DR. CÉLINE EIDEN (Orcid ID : 0000-0002-7839-9811)
DR. AMÉLIE DAVELUY (Orcid ID : 0000-0003-1922-8630)

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Health consequences of cocaine use in France: data from the French addictovigilance network

Running title: Health consequences of cocaine use in France

Céline **Eiden**[a], Marc **Vincent**[a], Chris **Serrand**[b], Anais **Serre**[a], Nathalie **Richard**[c], Marie-Christine **Picot**[b], Elisabeth **Frauger**[d], Nathalie **Fouilhé**[e], Amélie **Daveluy**[f], Hélène **Peyrière**[a] and the French Addictovigilance Network (FAN)[#]

[a]Département de Pharmacologie Médicale et Toxicologie, centre d'Addictovigilance, CHU Montpellier, Univ Montpellier, Montpellier, France

[b]Unité de Recherche Clinique et d'Epidémiologie, CHU Montpellier, Univ Montpellier, Montpellier, France

[c]ANSM Agence Nationale de Sécurité du Médicament et des Produits de Santé, 93285 Saint-Denis, France

[d]Service de Pharmacologie Clinique et Pharmacovigilance, Centre d'Evaluation et d'Information sur la Pharmacodependance Paca Corse, Hôpital de la Timone, 13005 Marseille, France

[e]Centre d'Addictovigilance, CHU de Grenoble, 38043 Grenoble cedex 9, France

[f]Centre d'Addictovigilance, Service de Pharmacologie Médicale, CHU de Bordeaux, INSERM, U657, Bordeaux, France

#Contributors: Authier N, Boucher A, Deheul S, Djezzar S, Gibaja V, Lapeyre-Mestre M, Le Boisselier R, Perault M-C, Victorri-Vigneau C, Gibaja V.

*Corresponding author:
EIDEN Céline, email: c-eiden@chu-montpellier.fr
Service de Pharmacologie Médicale et Toxicologie,
Hôpital Lapeyronie, 371 avenue du Doyen Gaston Giraud, 34295 Montpellier Cedex 5, France.
Tel: 33-4-67-33-05-40
Fax: 33-4-67-33-67-51

ABSTRACT

As the number and severity of complications related to cocaine use reported to the French Addictovigilance network have increased, the French health authorities requested a national epidemiologic study of the data collected by this network from 2010 to 2016.

For this purpose, the spontaneous reports (SR) linked to cocaine notified by health professionals were analyzed as well as the data from the pharmacoepidemiological surveys OPPIDUM (Observational survey on illegal psychotropic substances or diverted from their clinical use) and DRAMES (Deaths related to the abuse of licit and illicit psychoactive substances).

In total, 1,265 SRs were analyzed (510% increase from 2010 to 2016). Users were mainly men (952/1,261; 75%), with a median age of 35.0 years [IQ_{25-75}: 28-42]. Cocaine was consumed through the intranasal route by 52% of users (416/797), followed by intravenous administration (32%, 253/797), and inhalation (24%, 190/797). The use of cocaine powder and crack-cocaine was reported in 70% (475/674) and 23% (154/674) of SRs, respectively. Cocaine was consumed with other psychoactive substances and alcohol in 47% (603/1265) and 60% (387/649) of cases, respectively. The main cocaine-related complications were psychiatric complications (29%), neurologic complications (24%), and cardiovascular complications (23%). Analysis of the OPPIDUM survey data showed that in 2016, 15.9% and 2.4% of the included subjects consumed cocaine or crack-cocaine the week preceding the survey, the highest rate for the 2006-2016 period. The DRAMES survey indicated that cocaine-related deaths increased by 3-fold from 2014 to 2016.

These data confirm that cocaine use in France is worrying with an increase in the number of severe complications and deaths.

Keywords: cocaine use, crack-cocaine, complications, death

INTRODUCTION

Cocaine is the second most used recreative substance after cannabis in the European Union (EU). Surveys estimates suggest that about 4 million adults in the EU have used cocaine in the past year. Although cocaine consumption mainly concerns western and southern Europe, its consumption is also increasing elsewhere [1]. Cocaine is available as cocaine salt (powder form) and cocaine base ("crack-cocaine", "freebase"). Cocaine powder can be snorted, injected or taken orally, whereas cocaine base is mainly smoked, taken orally, or injected. These two forms exert the same pharmacological actions, once they reach the brain or other target organs [2]. However the route of administration is determinant in terms of severity, onset of action and duration of symptoms. As cocaine acts by inhibiting mainly the reuptake of dopamine and serotonin, and norepinephrine to a lower degree, the expected clinical manifestations include central nervous system excitation, diaphoresis, hypertension, hyperthermia, increased motor tone, mydriasis, and tachycardia [3]. Massive acute cocaine intoxication can lead to a severe sympathomimetic toxicity, resulting in agitated delirium that can be fatal [4]. The study based on the data (patients' self-reports) on acute toxicity collected by the European Drug Emergencies Network (Euro-DEN) between October 2013 and September 2014 showed that cocaine is the second among the top five substances involved in acute recreational drug toxicity events leading to emergency hospitalization in Europe [5].

