ?  
Comparison with cristallography
- ◆ Diversion with association of 2 marketed drugs

### 3. Kinetics and dynamics of drugs



- ◆ Forearm «Popeye syndrome»

Toxic venous effects of :

- maize starch ?
- magnesium stearate ?

- ◆ Snorted Suboxone case reports in USA :  
does naloxone cross nasal mucosal barrier?

### 3. Kinetics and dynamics of drugs



- ◆ Delayed serotonin syndrome with 4-MTA  
(4 methylthioamphetamine)
  - delayed absorption ?
  - interindividual differences ?
  - synaptic serotonin release
- ◆ Serotonin syndrome in Rats
- ◆ Risk of serotonin syndrome (no effects, 30 minutes after the first 4-MTA tablet : increase of doses)

### 3. Kinetics and dynamics of drugs

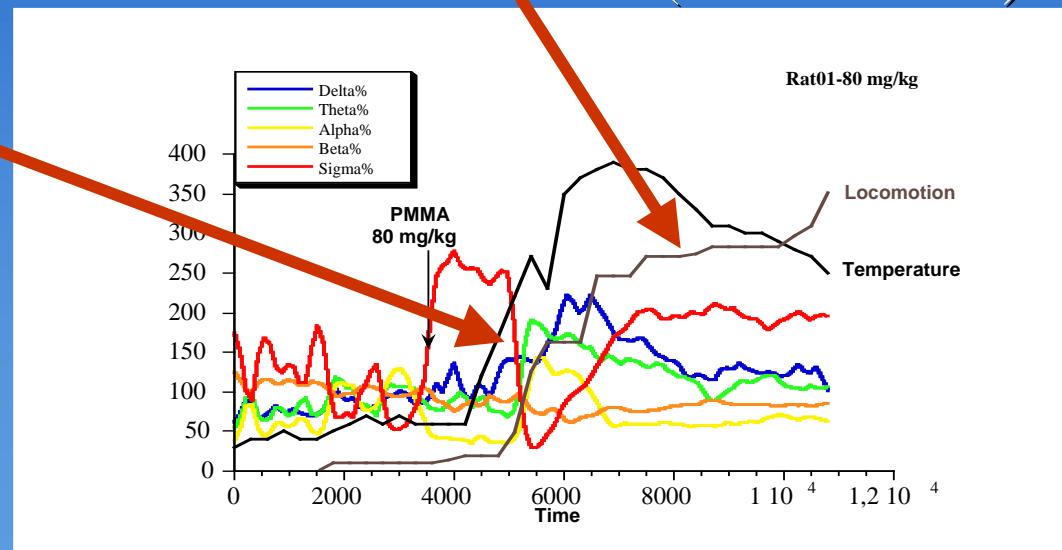


- ◆ Prevention of chemical submission may need colouring and / or bitter substances associated with the marketed drug
- ◆ **Kinetics, toxicological studies are necessary**



## 4. 1 Toxicological studies in order to explain clinical syndromes : **hyperthermia**

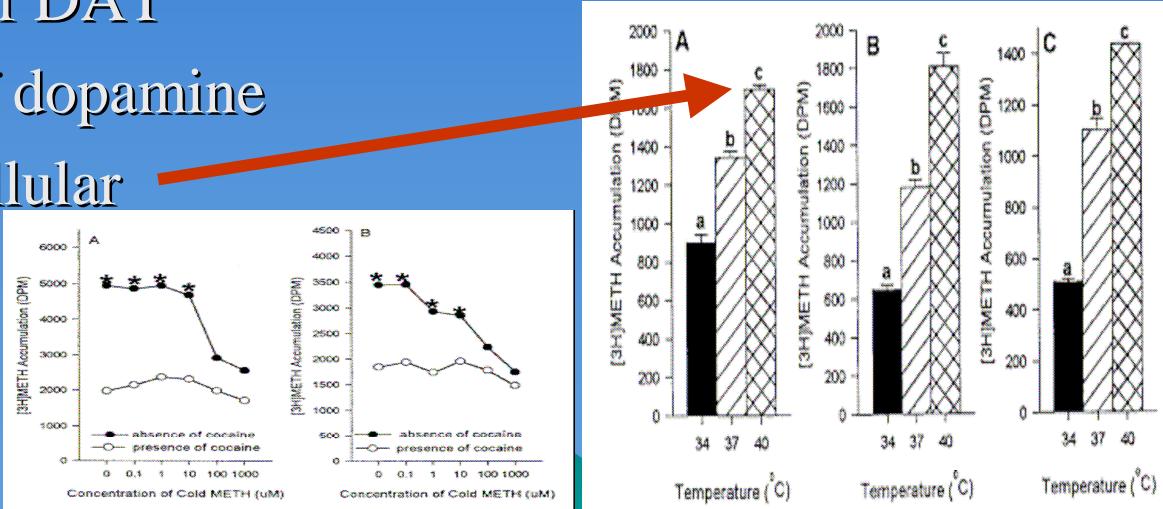
- ◆ It is not due to long time dancing (« exercise »!) !  
Hyperthermia before increase of locomotion (rats/ PMMA)



