

Direct drug-related deaths

Assessment of their number in France and recent developments

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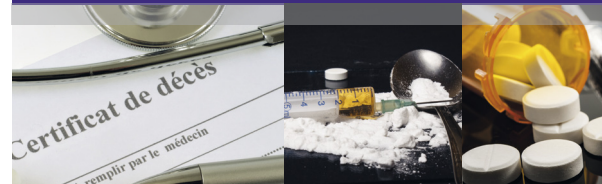
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The epidemic of opioid overdose deaths in the United States highlights the issue of drug-related deaths [1]. In response to the crisis on the other side of the Atlantic, the public authorities are mobilising in France and Europe to prevent any developments that could lead to this kind of situation. Beyond this specific concern, reducing these premature and preventable deaths, even when they appear to be fewer in number than in other countries, remains a major challenge for public policy in the field of drugs. In this context, it seems more necessary than ever to assess the number of deaths related to illicit drugs and opioid medications (substitution medicines or analgesics) in France.

What data is available? What are the limitations? What trends are emerging? These issues were already addressed in Tendances in 2010 [2]. At that time, drug-related deaths were still fully assimilated with overdose deaths by drug users. The concern today is also the deaths of people who have been prescribed opioids to treat pain.

Latest data available on deaths related to illicit drugs and opioid prescription drugs. Limitations and factors of variation.



This issue of Tendances is an update on direct drug-related deaths, as well as an update on their variation in numbers up to 2015-2017¹. It also explores possible explanations for these variations.

1. Last year available according to sources.

Opioids

An opioid [3] is any natural (morphine, codeine), semi-synthetic (heroin, oxycodone) or synthetic (methadone, buprenorphine, tramadol, fentanyl) substance that activates opioid receptors in the central nervous system.

■ There are two types of opioid analgesic drugs that can be distinguished by their indication:

- weak opioid analgesics are used for the symptomatic treatment of moderate to severe pain and for pain that does not respond to the use of non-opioid analgesics. The main weak opioids used in France are tramadol, codeine and opium powder;
- strong opioid painkillers are used for treating intense cancer pain or pain that is refractory to weak opioid analgesics and for treating intense pain that is not related to cancer and that is refractory to other painkillers, except for functional pain and headaches. The main strong opioids used in France are morphine, oxycodone and fentanyl.

■ Opioid drugs are also used as a substitution treatment for opioid addiction. High dose buprenorphine with or without naloxone and methadone have a marketing authorisation (MA) for this indication, while morphine sulphate is sometimes used in this indication without having an MA.

■ Finally, illicit opioids include all opioids which are not prescription drugs, heroin or new psychoactive substances (NPS), including fentanyl analogues.

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■ A shared definition in the European Union

Overdose deaths, direct drug-related deaths or drug user mortality: these terms, which are sometimes used interchangeably, do not have the same meaning and need to be clarified. In this field, reference can be made to the work carried out by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). The European Union agency in charge of monitoring the issue of illicit drugs has established five key indicators, including the drug-related deaths indicator, which is set out in a European protocol [4].

This indicator covers two elements which are both monitored by the EMCDDA. The first, which will not be discussed here, is that of drug user mortality, a concept that covers all drug users' deaths, whatever the cause. This piece of work focuses on the second element, direct drug-related deaths (DDRD), which are defined as deaths occurring shortly after the use of psychoactive substances (illicit drugs or psychoactive medicine being misappropriated and not used for their therapeutic purpose²) and which are caused by the intoxication from a substance itself and not by an indirect consequence of intoxication or drug use³. Most DDRDs can be described as overdoses that occur when the amount taken exceeds the dose limit tolerated by the user's body. The majority of fatal overdoses are caused by opioids, both in

France and internationally [1, 5]. These substances cause respiratory depression, which can lead to death, after varying doses have been used, depending on the individual and their addiction to these substances. The overdose risk is therefore particularly high among people who are first-time opioid users, those who go back to using opioids after a withdrawal period or those who take them with alcohol or benzodiazepines. These deaths can also occur in people who regularly use heroin or opioid prescription drugs (substitution or analgesics), and who accidentally take too high a dose (particularly due to the variability in heroin's purity or from purchasing substances that are different to those they thought they were buying⁴ [6, 7]) or who choose to take too high a dose, sometimes for suicidal purposes.

Other substances are also likely to cause overdose deaths, such as GHB.

The concept of DDRDs also includes deaths that cannot be considered as overdoses, as they are not dose-dependent, but which nevertheless fall under the European protocol definition. Substances such as cocaine [8] or cannabis [9] can cause cardiovascular complications (myocardial infarction, stroke) which can lead to death shortly after use, even in occasional users or when taken in small doses. These are often, but not always, people with risk factors for atherosclerosis or who already had pre-existing cardiac condi-

tions. The direct relation between these deaths and use of the substance is often discussed.

In order to have comparable data on DDRDs from different EU countries, the European protocol provides for using the data from forensic medicine and toxicology services (special registers) and statistics on causes of death (from general registers). To identify DDRDs in general registers, the protocol proposes a range of cause of death codes which refer to the 10th International Classification of Diseases (ICD10). The presence of one of these causes on the death certificate (as the underlying cause) allows it to be classified as a DDRD. This list of cause of death codes called "selection B" is outlined in the box below. For special registers, where deaths are not given a code by using the ICD10, the same criteria are used [4].