The 2019 European Drug Report highlighted for France an upward trend in cocaine use and showed that in 2017, the prevalence among young adults (18-34 years) was just above 3% (Spain: 2.8% and United Kingdom: 4.7%) [1]. Similarly, the number and severity of complications related to cocaine use reported by the French Addictovigilance Network (FAN) [6] have been steadily increasing. Therefore, the French health authorities requested a national epidemiologic survey to characterize the changes in cocaine/crack-cocaine consumption from 2010 to 2016 and its consequences in France using three FAN data sources. Here, we describe the results of this analysis.

METHODS

The FAN, under the supervision of the French National Agency for Medicines and Health Products Safety (ANSM for Agence Nationale de Sécurité du Médicament et des Produits de

Santé), was established in 1990 to monitor the abuse potential of psychoactive substances (with the exclusion of tobacco and alcohol), and to provide information on the risk of addiction and advice for public health decision-making [7]. This surveillance system is based on spontaneous reporting by healthcare professionals and patients, which is regulated by law, and on specific pharmacoepidemiological surveillance programs to complement the data collected by spontaneous notification [6]. The FAN relies on health professionals (physicians, pharmacists, toxicologists, nurses…), and other collaborators (harm reduction associations or associations of users, users and their entourage) to collect and distribute evidence-based information. The network covers the entire territory of metropolitan France and also the French overseas territories (French Polynesia, New Caledonia, Guadeloupe, Saint Martin, French Guiana, and Reunion Island).

Therefore, the present study used information from different sources:

1. ***Spontaneous reports*** (SRs): All cases of cocaine/crack-cocaine-related disorders reported to the FAN by health professionals and collaborators from 2010 to 2016 were analyzed. For each case, the following data were collected: age, sex, concomitant substances use, psychoactive substance use patterns, complications and associated severity criteria (clinical signs, hospitalization, death…). Cocaine use was categorized as i) experimental use, defined as trying the drug for the first time as an experiment; ii) use in the year, defined as once during the year; iii) regular use, at least once per week; and iv) daily use. Crack-cocaine use was identified when spontaneous reports included crack-cocaine, freebase or alkaloid cocaine and smoked cocaine use.

   Cases were defined as serious and not-serious using the World Health Organization (WHO) criteria. Cases resulting in the patient's death, life threatening, requiring hospitalization, or prolongation of existing hospitalization, and resulting in persistent significant disability or incapacity were defined as serious.

To describe the changes in cocaine/crack-cocaine exposure, the ratio between all SRs on cocaine/crack-cocaine use and the total number of SRs for that year (n= 2520 in 2010, n=2570 in 2011, n=2833 in 2012, n= 3347 in 2013, n= 3409 in 2014, n=3519 in 2015, and n=4407 in 2016) was calculated and then multiplied by 100.

To calculate the reported case rate, the INSEE data on the French population (Total men and women from 20 to 59 years of age) was used [8].

2. ***OPPIDUM survey*** (*Observation of illegal drugs and misuse of psychotropic medications*) is an annual, cross-sectional epidemiological survey on substance abuse/misuse. This anonymous survey was launched in 1990 and is performed every year to collect information on self-reported drug use by patients with drug dependency/abuse symptoms or treated with opioid maintenance therapy (OMT) in addiction treatment support and prevention centres for outpatients, hospital addiction units, treatment units for prison inmates, and harm reduction centres for drug users nationwide [9]. Crack-cocaine use was identified when patient self-reported the use of crack-cocaine. Drug dependence was defined according to the DSM IV criteria.
3. ***DRAMES survey*** (*Death related to abuse of licit and illicit psychoactive substances*) collects each year and analyzes all cases of death related to substances use (psychoactive drugs and illicit substances) [10]. In the case of violent death and/or suspicion of death caused by substance use, a request to the judicial authorities allows the forensic analysis with substance identification/quantification in the biological fluids of the deceased (drugs and/or illicit substances). These analyses are carried out in approved toxicology laboratories. Drug-related deaths are classified as directly attributed to drug use, and as indirectly attributed to drug use when caused, for instance, by falls, drowning, injuries, or asphyxia. In this study, only the deaths (directly or indirectly) caused by cocaine use were analyzed.

As this study was performed retrospectively using routinely collected anonymous data, it did not require any ethics committee approval, in line with the French regulations for mandatory reporting of addiction cases by health professionals [11].

Statistical Analysis

The normal distribution of quantitative variables was tested with the Shapiro-Wilk normality test. Results are presented as the mean ± standard deviation (SD) for quantitative variables showing a Gaussian distribution, otherwise as median and interquartile range (IQR). Categorical variables are described using frequencies and percentages. Missing data (unknown data) were not taken into account in the calculation of percentages.

RESULTS

Spontaneous reports

During the study period (2010 to 2016), 1265 SRs for cocaine/crack-cocaine were collected and analyzed (75% of men, median age 35.0 years [$IQR_{25-75\%}$: 28-42]). A significant increase ($p<0.0001$) in SRs of severe cases was observed (Fig. 1), particularly between 2015 and 2016 (close to doubling). This increase concerned mainly cocaine powder, and to a lower extent, crack-cocaine. The cocaine users' sociodemographic characteristics and substance use behaviors are summarized in Table 1.