- ◆ Central effect ; sensitivity to room temperature

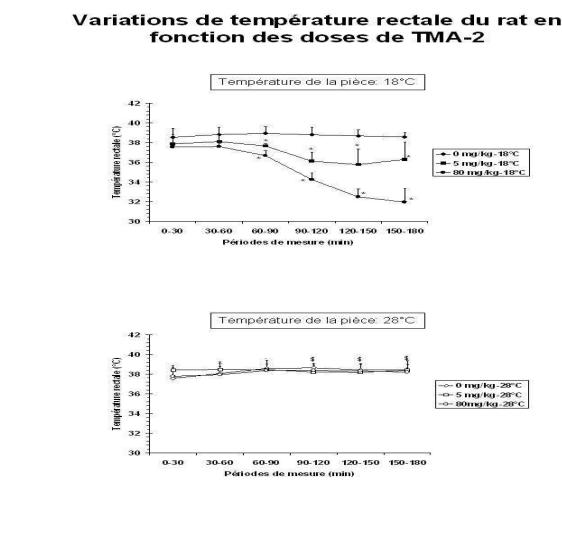
## 4.1 hyperthermia and acute consequences (methamphetamine; Xie, 2000)

- ◆ Ambient temperature : 22°C / 6°C
- ◆ Ambient temperature : 22°C ; meth. induces hyperthermia
- ◆ When core t° is 40°C :
  - increased activity of DAT
  - increased uptake of dopamine
  - accumulation of cellular methamphetamine



## 4.2 hypothermia and toxic consequences (TMA-2 ; methamphetamine; Xie, 2000)

- ◆ Low ambient temperature
  - TMA-2 induces Rat hypothermia
  - methamphetamine “ ” ”
- ◆ Core hypothermia decreases methamphetamine dopaminergic neurotoxicity ( decreased methamphetamine accumulation)
- ◆ Risk of severe hypothermia in case of low ambient t°