According to the EMCDDA, DDRDs therefore include the deaths of people who use illicit drugs or who misappropriate drugs and do not use them for their proper use to treat addiction, chronic pain or even for a one-time use. It seems relevant to analyse the developments to try and distinguish these different profiles, even if in some cases they may overlap.

■ Flawed data sources

Data on DDRDs currently come from three different sources in France⁵.

The first is the basis of medical causes of death produced by the Epidemiology Centre on Medical Causes of Death (CépiDc) from death certificates. The DDRDs are retrieved by the CépiDc by selecting the deaths where the underlying cause corresponds to a code from selection B. As the T codes that provide information on the relevant substances are not widely used in France, some codes from selection B were not used. The French adaptation factors in codes X42, X62, Y12, F11, F12, F12, F14, F15, F16 and F19, thereby excluding some cases of DDRD [10]. The data sent by the CépiDc is then used by

Selection of codes for retrieving cases which correspond to the European definition of DDRDs from general registers, also known as "Selection B"

This list of codes includes:

- accidental intoxication from narcotics or hallucinogens (X42), intoxication for suicidal purposes (X62) or for an undetermined reason (Y12), together with intoxication from opium (T40.0), heroin (T40.1), other opioids: codeine, morphine (T40.2), methadone (T40.3), other synthetic narcotics (T40.4), cocaine (T40.5), other unspecified narcotics (T40.6), cannabis (T40.7), lysergide or LSD (T40.8) or other unspecified hallucinogens (T40.9);
- accidental intoxications from anticonvulsant, sedative, hypnotic, antiparkinson and psychotropic drugs (X41), for suicidal purposes (X61) or with undetermined intent (Y11), together with intoxication from psychostimulants with a risk of abuse, excluding cocaine (T43.6);
- accidental intoxications from prescription drugs and biological substances (X44), for suicidal purposes (X64) or whereby the intent is not determined (Y14) in combination with the T43.6 or T40.0-9 codes;
- mental and behavioural disorders related to using opioids (F11), cannabis (F12), cocaine (F14), other psychostimulants (F15), hallucinogens (F16) and combinations of substances or unknown substances (F19), whether this is acute intoxication (.0), use that is harmful to health (.1), addiction symptoms (.2), withdrawal symptoms (.3), delirium as a withdrawal symptom (.4), a psychotic disorder (.5), symptoms of amnesia (.6) or a residual or late onset psychotic disorder (.7).

This list does not include death codes that are only related to alcohol or tobacco, since the presence of at least one illicit substance and/or opioid is required to be included under the European definition.

2. This definition is similar to the one proposed by the EMCDDA, which, however, only refers to the use of illicit psychoactive substances.

3. Deaths considered to be indirectly related to drug use are those caused by disease (particularly infectious diseases), accidents from being under the influence of narcotics (falling from a high place, drowning, car accident, etc.) and violence or suicide (excluding intoxication from a psychoactive substance).

4. In seizures in the United States and Canada, police found fentanyl or analogues that were sold as counterfeit drugs (benzodiazepines) or as cocaine. This type of seizure is rare in Europe but a few cases have been reported since 2016, notably in Sweden.

5. Until the end of the 2000s, the Central Office for the Repression of Drug-Related Offences (OCRITS) also published data on overdose deaths from illicit drugs recorded by the police and gendarmerie. This data, which is no longer sent systematically, has not been published since. However, some death cases continue to be sent to the OCRITS.

the OFDT. The indicator for the total number of these deaths is supplemented by a second indicator for the number of deaths among under 50s, in an attempt to understand the developments in deaths for this specific drug user profile. The increasing proportion of people aged 50 and over (particularly over 65s) represented in DDRDs suggests that people are dying for reasons other than drug use. Due to long processing times for death certificates, the latest available data is from 2015⁶.

The second source is the Drug and Substance Abuse-Related Deaths survey (DRAMES), coordinated by the National Agency for Medicines and Health Products Safety (ANSM) and the Network of the Regional Abuse and Dependence Monitoring Centres (CEIP-A) in Grenoble. DRAMES aims to identify the substances involved (narcotic prescription drugs, opioid substitution drugs - opioid substitution medications, illicit substances and all emerging substances) to assess how dangerous they are and to track developments. This survey of experts carrying out toxicological analyses for the legal authorities makes it possible to collect death cases every year that are related to the misuse of psychoactive substances. These cases come under the European definition of DDRDs for special registers, excluding suicides from drugs and deaths from analgesics abuse when experiencing pain, with this being identified in the survey investigating analgesia-poisoning deaths (DTA, see below). A substance's part in leading to death is assessed by assigning it an accountability score that is calculated based on the concentration of the substances in the blood or, failing that, in different forms (hair, tissues, body fluids). It also makes it possible to rank the molecules based on their involvement in the death and to identify these molecules. Experts' participation in the survey is voluntary and, despite an increasing number of participants, the national territory is not fully covered. Due to the increasing number of experts participating in the scheme, it is not possible to assess the annual development in the total number of deaths through DRAMES data. However, it is possible to analyse the annual development of the substances involved by comparing the respective proportion of each of them. The latest available figures are from 2017.