The complications related to cocaine use listed in the SRs (N=1433, Table 2 and Figure 2) were psychiatric complications (29%, n= 416), neurological complications (24%, n=342) cardiovascular complications (23%, n=330), infectious complications (11%, n=152) respiratory complications (6%, n=81), other complications (5%, n=77) and otorhinolaryngology complications (2%, n= 35).

OPPIDUM surveys

Data on cocaine powder users:

A total of 54,815 subjects were included in the OPPIDUM surveys between 2006 and 2016, including 6,138 cocaine users (11%). In 2016, 16% of all included subjects had consumed cocaine the week preceding the survey (i.e., the highest percentage for the 2006-2016 period) (Table 3). Cocaine users (n=6,138) were predominantly men (78%), and the mean age was 33.2 ± 8 years. Polydrug use (mean=3±1 substances) was reported by more than 90% of cocaine users, and alcohol dependence was mentioned by 20 to 30% of individuals. In 2016, 68% of cocaine users included in the OPPIDUM surveys were on OMT. Concerning the consumption patterns, the intravenous route was used by about 27% of cocaine users, the nasal route by 58% of users (with a peak of 70% in 2009), while inhalation by 31% of users in 2016. Concomitant alcohol intake was reported by 43% of cocaine users and 92% were long-term cocaine users (more than 1 year). The proportion of subjects self-reporting cocaine dependence remained relatively stable during the study period (26-30%).

Data on crack-cocaine users:

Among the 54,815 subjects included in the OPPIDUM surveys between 2006 and 2016, 628 (1.1% of the entire population) reported crack-cocaine consumption (Table 4). In 2016, 2.4% of

subjects included in the OPPIDUM surveys consumed crack-cocaine the week preceding the survey, the highest rate for the 2006-2016 period. Crack-cocaine users (n=628) were predominantly men (76%) with a mean age of 38.2 ± 9 years. Polydrug intake was reported by 82% (3±2 substances), and alcohol dependence by 32% of crack-cocaine users.

In 2016, 45% of crack-cocaine users included in the OPPIDUM surveys received OMT (a reduction compared with the previous years). Heroin consumption also decreased among crack-cocaine users over the last 3 years (22% in 2014, 14% in 2015, and 11% in 2016). Conversely, the concomitant intake of alcohol increased to 49% in 2016 (the highest rate since 2006). Self-reported crack-cocaine dependence ranged from 27% in 2007 to 63% in 2015 with fluctuations (47% in 2016).

DRAMES survey

Among the 2,465 deaths included in the DRAMES surveys between 2010 and 2016, 2,114 were directly related to the use of a psychoactive substance, and 326 directly related to cocaine use (15.4% of 2,114) (Table 5). Cocaine-related deaths (n=326) concerned predominantly men (78.4%). The number of deaths directly attributable to cocaine remained relatively stable (n=25-36) between 2010 and 2014, but increased in 2015 (n=44) and 2016 (n=75). The main associations were cocaine-heroin, and cocaine-methadone. In 2016, the mean cocaine post-mortem blood concentrations was 1,747 µg/l (toxic cocaine blood concentration: from 500 to 1,000 µg/l), the highest value for the study period.

DISCUSSION

The aim of this study was to characterize cocaine/crack-cocaine use and its consequences in France using different pharmaco-epidemiological data sources. Data from the French National Institute of Statistics and Economic Studies showed that the French population characteristics (age, and sex distribution) remained stable during the study period, thus eliminating an age-related bias [8]. Moreover, the reporting rate during the study period increased from two SRs in 2010 to twelve SRs per million inhabitants in 2016. In the same period, the SR data collection networks did not change.

Socio-demographic analysis of cocaine users

The analysis of data from the three sources highlighted similar cocaine user profiles. Cocaine use concerned mainly men with a median age of 35 years, as reported in other European and United States of America (USA) surveys [1, 12].

Cocaine use

Data from SRs showed a significant increase in the number of severe cases, but not of non-serious cases, possibly related to multifactorial criteria, one explanation can be the increase in cocaine purity, reported in the same time in France [13]. Moreover, severe cases, often associated with hospitalization, are more likely to be reported to the FAN. Cocaine was often used daily or regularly via the intranasal route. Although cocaine salt was the main described form, the proportion of cases concerning crack-cocaine has been progressively increasing (SRs and OPPIDUM data). The profile of people who reported crack-cocaine consumption was different from that of cocaine users. Crack-cocaine users appeared to be more often in situations of social precarity (from 11 to 40% vs 10 to 14% for cocaine powder users in OPPIDUM data), older (mean age in 2016: 40±10 years, vs 35±9), and lived mainly in the French overseas territories and Paris. This is in agreement with the results of studies, suggesting that frequent crack-cocaine users tend to be more marginalized socially and economically and are less likely to have jobs [14, 15]. Moreover powder cocaine tends to be sold in grams and seems to be ”more expensive”, whereas crack-cocaine is more often sold in smaller unit sizes, and thus is preferred by people with low income [16]. The proportion of crack-cocaine users was different according to the sources: 23% of SRs and approximately 2% of all patients included in the OPPIDUM survey. This discrepancy could be explained by the fact that crack-cocaine consumption leads to more severe complications, which are more likely to be reported to addictovigilance centers. Another hypothesis is that crack-cocaine users tend to be more marginalized and therefore, do not go to specialized drug treatment and prevention centers for outpatients.