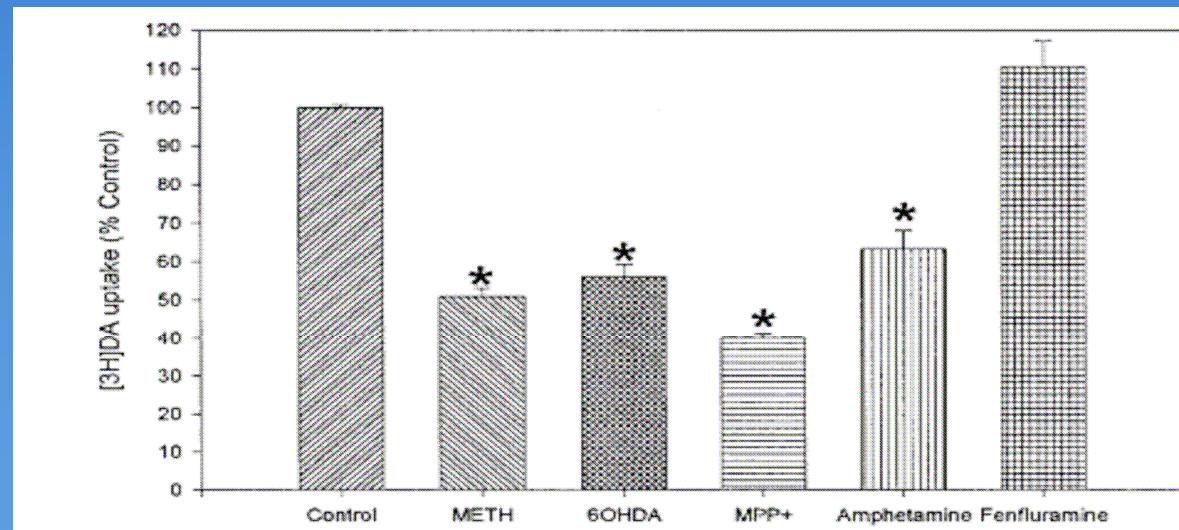


## 4.1 Acute consequences (methamphetamine *in vitro*; Saejong, 2000)

- ◆ Methamphetamine dopamine nerve terminal toxicity

Rat striatal synaptosomes : decreased DA uptake

MPP+ > Meth > 6OHDA > Amph > Fenfluramine



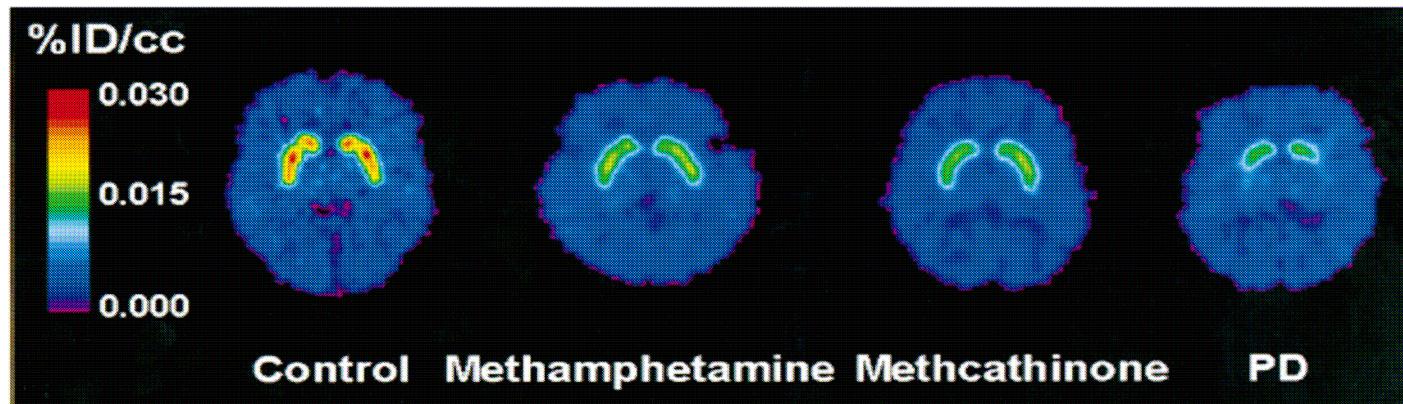
## 4.1 Consequences of methamphetamine and methcathinone

- ◆ ↓ binding potential of  $[^{13}\text{C}] \text{WIN}-35,428$

Caudate and putamen  
in abstinent meth  
Methcath patients

Table 3. Binding potentials of  $[^{11}\text{C}]\text{WIN}-35,428$  in the caudate nucleus and putamen of control subjects, abstinent methamphetamine users, abstinent methcathinone users, and Parkinson's disease patients

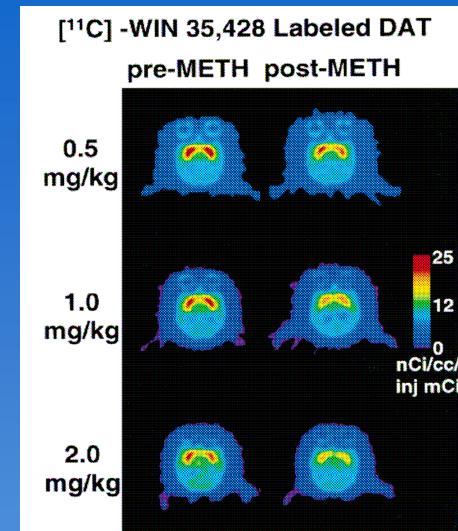
	<i>n</i>	Caudate nucleus ( $k_3k_4$ )	Putamen ( $k_3k_4$ )
Control	10	$7.5 \pm 1.7$ ( $8.7 \pm 1.6$ )	$7.3 \pm 1.4$ ( $8.3 \pm 1.4$ )
Methamphetamine	6	$5.8 \pm 1.0^*$ ( $7.0 \pm 1.2$ ) <sup>*</sup>	$5.5 \pm 0.9^*$ ( $6.7 \pm 0.9$ ) <sup>*</sup>
Methcathinone	4	$5.7 \pm 0.9^*$ ( $6.7 \pm 1.3$ ) <sup>*</sup>	$6.1 \pm 0.4^*$ ( $7.1 \pm 0.6$ )
Parkinson's disease	3	$4.0 \pm 0.9^*$ ( $5.4 \pm 1.2$ ) <sup>*</sup>	$2.3 \pm 0.4^{**}$ ( $3.1 \pm 0.6$ ) <sup>**</sup>