The third source of data, the annual survey on analgesia-poisoning deaths (DTA in French) that has been carried out by the CEIP-A of Grenoble and the ANSM since 2013, gathers death cases related to the use of analgesic drugs [11]. Like DRAMES, this survey is conducted among toxicologists and relates to deaths that have been inves-

DDRDs and death certificates

The certificate completed by the physician who recorded the death comprises:

- an administrative section including the certification of the death, with the date and time of death, details about the civil status of the deceased person and the funeral details, including cases where the burial was prevented for forensic purposes. When the physician suspects a DRD, they must prevent the burial for forensic purposes and they often only partially complete the death certificate. If the causes of death are not mentioned, they are temporarily classified by the CépiDc as "unknown or poorly defined causes" pending the results of the forensic examinations. A legal procedure is opened, and the Public Prosecutor's Office may order an autopsy and/or toxicological tests to be carried out;
- an anonymous medical section, which includes the cause(s) of death based on the information available at the time of death;
- an additional section, created in 2018, designed to provide information on the causes of death when these causes are known several days after the death has been recorded.

The medical section of this document, completed by the physician who certified the death, describes the causal sequence of the diseases that directly led to the death, from the underlying cause⁷ to the immediate cause. These causes are coded by the CépiDc using the ICD10. In the event of forensic investigations, once the results are known, the forensic medical expert must complete an additional section to be sent to the CépiDc, which will update the causes of death. But this obligation is rarely respected. However, if the forensic medical expert does not receive the results of the toxicological analyses intended for the Public Prosecutor's Office, which is often the case, they will not be able to complete this section.

tigated so that the court can research the causes of death. A death cannot be recorded in both the DRAMES and the DTA survey. Deaths occurring from drug abuse and addiction are not included in the DTA survey (and are included in DRAMES⁸), those occurring for suicidal purposes are included in the DTA survey (and are excluded from DRAMES⁹).

In total, the criteria for selecting deaths in the DRAMES scheme are more restrictive than the selection B criteria used to process CépiDc data. But combined with those of DTA, they are very similar to the European selection B.

By examining these three available sources, changes in the number of deaths can be analysed from CépiDC data and the breakdown of deaths can be studied from DRAMES and DTA data.

Large variations in deaths after an increase over the 2000s

In 2015, 373 DDRDs were recorded in the general mortality register. This number peaked in the mid-1990s (451 deaths in 1994), then declined rapidly with the spread of opioid substitution treatments, which reduced heroin use, which was a great cause of death at the time. During the 2000s, deaths increased sharply again and then changed dramati-

cally in the early 2010s (Figure 1, p.4). The number of deaths fell by a third between 2010 and 2012, largely due to a decrease in the number of deaths of under 50s. The rapid increase that followed, however, was mainly from people who were aged 50 and over at the time of death.

The substances in question are poorly documented in the CépiDc database. In 2015, 58% of death certificates directly related to drugs did not indicate the substance involved. Even when the substances are specified, the most commonly selected codes do not indicate them. Indeed, these codes - X42 for accidental intoxication from narcotics or hallucinogens without the associated T code or F19 for mental and behavioural disorders related to use of multiple substances - do not correspond to any substance in particular. Deaths related to opioid analgesics are included in selection B and are therefore included in the CépiDc's DDRD data. They cannot be identified from ICD codes that do not provide sufficient information on the substances involved, but only from the causes of death which are indicated in plain text on the certificates. Only 18 cases were

6. France, Poland and Belgium are the European Union countries that take the longest to produce death statistics (three years or more).

7. The WHO defines the underlying cause of death as "the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury".

reported in 2015, 14 of which were morphine-related (excluding cases of morphine overdoses in people at the end of their lives), which seems very low compared to the number of opioid analgesic-related cases reported in the DTA and DRAMES surveys.

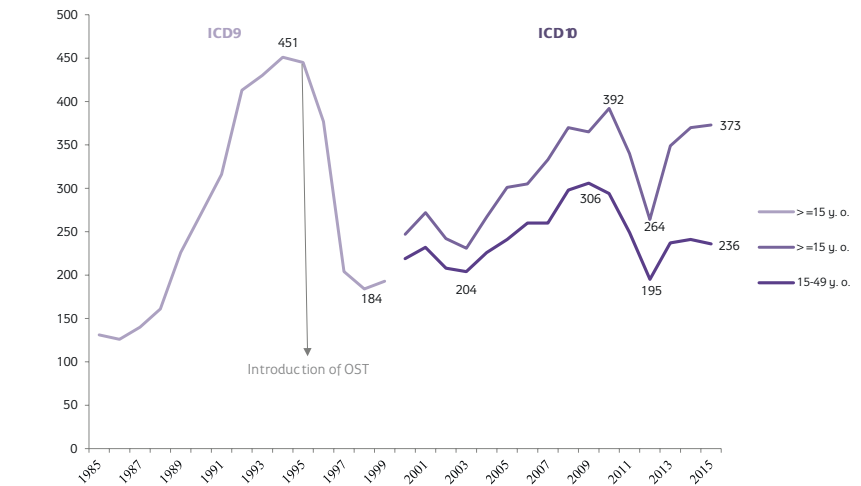
The observation of the distribution of substances involved in deaths is therefore based on data from the DRAMES and DTA schemes. Both schemes are systematically supported by toxicological analyses and provide detailed information about the substances involved in DRDs.