Co-ingestion of substances

The consumption of cocaine with other substances, particularly alcohol and other psychoactive substances, was frequent. Alcohol and cocaine remain the most frequently co-ingested substances in cases of acute intoxication that requires emergency medical care [5]. Similarly, a Swiss study on acute cocaine-related health problems in patients presenting to the emergency department (n=165 patients) found that cocaine alone was used by 16% of these patients, whereas the intake

of at least another substance, mainly alcohol (41%), opioids (38%), or cannabis (36%), was reported by 84% of patients. This was confirmed by the detection of the different substances in their blood samples [17].

Pharmacological reasons could explain the concurrent use of multiple substances (i.e., to attenuate the cocaine crash or to counteract the agitation and other adverse-effects of cocaine). Moreover, the combination of cocaine and alcohol leads to the formation of the cardiac and neurotoxic cocaine metabolite called cocaethylene that can be found in toxicological analyses, as reported in the DRAMES survey [18].

Cocaine-related complications

The percentage of *SRs* on cocaine/crack-cocaine has been increasing in the last 8 years (2.7% in 2010 versus 9.4% in 2016, Figure 1). The reported complications reflected the pharmacologic properties of cocaine (psychiatric complications, cardiac complications, neurological complications). A trend to more severe cases, mainly psychiatric complications, was also observed (26% in 2010 to 40% in 2016).

Relative to the number of cocaine users in France (600 000 in 2017, [19]) and cocaine toxicity, the number of complications reported to the FAN via SRs seems rather low. However, our results may be an underestimation, because, under-reporting is the main limitation of such spontaneous reporting-based systems that are primarily a tool to generate "signals" or "warnings" concerning severe drug-associated events. The low notification rate (SR exhaustiveness was 0.4% ($_{95\%}$CI = 0.2-0.6) in 2012, estimated using the capture-recapture method), is one of the reasons that led to the establishment of additional epidemiological tools (e.g., OPPIDUM, DRAMES) by the FAN [20]. Moreover, for some criteria, there are a lot of missing data (i.e up to 80% for socio demographic characteristics as stable accommodation or employment).

Data analysis from the **OPPIDUM surveys** 2006-2016 highlighted an increase in the number of cocaine and crack-cocaine users in addiction care centers, but cocaine use disorders remained stable over the period. Results must be interpreted according to the methodological limitations of the OPPIDUM survey. Indeed, this survey is based on the willingness by health structures to perform them, and therefore, they cannot provide an exhaustive description of psychoactive substance consumption by all addict subjects in France [21]. Another limitation is that the data are collected by one person from the care team and consequently, some abusive behaviors by the patients may be under-reported. However, a retrospective study found that the concordance

between self-reported cocaine use and toxicological findings was high, suggesting that the results of such studies are valid [22].

Finally, the **DRAMES surveys** for 2010-2016 highlighted an increase in cocaine-related deaths from 2014 (13% of deaths directly related to cocaine). This constitutes another signal of the progressive increase of cocaine-related severe complications. In addition, recent OCTRIS *(French national agency for the suppression of illicit traffic in psychoactive/narcotic drugs)* data showed an increase in the number of cocaine confiscations in France. Concomitantly, an increase of cocaine purity was noted (mean content: 68%; min-max: 11%-99 % [13]). Although the acute response to cocaine is variable and the correlation between cocaine plasma concentrations and toxic effects is poor, cocaine adverse effects are generally observed with blood concentrations between 250 and 5 000 µg/L [23]. Cocaine plasma concentrations can vary by 100-fold in fatal cases, with lethal concentrations starting from 1 000 µg/L. In the DRAMES study, the delay between cocaine intake and blood collection, routes of administration, duration of use, amount of cocaine consumed and cocaine/crack-cocaine purity were not recorded. Nevertheless, the mean cocaine blood levels were generally higher than 500 µg/L, except in 2011. In the 2017 DRAMES survey, the results of which are available on the ANSM website, cocaine-related deaths exceeded those related to heroin for the first time in France.

The main limitation of the DRAMES survey is that they are based on the expert toxicologist's willingness to report the cases and therefore, cannot provide an exhaustive description of drug-related deaths in France. Moreover, only the judicial authorities can decide to carry out toxicological investigations.

The three data sources used for this study provide complementary data, but have some limitations:

- Data collection was heterogeneous in terms of completeness and accuracy. For example, in SRs, data completeness varies in function of the person who fills in the report.
- Data on the users' characteristics were limited: for example, some clinical features were missing (e.g., psychiatric disorder history, psychiatric/developmental vulnerabilities…).
- These sources include very few data on cocaine users without clinical complications and followed by general practitioners (primary care settings) [24].

CONCLUSION

By integrating data from different signal detection systems (SRs, OPPIDUM, and DRAMES), we found that cocaine/crack-cocaine use is widely involved in the reported complications, although

the real frequency is certainly underestimated. Health professionals should not undervalue cocaine/crack-cocaine consumption because complications can be potentially fatal. Information on the risks associated with cocaine/crack-cocaine use should be made available to users and health professionals involved in patient management and in risk reduction programs (physicians, nurses, psychologists). To this end, the French health authorities have published an information brochure summarizing the results presented in this study [25].