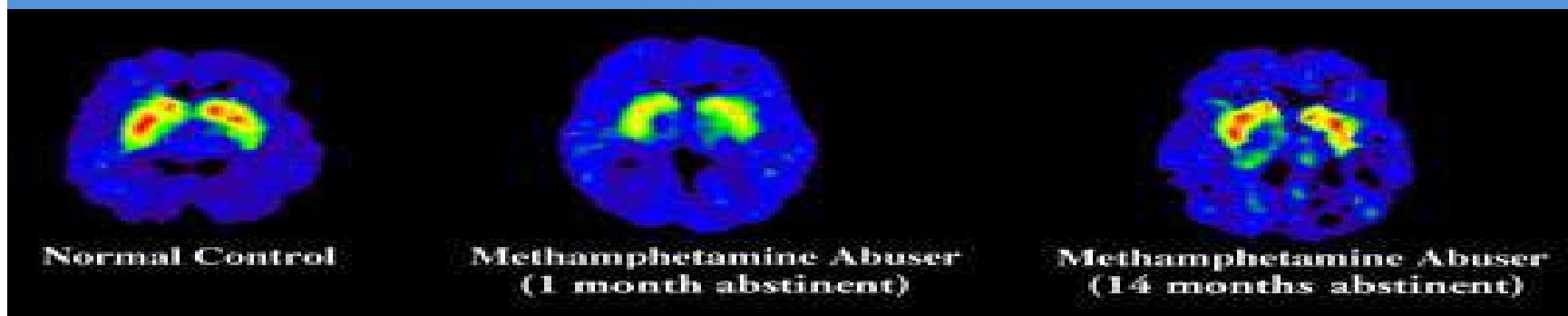
## 4.1 Methamphetamine : acute and long term effects

- ◆ Decreased DAT and DA axonal markers

Baboons (Villemagne, 1998)



- ◆ Humans : functionnal « recovery » after 14 months abstinence

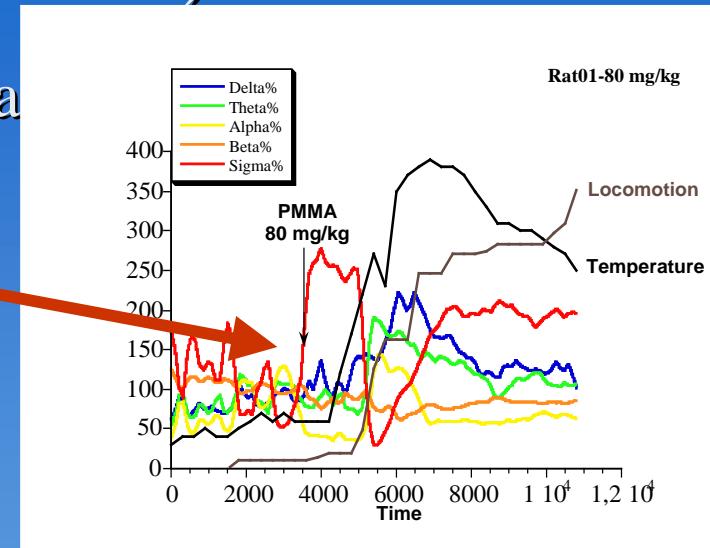


## 4.1 Consequences of long-term intravenous administration of MDMA by rhesus monkeys (Fontegrossi, 2004)

- ◆ Reinforcing effects of MDMA are attenuated after 18 months self-administration
- ◆ 2 months drug abstinence : no decrease of brain serotonin, DA

## 4.3 Seizures : aetiology and consequences (PMMA ; MDMA)

- ◆ Central effects before hyperthermia



- ◆ Hyponatraemia (Inappropriate secretion of ADH) may induce seizures
- ◆ Excess of water intake may increase the seizure risk in humans

## 4.4 Chemical submission\*

- ◆ Amnesia and benzodiazepines
- ◆ Disruptive effects of zolpidem (hallucinations)
- ◆ Sedative effects
- ◆ Decreased danger recognition
- ◆ Decreased defence reactions
- ◆ Disinhibition

**Studies are needed !**

\* (CEIP ; Paris : coord.)

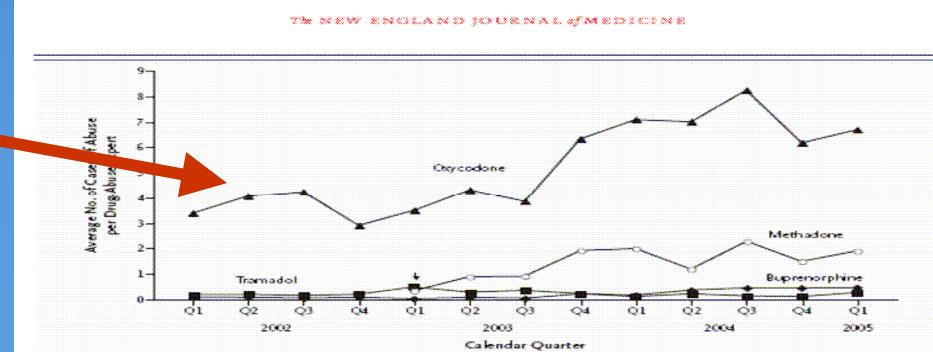
## 4.5 Drug addict questionnaires ; Polyprescriptions



(CEIP ; Marseille : coord.)