Substances involved: major implication of opioids

Opioids play an overwhelming role in deaths (78% in 2017), with methadone and heroin being the most common (37% and 25% respectively), which is considerably more than any other opiate drugs (13%) and buprenorphine (8%) (Figure 2). In addition to opioids, other substances are also involved: cocaine in 26% of cases of death, cannabis in 6% of cases, amphetamines in 6% of cases too and new psychoactive substances (NPS) in 3% of cases. The category “other substances” includes a fairly broad range of substances, predominantly benzodiazepines (with this substance always being taken with another substance because deaths only caused by benzodiazepine cannot be included in the survey). Since several substances may be involved in the same death, the sum of the percentages is greater than 100%.

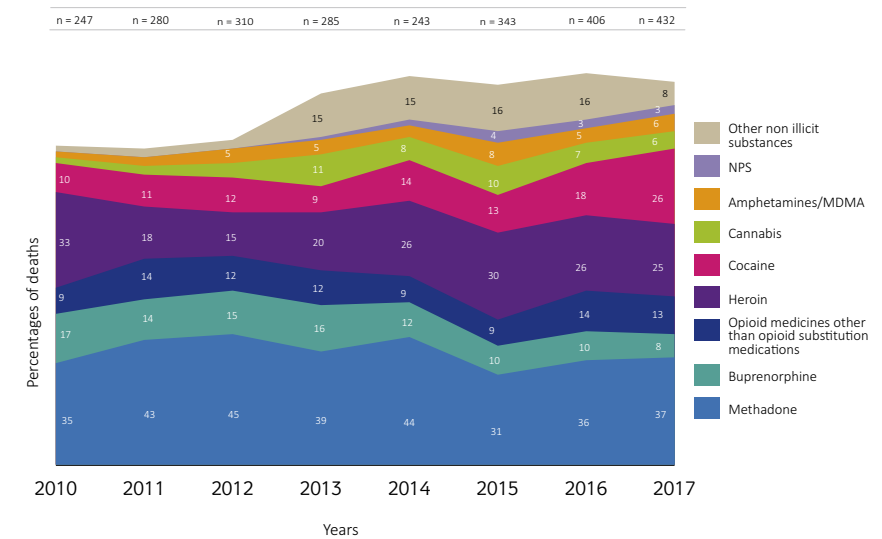
The proportion of deaths attributable to opioids has fluctuated moderately between 75% and 84% since 2010. In terms of opioids, the proportions of deaths attributable to heroin and methadone change inversely: when one increases, the other decreases and vice versa. The proportion of deaths involving buprenorphine is decreasing (from 17% in 2010 to 8% in 2017); the proportion attributable to other opioid medication (excluding opioid substitution medications) is fluctuating between 9% and 14% with no clear evolutionary trend. Apart from opioids, cocaine was the only other drug that played a significant role in deaths in 2010 (10%). Since then, its involvement seems to have been increasing, especially from 2014 onwards. The proportion of deaths involving cannabis, amphetamines, MDMA, NPS and other substances (particularly benzodiazepines), which was low in 2010, has gradually increased, largely due to experts having a better understanding of benzodiazepines’ and cannabis’ involvement in deaths. These proportional developments apply to a

Figure 1. Changes in the number of direct drug-related deaths in the CépiDc general register



Source: CépiDc-INSERM, processed by OFDT
ICD 10 codes: F11, F12, F14, F15, F16, F19, X42, X62, Y12.

Figure 2. Changes in substances involved from 2010 to 2017



Source: DRAMES, CEIP-A of Grenoble, ANSM

total number of deaths that has been increasing since 2010, an increase that is partly due to a better participation in the data collection scheme (51 experts from 28 facilities, representing 70% of France, contributed in 2017, compared to 31 experts in 2010). With regard to the development in the number of deaths recorded in the DRAMES survey, it therefore seems difficult to distinguish what changes have come from improvements in the tool and what is due to the objective increase in the number of deaths.

The DTA survey recorded 105 deaths involving analgesics in 2017 (excluding deaths involving salicylic acid and paracetamol). Since the beginning of the survey, the three main medications involved have been tramadol

(47% of deaths in 2017), morphine (29% of deaths) and codeine⁸ (18%). The proportion of deaths involving oxycodone has increased significantly (17% of deaths in 2017 compared to 7% in 2013), while the number of deaths involving fentanyl has never exceeded 4 cases. In 27% of cases, it was suicide and in the other cases, toxic death without any further details. After little change between 2013 and 2016, the number of deaths recorded in the DTA survey increased in 2017, going from 83 to 105. As with the

8. The number of codeine-related deaths reported in the DRAMES and DTA surveys decreased slightly from 28 to 24 cases between 2016 and 2017, while in July 2017, drugs containing codeine, ethylmorphine, dextromethorphan and noscapine were removed from the list of drugs available over the counter, following the reporting of several cases of substance abuse, particularly among adolescents and young adults. Legislative order of 12 July 2017.