FUNDING

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CONFLICT OF INTEREST

No conflicts of interest

KEY POINTS

- In France, cocaine/crack-cocaine-related severe complications have increased from 2010 to 2016.
- Cocaine/crack-cocaine use by patients attending addiction care centers has increased, whereas cocaine/crack-cocaine dependence seems to be stable in France (OPPIDUM data).
- The number of cocaine/crack-cocaine-related deaths has increased in France (DRAMES data).

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Table 1 Socio-demographic characteristics and addictive behaviors of the data from SRs during the 2010-2016 period (N=1265)

	2010	2011	2012	2013	2014	2015	2016	All
Living as a couple								
Missing data	*52*	*46*	*113*	*125*	*163*	*152*	*291*	*942*
Yes	11 (69%)	7 (44%)	20 (59%)	21 (62%)	27 (61%)	30 (55%)	72 (58%)	188
No	5 (31%)	9 (56%)	14 (41%)	13 (38%)	17 (39%)	24 (45%)	53 (42%)	135
Stable accommodation								
Missing data	*61*	*54*	*122*	*131*	*175*	*165*	*324*	*1032*
Yes	7 (100%)	6 (75%)	21 (84%)	21 (75%)	27 (85%)	32 (78%)	77 (84%)	191
No	0 (0%)	2 (25%)	4 (16%)	7 (25%)	5 (15%)	9 (22%)	15 (16%)	42
Employment								
Missing data	*52*	*51*	*120*	*130*	*160*	*147*	*295*	*955*
Yes	5 (31%)	5 (45%)	16 (59%)	9 (31%)	17 (36%)	20 (34%)	52 (43%)	124
No	11 (69%)	6 (55%)	11 (41%)	20 (69%)	30 (64%)	39 (66%)	69 (57%)	186

Cocaine form								
Missing data	*39*	*30*	*52*	*69*	*90*	*100*	*211*	*591*
Powder form	24 (83%)	28 (86%)	61 (64%)	59 (66%)	91 (78%)	75 (71%)	137 (67%)	475
Crack-cocaine form	4 (14%)	3 (9%)	29 (31%)	21 (23%)	23 (20%)	27 (25%)	47 (23%)	154
Crack + Powder form	1 (3%)	1 (3%)	5 (5%)	10 (11%)	3 (2%)	4 (4%)	21 (10%)	45
Concomitant alcohol use								
Missing data	*43*	*35*	*49*	*70*	*114*	*104*	*201*	*616*
Yes	17 (68%)	24 (89%)	61 (62%)	46 (52%)	49 (53%)	57 (56%)	133 (62%)	387
No	8 (32%)	3 (11%)	37 (38%)	43 (48%)	44 (47%)	45 (44%)	82 (38%)	262
Frequency of cocaine use								
Missing data	*52*	*46*	*91*	*92*	*124*	*110*	*224*	*739*
Experimental	1 (6%)	1 (6%)	4 (7%)	2 (3%)	1 (1%)	2 (2%)	5 (2%)	16
In the year	3 (19%)	2 (12%)	5 (9%)	8 (12%)	6 (7%)	5 (5%)	14 (7%)	43
Regular	5 (32%)	5 (32%)	18 (32%)	28 (42%)	34 (41%)	38 (40%)	77 (41%)	205
Daily	7 (43%)	8 (50%)	29 (52%)	29 (43%)	42 (51%)	51 (53%)	96 (50%)	262
Route of Administration								
• **Intranasal**								
Missing data	*24*	*22*	*46*	*59*	*74*	*72*	*171*	*468*
Yes	20 (45%)	21 (53%)	44 (43%)	51 (51%)	63 (47%)	69 (52%)	148 (60%)	416
No	24 (55%)	19 (47%)	57 (57%)	49 (49%)	70 (53%)	65 (48%)	97 (40%)	381
• **Intravenous**								

Missing data	*25*	*24*	*46*	*60*	*74*	*71*	*168*	*468*
Yes	17 (39%)	16 (42%)	35 (34%)	29 (29%)	50 (37%)	39 (29%)	67 (27%)	253
No	26 (60%)	22 (58%)	66 (65%)	70 (71%)	83 (62%)	96 (71%)	181 (73%)	544
• **Inhalation**								
Missing data	*23*	*27*	*46*	*58*	*75*	*74*	*171*	*474*
Yes	6 (13%)	3 (9%)	30 (30%)	29 (29%)	25 (19%)	33 (25%)	64 (26%)	190
No	39 (87%)	32 (91%)	71 (70%)	72 (71%)	107 (81%)	99 (75%)	181 (74%)	601
Time of consumption								
Missing data	*56*	*55*	*101*	*114*	*142*	*122*	*238*	*828*
≤1 year	1 (8%)	0 (0%)	14 (30%)	4 (9%)	6 (9%)	12 (15%)	36 (20%)	73
> 1 an	11 (92%)	7 (100%)	32 (70%)	41 (91%)	59 (91%)	72 (85%)	142 (80%)	364
Concomitant psychoactive substance								
• ***One substance***								
No	26 (38%)	30 (48%)	87 (59%)	103 (65%)	116 (56%)	101 (49%)	199 (48%)	662
Yes	42 (62%)	32 (52%)	60 (41%)	56 (35%)	91 (44%)	105 (51%)	217 (52%)	603
• ***Two or more substances***								
No	53 (78%)	54 (87%)	122 (83%)	141 (89%)	182 (88%)	172 (83%)	331 (79%)	1055
Yes	15 (22%)	8 (13%)	25 (17%)	18 (11%)	25 (12%)	34 (16%)	85 (20%)	210
History of cocaine withdrawal								