- ◆ 3 / 12 kg of **buprenorphine** were polyprescribed (diverted) in one French department
- ◆ Dependence liability may be predicted by **experimental studies in Animals or Humans**
- ◆ Diversion depends if drug is easily available or not (differences USA / France)

**USA : 1 Oxycodone**



## 4.6 Prescription sheet forgeries : sign of abuse / dependence

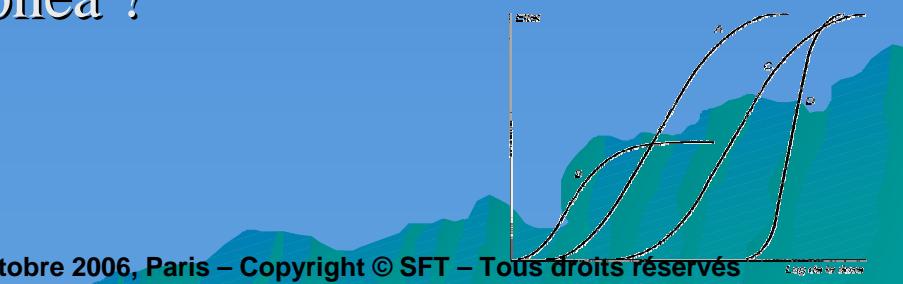
- ◆ OSIAP (ordonnances suspectes indicateur d'abus, de pharmacodépendance) : pharmacist network with CEIP (CEIP ; Toulouse : coord.)
- ◆ **Diversion ratio : 1 flunitrazepam ; 2 : clonazepam**
- ◆ **OSIAP Europe** funded in 2003 ; start : 2006
- ◆ Experimental behavioural studies should be done in order to find new hypnotics with a decreased dependence liability



## 4.7 Fatalities ; DRAMES

(Décès en relation avec abus de médicaments et de substances)  
(CEIP ; Marseille : coord.)

- ◆ Fatalities : Heroin ↓ ; methadone ↑ ; buprenorphine ↔ ?
- ◆ Toxicological studies are needed
- ◆ Methadone/Buprenorphine and benzodiazepines ; intravenous injection
- ◆ Risk factors ? Sleep, sleep apnea ?
- ◆ Unknown mechanisms ?



## 5 European Evaluation

- ◆ Each country evaluates drug dependence and toxicity
- ◆ EMCDDA (OEDT) : increasing network
- ◆ EMEA There is a need of :
  - drug dependence potential studies
  - studies of consequences of abuse, misuse and diversion
  - dependence and risk management plans (toxicological studies)
- ◆ **Why don't we work together ?**

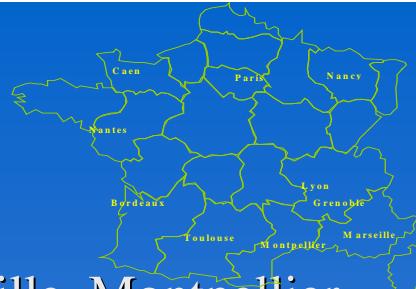
«L'Union fait la force ;Union is strength ;einigkeit macht stark»

# Conclusions

- ◆ Clinical data may give a **rapid alert** in case of abused or diverted drugs, but...
- ◆ Informations may lack or may be delayed
- ◆ Risk management plans are not be sufficient
- ◆ **Experimental studies** for illicit and marketed drugs are **necessary** to evaluate and avoid drug abuse, dependence and diversion
- ◆ **Collaborative European works** with experimental laboratories, analytical toxicologists and clinicians are necessary
- ◆ **Quality controls of the ongoing network**



## Thanks to



- ◆ Network of CEIP : Bordeaux , Caen, Lyon, Marseille, Montpellier, Nancy, Nantes, Paris, Toulouse and... Grenoble
- ◆ AFSSAPS, MILDIT, OFDT, EMCDDA, EMEA
- ◆ Dr Maurice Dematteis
- ◆ Pharmacists, G.P., psychiatrists of the network
- ◆ Pharmacists, M.D. of analytical toxicological and forensic studies

We hope an European network as friendly  
as the « french réseau »