DRAMES survey, however, this development occurred in a context where the number of participating experts also increased significantly (from 26 to 36 between 2016 and 2017).

These numbers of deaths related to opioid analgesics can be put into perspective with the prescriptions for these substances. In 2015, 17% of French people received reimbursement for an opioid analgesic, representing nearly 10 million people [12]. For nearly 98% of these people, it was a weak opioid. Between 2006 and 2017, the use of weak opioid analgesics⁹ decreased by 59%, going from 59 to 24 defined daily doses (DDD)/1,000 inhabitants/day, while the number of people using strong opioids increased by 45% from 2.0 to 2.9 DDD/1,000 inh./day [12]. A very small proportion of this population had problems with or were addicted to opioids and were at risk of overdose [13]. Opioid substitution treatment (OST) benefits a much smaller population (around 180,000 people) [14] which has a more severe addiction to opioids, with a significant overdose risk, even if it is less than if no treatment were taken. The periods of initiation and cessation of treatment are particularly at risk.

■ Increasing age at death

Among the cases recorded in DRAMES, the average age at death has increased rapidly since 2011 (33.7 years), going up to 38.3 years old in 2017. The youngest victim was 15 years old, the oldest was 68 years old and the median was 39 years old. These deaths were mainly among men (85% in 2016) [15]. This large predominance of men, with a similar average age that is increasing, is also found among people who have been reimbursed for opioid substitution medications, and in users attending harm reduction facilities (CAARUD) or specialised addiction treatment centres (CSAPA). In the 2015 CépiDc data, after excluding cases that were wrongly classified as DDRDs, the average age (40.7 years old) and proportion of male subjects (85%) are comparable to the figures observed in the DRAMES data.

The predominance of men is less considerable for analgesic deaths (53%). However, there are still slightly more men, while almost 60% of opioid analgesic users are women [12]. The average age is 48.8 years old (compared to 43 years old in 2015) and the median is 49 years old. The age of the victims ranges from 3 to 89 years old. The deaths recorded in the DTA scheme therefore concern people with a very different profile from those recorded in the DRAMES scheme.

■ A widely underestimated death rate

The assessment of the number of DDRDs in France faces many problems. The first concerns selecting DDRD cases from the death certificates. A detailed examination of all the causes of death listed on death certificates that were reported as DDRDs by the CépiDc in 2015 shows first of all that 31% of them were wrongly classified in this category. 21% of the instances of this were polypathological elderly people or people with multi-metastasis cancer (the median age of this group as a whole was 82.5 years old) whose death certificate mentioned a morphine overdose that should not have been considered as the underlying cause of death. In 10% of cases, it concerned people who were dependent on psychoactive substances and whose death was not related to intoxication but to a pathology that was more often than not infectious (endocarditis, pneumopathy or septicæmia). Therefore, 257 cases out of 373 actually corresponded to a DDRD in the general mortality register in 2015. The vast majority of these cases were in the under-50 age group.

But on the other hand, the figures on the mortality register largely underestimate the number of DDRDs for several reasons. The first is that death certificates are often not sent to the CépiDc in cases where an autopsy or toxicological analyses are carried out, particularly in Paris and Lyon. As a result, these deaths remain among those classified as the reason for death being unknown¹⁰ and therefore never appear among the DDRDs. Secondly, the doctor certifying the death may not apply the guidelines in the event of a suspicious death and may not prevent burial for various reasons (lack of knowledge about the guidelines, pressure from family members or from judicial police officers) [16]. Even if legal proceedings are initiated, toxicological analyses may not be requested, as practices vary from one region to another, particularly depending on how difficult it is to perform an autopsy [16, 17]. According to CépiDc data, an autopsy is recommended by the certifying physician in one third of suspected DDRD cases when reporting the death. But the result is rarely known when writing the certificate (only in 8% of cases). More than half of the deaths did not result in an autopsy being recommended and this information is missing in 15% of death certificates. Autopsies are therefore far from being systematic in direct drug-related deaths. Finally, due to the adaptation of selection B excluding certain codes, a small proportion of the DDRDs are not included in the calculation [10].

In theory, the DDRDs from the CépiDc database should include most of the DRAMES and DTA deaths, plus all the DDRD cases that have not been subject to a forensic investigation. In reality, this is far from the case since the DRAMES and DTA schemes, although not exhaustive, recorded two thirds more DDRDs than the CépiDc in 2015 (343 cases plus 82 cases compared to 257 cases) and a total of 537 DDRDs in 2017 (432 and 105 deaths respectively). By estimating the number of DDRDs, by cross-referencing data sources in accordance with the capture-recapture method¹¹, it was indicated that the number of these deaths was underestimated by at least 30% in the early 2000s [18]. However, these estimates pose complex methodological issues. The results obtained are accompanied by very wide confidence intervals that depend on the quality and level of cross-referencing of the different sources.