Missing data	*26*	*27*	*51*	*58*	*52*	*44*	*72*	330
No	41 (98%)	33 (94%)	90 (94%)	94 (93%)	138 (89%)	151 (93%)	316 (92%)	863
Yes	1 (2%)	2 (6%)	6 (6%)	7 (7%)	17 (11%)	11 (7%)	28 (8%)	72

Table 2 Complications related to cocaine use listed in the SRs (n=1265)

	2010	2011	2012	2013	2014	2015	2016	All
Psychiatric complications								
Missing data	*14*	*7*	*16*	*10*	*6*	*15*	*31*	*99*
Yes	**14 (26%)**	**17 (31%)**	**42 (32%)**	**55 (37%)**	**64 (32%)**	**70 (37%)**	**154 (40%)**	**416**
No	40 (74%)	38 (69%)	89 (68%)	94 (63%)	137 (68%)	121 (63%)	231 (60%)	750
Cardiovascular complications								
Missing data	*15*	*15*	*20*	*11*	*9*	*17*	*29*	*116*
Yes	**11 (21%)**	**19 (40%)**	**34 (27%)**	**48 (32%)**	**57 (29%)**	**59 (31%)**	**102 (26%)**	**330**
No	42 (79%)	28 (60%)	93 (73%)	100 (67%)	141 (71%)	130 (69%)	285 (74%)	819
Neurological complications								
Missing data	*14*	*13*	*18*	*12*	*10*	*15*	*31*	*113*
Yes	**22 (41%)**	**18 (37%)**	**46 (36%)**	**39 (26%)**	**58 (29%)**	**61 (32%)**	**99 (26%)**	**343**
No	32 (59%)	31 (63%)	83 (64%)	108 (73%)	139 (71%)	130 (68%)	286 (74%)	809
Infectious complications								
Missing data	*15*	*13*	*20*	*12*	*9*	*17*	*38*	*124*
Yes	**10 (19%)**	**10 (20%)**	**22 (17%)**	**20 (14%)**	**35 (18%)**	**20 (10%)**	**31 (8%)**	**148**

No	43 (81%)	39 (79%)	105 (83%)	127 (86%)	163 (82%)	169 (89%)	347 (92%)	993
Respiratory complications								
Missing data	*16*	*14*	*20*	*11*	*9*	*17*	*31*	*118*
Yes	**1 (2%)**	**7 (15%)**	**13 (10%)**	**14 (9%)**	**22 (11%)**	**9 (5%)**	**23 (6%)**	**89**
No	51 (98%)	41 (85%)	114 (90%)	134 (91%)	176 (89%)	180 (95%)	362 (94%)	1058
Otorhinolaryngology complications								
Missing data	*16*	*13*	*17*	*11*	*11*	*17*	*32*	*117*
Yes	**1 (2%)**	**2 (4%)**	**8 (6%)**	**4 (3%)**	**7 (4%)**	**2 (1%)**	**11 (3%)**	**35**
No	51 (98%)	47 (96%)	122 (94%)	144 (97%)	189 (96%)	187 (99%)	373 (97%)	1113

Table 3. Main characteristics of cocaine users from the OPPIDUM survey in France. Between 2006-2016: 54 815 subjects included in the entire France among whom 6 138 were cocaine users

	2006	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**
Cocaine users	422	585	671	471	470	482	476	592	568	574	827
% Cocaine users (/total subject included)	(11%)	(11%)	(12%)	(10%)	(9%)	(9%)	(10%)	(11%)	(11%)	(11%)	(16%)
Men (%)	79%	77%	76%	79%	78%	79%	78%	77%	82%	79%	77%
Age (year, mean ± sd)	31± 7	31± 7	32± 8	32± 8	32± 8	33 ± 8	33 ± 8	34 ± 8	34 ± 8	35 ± 8	35 ± 9
Social precarity (%)	12%	10%	13%	10%	13%	11%	14%	12%	13%	13%	11%
Alcohol dependence	24%	20%	23%	28%	26%	26%	27%	28%	30%	30%	28%
Polydrug users (≥2 PS)	94%	96%	95%	95%	95%	94%	91%	93%	93%	94%	91%
Cocaine consumption characteristics (%)											
Intravenous administration	34%	28%	26%	27%	30%	27%	27%	30%	30%	27%	27%
Nasal administration	57%	63%	64%	70%	63%	62%	62%	59%	61%	60%	58%
Inhalation	23%	27%	29%	18%	20%	27%	21%	30%	28%	28%	31%