■ Impact of the availability and purity of heroin

The development in the number of DDRDs among under 50s appears to be strongly linked to the availability and purity of heroin. A similar trend can be observed in the overall number of DDRDs, the proportion of heroin-related deaths, the quantities of heroin seized and the potency of heroin in seizures [7, 19]. The variation in the amount of heroin seized between 2000 and 2015 therefore seems to largely explain the change in the number of deaths per DDRD during this period (correlation coefficient $r=0.76$, $p<0.001$) (Figure 3). As the OFDT's monitoring system, Emerging Trends and New Drugs (TREND) has already observed, the monitoring of heroin diffusion cycles is crucial insofar as its high availability generally seems to lead to new opioid users, but also to an increase in overdoses [20].

Similarly, between 2010 and 2017, the development in the proportion of deaths attributable to heroin appears to be strongly related to heroin purity (correlation coefficient $r=0.77$, $p=0.02$)

9. The prevalence of use of weak analgesics decreased between 2008 and 2012 in line with the decrease in dextropropoxyphene/paracetamol prescriptions as early as 2008, before it was withdrawn in 2011 (due to a large number of deaths from intentional or accidental intoxication). The switch to other weak analgesics was partial and preceded the discontinuation of dextropropoxyphene/paracetamol. Since 2012, the prevalence of use of weak analgesics has been stable.

10. The category of ill-defined and unknown causes of death represented 4.2% of all deaths in 2015, i.e. almost 25,000 deaths, which shows the extent of the problem in France. DDRDs only represent a very small percentage of them.

11. A statistical method used to estimate a population's size that is difficult to quantify. The total size of the population is calculated from at least two independent captures from the members of this population. The number of members captured in both samples is used to infer an estimate of the total number of individuals in the demographic.

(Figure 4). The more heroin is available and the purer the heroin, the greater the number of people addicted to opioids, which leads to an increase in the number of fatal overdoses from heroin but probably also in overdoses for all opioids combined (among under 50s).

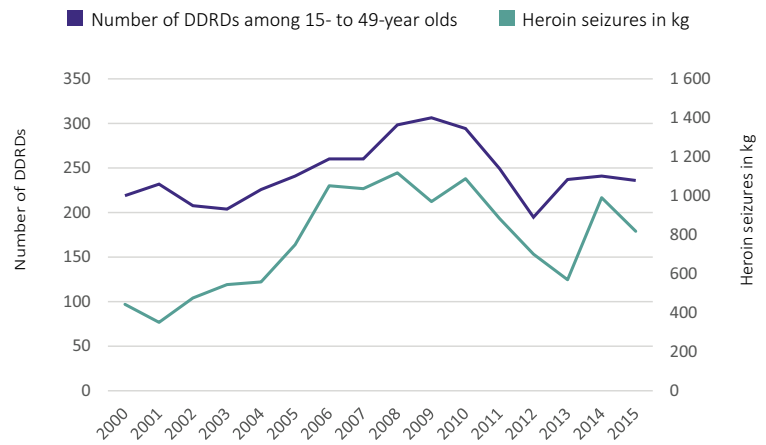
The three-fold increase between 2013 and 2017 in the proportion of cocaine-related deaths (from 9% to 26% of deaths in the DRAMES scheme) can also be linked to the increase in the number of people using cocaine aged 18 to 64 [21] or in those who have been attending CAARUDs (harm reduction facilities) since 2015 and CSAPAs (specialised addiction treatment centres) since 2016 [22-24].

■ One of the lowest death rates in Europe

France and most EU Member States, as well as Norway and Turkey, provide the EMCDDA with standardised data on the number of DDRDs [5], which can therefore be compared in principle. The figures for France are those from CépiDc (373 deaths in 2015). With a number from 4 to 6 DDRDs per million inhabitants¹² aged 15 to 64, France is one of the countries with the lowest rates, along with Belgium, Portugal, Italy and several Eastern European countries. The countries with the highest rates are all in Northern Europe. Estonia leads with 130 deaths per million inhabitants, followed by Sweden (92 deaths), Norway (75), the United Kingdom (74) and Ireland (69). Germany (21), Austria, the Netherlands, Slovenia, Croatia and Spain are somewhere in the middle (between 10 and 40 deaths per million inhabitants). These discrepancies can be caused by various factors: the prevalence of opioid use, access to treatment, particularly OST, the type of OST favoured, the practices for investigating suspicious deaths and the quality and coverage of the death information system. Mortality rates related to drug use generally appeared to be stable in Europe between 2006 and 2016, despite very different developments in different countries.