Frequency of use											
• Occasional	60%	56%	55%	53%	57%	59%	57%	58%	60%	57%	55%
• Weekly	22%	26%	24%	27%	26%	26%	29%	28%	29%	31%	31%
• Daily	18%	18%	20%	20%	17%	15%	14%	14%	11%	12%	14%
Increase consumption in the last 6 months	23%	18%	21%	19%	18%	15%	19%	17%	17%	20%	20%
Beginning of consumption											
• Few weeks	2%	3%	3%	2%	2%	1%	2%	3%	3%	3%	2%
• Few months	8%	10%	7%	9%	7%	11%	9%	5%	7%	6%	6%
• >1 year	90%	87%	90%	90%	91%	88%	89%	92%	89%	91%	92%
Cocaine dependence	30%	29%	27%	31%	30%	31%	29%	26%	27%	30%	30%
Concomitant alcohol use	36%	33%	37%	43%	40%	38%	40%	40%	45%	42%	43%
Concomitant OMT*	64%	65%	65%	63%	67%	71%	64%	68%	67%	65%	68%
• Methadone	35%	41%	40%	42%	47%	52%	44%	48%	48%	49%	50%
• Buprenorphine (Subutex® or	28%	24%	24%	21%	19%	18%	19%	19%	17%	15%	17%

generics **and buprenorphine-naloxone** Suboxone®)											
• Morphine sulfate	1%	-	1%	-	1%	1%	1%	1%	2%	1%	1%
Concomitant benzodiazepine use	24%	21%	17%	18%	21%	18%	18%	22%	20%	19%	20%
Concomitant cannabis use	45%	48%	40%	50%	46%	41%	45%	40%	41%	49%	43%
Concomitant heroin use	46%	50%	48%	41%	43%	38%	29%	32%	36%	29%	27%

**OMT: Opioid Maintenance Treatment; PS: psychoactive substances*

Table 4. Main characteristics of crack users from the OPPIDUM survey in France. Between 2006-2016: 54,815 subjects were included in the entire France among whom 628 were crack users

	2006	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**
Crack users	15	28	54	46	63	50	81	46	63	59	123
% crack users (/total subject included)	(0.4%)	(0.5%)	(1.0%)	(1.0%)	(1.2%)	(1.0%)	(1.7%)	(0.9%)	(1.3%)	(1.2%)	(2.4%)
Men (%)	60%	70%	76%	74%	73%	74%	77%	69%	79%	91%	77%
Age (y, mean ± sd)	36± 5	34± 8	34± 8	36± 7	38± 9	39± 8	40± 8	38± 9	37± 9	39± 9	40± 10
Social precarity (%)	20%	16%	11%	16%	36%	18%	40%	25%	36%	27%	23%
Alcohol dependence	7%	25%	26%	33%	39%	41%	37%	20%	27%	25%	41%
Polydrug use (≥2 PS)	93%	93%	94%	89%	56%	90%	88%	87%	82%	88%	73%
Crack consumption characteristics (%)											
Intravenous administration	7%	0%	2%	2%	7%	4%	1%	0%	7%	2%	2%
Nasal administration	0%	4%	9%	2%	3%	6%	5%	2%	2%	2%	1%
Inhalation	87%	96%	91%	98%	93%	94%	97%	98%	92%	98%	98%
Frequency											
• Occasional	43%	32%	32%	37%	35%	43%	24%	20%	27%	29%	33%
• Weekly	36%	54%	41%	30%	30%	23%	40%	50%	38%	42%	32%
• Daily	21%	14%	26%	33%	35%	34%	35%	29%	35%	29%	34%
Increase consumption in the last	7%	33%	19%	24%	25%	20%	24%	7%	18%	29%	35%

6 months											
Beginning of consumption											
• Few weeks	0%	0%	2%	2%	2%	4%	3%	7%	0%	2%	4%
• Few months	7%	37%	6%	2%	10%	4%	4%	2%	8%	10%	11%
• >1 year	93%	63%	92%	96%	88%	92%	93%	91%	91%	88%	85%
Crack dependence	53%	27%	49%	57%	58%	42%	57%	51%	60%	63%	47%
Concomitant alcohol use	20%	25%	19%	41%	49%	48%	42%	39%	26%	33%	49%
Concomitant OMT*	67%	68%	78%	61%	40%	62%	50%	58%	63%	59%	45%
• Methadone	40%	54%	54%	44%	29%	50%	38%	41%	43%	30%	32%
• Buprenorphine (Subutex® or generics **and buprenorphine-naloxone** Suboxone®)	27%	14%	24%	17%	11%	12%	12%	17%	20%	29%	12%
• Morphine sulfate	-	-	-	-	-	-	-	-	-	-	1%
Concomitant benzodiazepine use	13%	14%	13%	20%	16%	22%	22%	28%	22%	22%	18%

Concomitant cannabis use	40%	39%	31%	37%	19%	32%	47%	37%	40%	42%	36%
Concomitant heroin use	33%	32%	35%	35%	25%	12%	6%	9%	22%	14%	11%