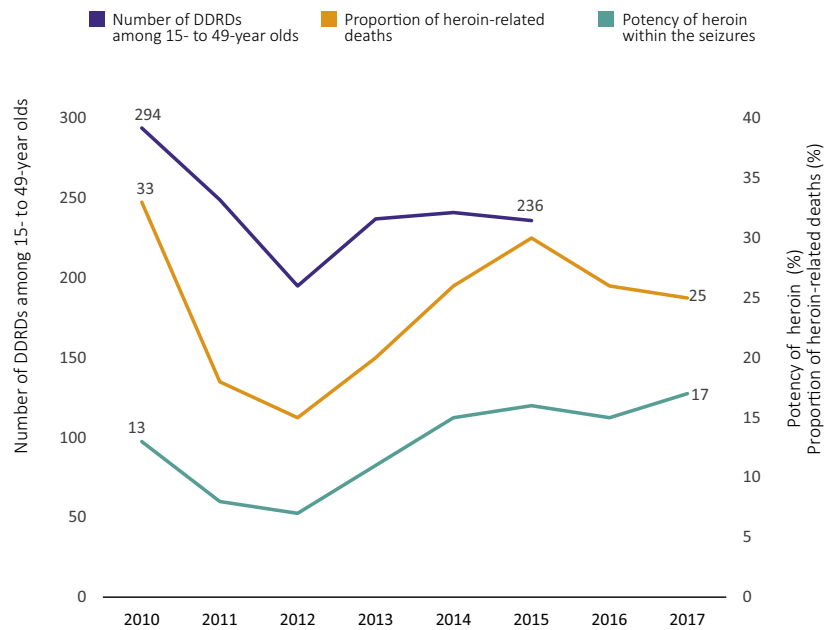
The highest death rate in Europe remains considerably lower than that of the United States, which reached 217 DDRDs per million inhabitants in 2017, which is a significant increase since the early 2000s, particularly since 2015. Between 1999 and 2017, the number of DDRDs more than quadrupled, going from 16,850 to 70,250 deaths. Three waves of deaths followed one after the other and built up. The first is related to opioid analgesic prescriptions (particularly

Figure 3. Comparative changes in the number of direct drug-related deaths among 15-49-year-olds and in the quantities of heroin seized between 2000 and 2015



Sources: CépiDc for the number of DRDs, OCRTIS for the quantities of heroin seized

Figure 4. Comparative changes in the number of DDRDs among 15-49-year-olds, the proportion of heroin-related deaths in the DRAMES scheme and the average heroin potency in brown heroin seizures between 2000 and 2017



Sources: CépiDc for the number of DRDs, DRAMES (CEIP-A of Grenoble, ANSM) for the proportion of heroin-related deaths, STUPS (Système de traitement uniformisé des produits stupéfiants), INPS for the average heroin levels (brown heroin).

oxycodone) [25]. The second is associated with heroin, which users addicted to opioids turned to when prescription control measures were put in place. Finally, more recently, the availability of fentanyl and its analogues, which are easily accessible through the darknet for a very low price, has led to new deaths [26]. The overdose risks of these synthetic opioids seem to be serious, with even very small doses being fatal: thus, the lethal dose of carfentanyl is 1 mg. The main substances concerned in 2017 were fentanyl and its analogues,

opioid prescription drugs (oxycodone, hydrocodone and methadone) and heroin [1, 27]. In Canada, opioid overdoses represented 109 deaths per million inhabitants in 2017, with the majority of these deaths involving fentanyl or its analogues [28]. However, this rate remains lower than that of Estonia.

¹². Nearly 4, excluding cases that were wrongly classified as DRDs, nearly 6 if we keep all the cases identified from the French adaptation of selection B in the CépiDc register.

Nevertheless, it is important to be weary when comparing the number of DDRDs per capita in different countries, even within the European Union. Despite standardisation in Europe of the selection codes, there are still significant variations between countries in how often these forensic investigations take place (performing autopsies and/or toxicological analyses) [29] and in the coding and registration practices of DDRDs that may influence the data.

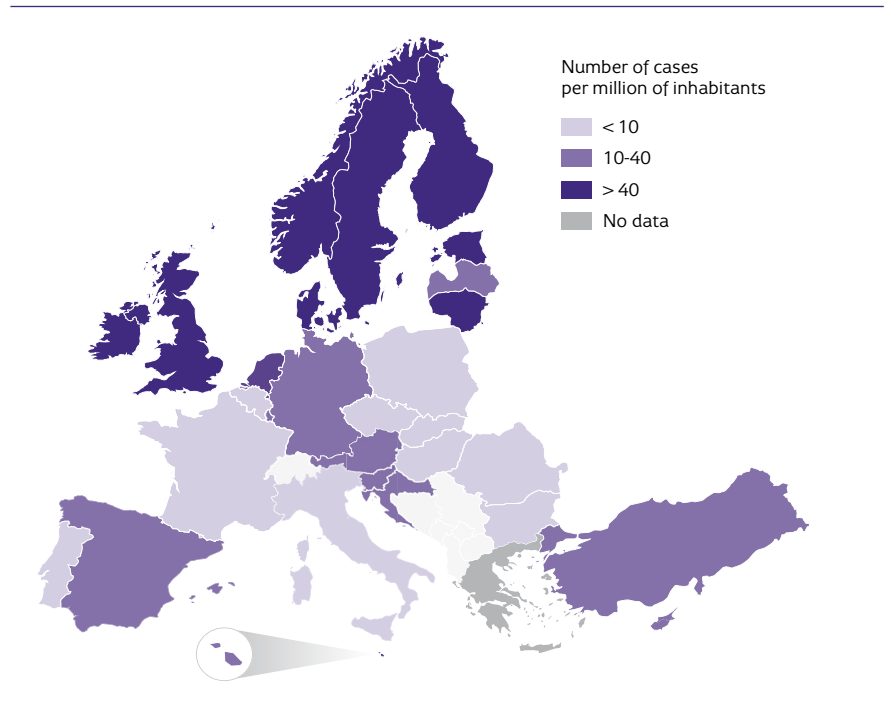
Age at death in France (40.7 years old or 38.9 years old, depending on the sources) is comparable to that of the United Kingdom (42 years old), Spain, the Netherlands and Ireland (39 years old) and Germany (38 years old). The proportion of people over the age of 40 among the victims, which is higher in Western European countries, reflects the increasing age of the population that is consuming opioids in these countries. Opioids are responsible for 78% of fatal overdoses reported in Europe. Heroin is involved in the majority of these deaths.

The difference between the rate of DDRDs observed in France and in the United Kingdom (which is more than ten times higher) or in Germany, which are all similar on an economic and cultural level, seems to support the hypothesis that the number of these deaths is being greatly underestimated in France. As mentioned above, the number of DDRDs from the cause-of-death database is certainly not representative of all of these deaths. But there is such a difference compared to the United Kingdom, for example, that it seems unlikely that it is entirely due to the limitations of the French information system on overdose deaths. France's policy of unrestricted access to buprenorphine as an opioid substitution medicine, a molecule that has much lower risks of fatal overdose than methadone, which is favoured by the United Kingdom and Germany, is also probably one of the reasons behind the difference in mortality rates in France and these countries.

■ Conclusion

Measuring the number of DDRDs and the development of this number is complex. Nevertheless, it can be confirmed that it was at least 537 in 2017 and it can be concluded that there was a clear trend towards an increase in the number of DDRDs between 2000 and 2015. The continuous increase during the 2000s was followed by a sharp decrease in 2011 and 2012, an increase in 2013 and 2014, before stabilising in 2015. While the vast majority of deaths are related to opioids, the number of cases where cocaine was

Figure 5. Direct drug-related mortality rates among 15-64-year-olds in 2017 (or last year available) in the European Union, Norway and Turkey



Source: EMCDDA

involved has grown rapidly since 2014. The number of deaths that can be attributed to other substances, whether marginal or non-existent in 2010, have increased, such as deaths related to cannabis, MDMA and amphetamines, or have emerged, such as those related to NPS. However, this development with regards to other substances could be partly linked to the greater attention paid by the monitoring scheme to include these substances within the scope of a DDRD.

The overall increase in the number of DDRDs identified by CépiDc seems to be due to two factors. Firstly, there is the increase in the number of deaths among opioid-using drug users, the vast majority of whom are male, middle aged and around 40 years old, which appears to be strongly related to the availability and purity of heroin. At the same time, an increase in deaths can be seen among elderly people and those at the end of their life who use opioids during palliative care. There is a third profile of younger people who use opioids to treat acute or chronic pain that is not related to them being at the end of their life or to cancer pain. It is this bracket of users that is behind the opioid crisis in the United States. The current monitoring scheme in France identified just over a hundred deaths for this type of use in 2017. But perhaps even more so than for the other categories, this number is most certainly underestimated.

The number of DDRDs in France appears low compared to the situation in other European countries and incomparably lower than in the United States. The high accessibility of opioid substitution treatments in France, particularly buprenorphine, partly explains this difference. However, there are several indications that the number of DDRDs is underestimated.

Preventing DDRDs requires the public authorities to really commit to the cause, both in terms of combating drug trafficking and fake drug trafficking and in access to health care and harm reduction in general medicine, local pharmacies, prisons and specialised settings (CAARUDs, CSAPAs and hospitals). France was initially behind in implementing OSTs but it is now one of the countries with one of the highest coverages in the European Union, as it is estimated to be around 85% (proportion of at-risk opioid users using OST). On the other hand, other harm reduction measures to prevent overdoses are being implemented very slowly, such as take-home naloxone, an antidote to opioid overdoses which has been marketed for more than 40 years, to the most at risk opioid users as well as the development of two drug consumption rooms in France, compared to 24 in Germany and 31 in the Netherlands.

The quality of the data, that knowledge about DDRDs relies on, remains a major challenge. The improvement of the information system on overdose deaths requires the information on the causes of death to be sent systematically by forensic medical experts through the additional section, through a more precise coding system for the causes of death so that information on the substances in question can

be archived and the initial cause of death can be identified correctly. In addition, the time periods for CépIdc data becoming available are too long. Knowledge of the substances involved in the death and the steps leading to death requires systematic toxicological analyses and autopsies. The latter must take the constant evolution of new information on new synthetic products into account in order to be able to research them.

For its part, the OFDT will endeavour to provide a new estimate of the number of DDRDs. This is the objective of the ERASM study (estimation of the number of fatal overdoses) in France, by cross-referencing the sources of the CépIdc, DRAMES and DTA schemes and of the Central Office for the Repression of Drug-Related Offences (OCRTIS) on DDRDs, focusing on DDRDs that occurred in 2019.

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