**OMT: Opioid Maintenance Treatment; PS: psychoactive substances.*

Table 5. DRAMES survey: data from 2010 to 2016

	2010	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**
Number of subjects included*	276	388	346	328	283	395	449
Age (years, average [range])	33.7 [17-63]	34.3 [13-78]	35.1 [13-63]	35 [12-64]	36.1 [11-65]	36.2 [15-63]	37.4 [16-67]
Men (%)	88	81	81	80	82	84	86
Death directly related to drug, n (%)	247 (89%)	280 (72%)	310 (89%)	285 (86%)	243 (86%)	343 (87%)	406 (90%)
Cocaine-related death:	34 (12%)	41 (10%)	43 (12%)	34 (10%)	42 (15%)	51 (13%)	81 (18%)
• Directly	25	30	36	25	33	44	75
• Age (years, average [range])	36.5 [22-55]	39.5 [21-66]	38.5 [16-59]	34.3 [19-55]	36.1 [24-53]	37.7 [18-63]	39.4 [25-62]
• Men (%)	88	80	67	76	79	75	84
Concomitant opioid use (n=)							
• heroin	7	11	9	4	12	13	16
• methadone	4	7	4	4	7	9	21
• buprenorphine	-	1	2	3	3	1	2
Post-mortem cocaine blood concentrations (µg/l)							
Range	1.3-21,400	2-1,391	2.5-19,919	0.7-1,940	1-9,787	0.6-8,175	3.0-23,100
Mean	1 098	230	1 710	550	694	600	1 747

* directly and indirectly drug-related deaths (indirectly: death by drowning, trauma, behavioral disorder…)

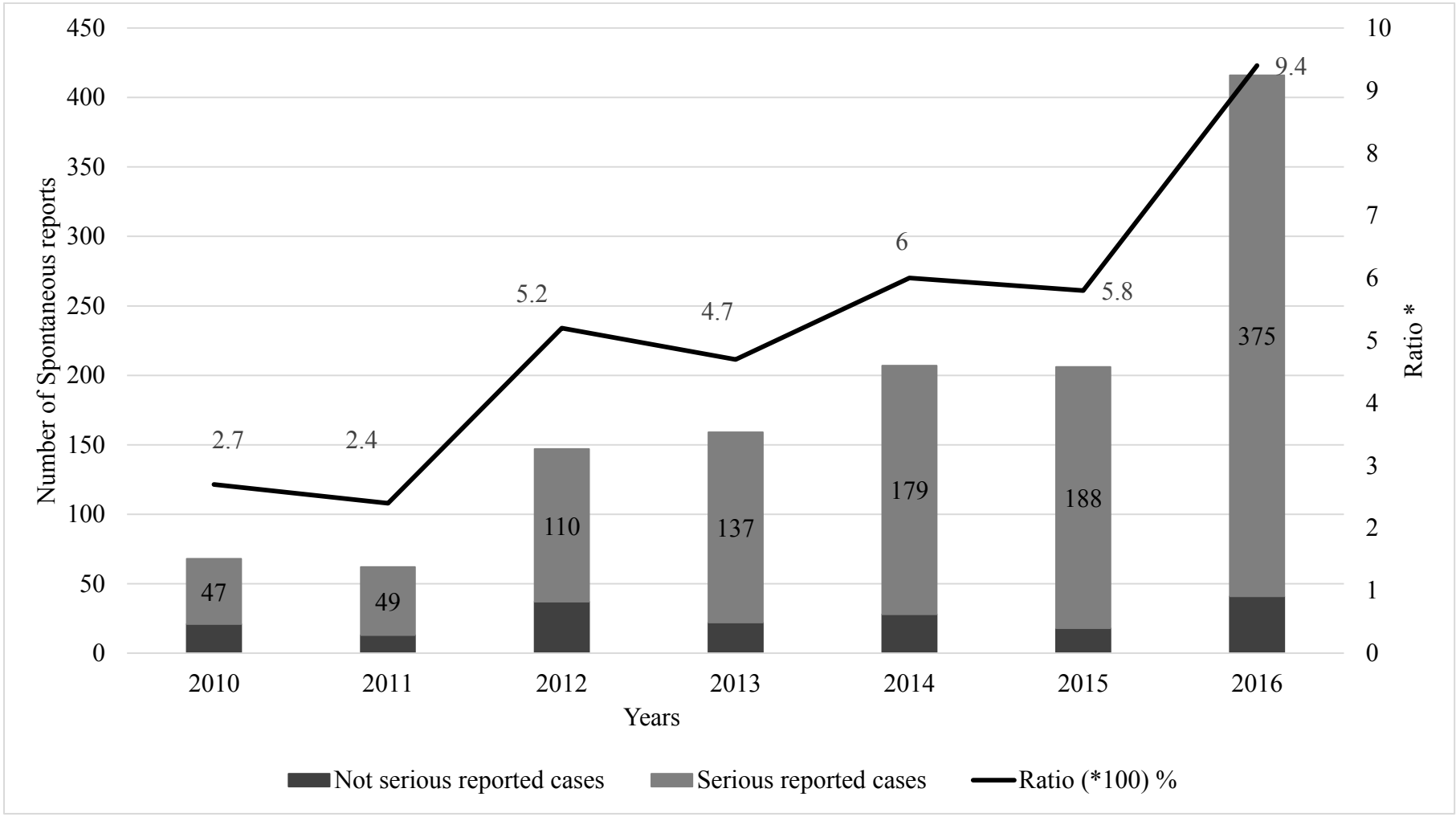

Figure 1: Cocaine/Crack-cocaine reported cases from Spontaneous reports (SRs); n=1265, 2010-2016

**Calculated ratio between cocaine/crack-cocaine reported cases and the total of reported cases to the FAN via the Spontaneous Reports system.*

Figure 2. Complications related to cocaine use listed in the SRs during the period 2010-2016 (N=1433 from 1265 SRs)