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Drug-related deaths in Sweden

– Estimations of trends, effects of changes in recording practices and studies of drug patterns

CAN Rapport 158

Håkan Leifman

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Contents

Foreword

CAN is an NGO and a national centre of competence with core funding from the Swedish government. Our major tasks are to monitor the drug trends in Sweden and disseminate our findings. We collect data on consumption, morbidity and drug-related mortality in the population, among other areas. In order to fulfil our major tasks, indicators of high validity are a necessity. As a consequence, CAN is often engaged in different kinds of validity studies and in developing methods. This report is a result of that type of commission.

The report describes the situation of drug-related mortality in Sweden and constitutes a basis for the expert meeting in Stockholm in September 2016 as part of an EMCDDA project on drug-related deaths which focuses on seven European countries (project title: To contribute to the EMCDDA assessment of the drug-induced deaths data and contextual information in selected countries).

The main focus is on the statistics used to monitor drug-related deaths; if they have been subject to changes in recording practices and to what extent such changes may have affected the reported mortality rates over time, as well as the comparability with the data produced according to the EMCDDA European protocol. Suggestions for improvements are also presented.

The report also includes a description of gender and age differences in drug-related mortality, as well as of polydrug use patterns among the deceased. The matter of possible causes for the changes observed is not addressed in this report, but will be the main theme in a second forthcoming report.

Although several of the analyses in the study have been conducted by CAN in dialogue with the National Board of Forensic Medicine, the author is solely responsible for all reporting, interpretations and conclusions.

Stockholm, August 2016

Håkan Leifman
Director, CAN

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Svensk sammanfattning (Swedish summary)

Denna rapport ger en närmare beskrivning av narkotikarelaterad dödlighet i Sverige. Rapporten utgör ett underlag för ett expertmöte i Stockholm i september som en del av ett projekt om narkotikarelaterad dödlighet initierat av EU:s narkotikamyndighet EMCDDA.

Enligt den statistik som används i Sverige har den narkotikarelaterade dödligheten mer än fördubblats under de senaste tio åren, framförallt som ett resultat av fler dödsfall med opioider. Men tillförlitligheten av statistiken har ifrågasatts av både myndigheter och forskare och frågan har därför väckts om ökningen verkligen varit så pass kraftig som en fördubbling. Framförallt har man pekat på att olika metodförändringar i analysarbetet kan ha bidragit till att ge en felaktig bild av utvecklingen.

Huvudsyftet med studien är att försöka ge en så god bild som möjligt av den faktiska utvecklingen genom att ta hänsyn till olika metodförändringar som genomförts över tid.

Analyserna baseras i huvudsak på rättsmedicinska toxikologiska data och täcker alla rättsmedicinskt undersökta dödsfall under de senaste 15–20 åren. Enligt svensk lag ska alla onaturliga dödsfall rapporteras till polisen av den läkare som utfärdar dödsorsaksintyget och för i stort sett alla dessa fall begär polisen sedan en rättsmedicinsk undersökning. Onaturliga dödsfall är sådana dödsfall där man kan misstänka att döden beror på en yttre orsak, till exempel våld eller förgiftning men också när den avlidnes identitet inte kan fastställas eller om kroppen genomgått betydande förändringar.

Nästan alla dödsfall som bedöms som narkotikarelaterade har genomgått rättsmedicinsk undersökning, inklusive toxikologiska analyser. Rättsmedicinska data utgör därför basen för *alla* de indikatorer över narkotikarelaterade dödsfall som används i Sverige. Över 5 000 dödsfall genomgår varje år rättsmedicinsk undersökning av totalt ca 90 000 dödsfall per år. Andelarna har varit förhållandevis konstanta under de senaste ca 20 åren. Analyserna i denna studie har genomförts av CAN men i flera fall i dialog med Rättsmedicinalverket (RMV), som är central förvaltningsmyndighet för rättspsykiatrisk undersökningsverksamhet, rättsmedicin, rättskemi och rättsgenetik. På RMV:s avdelning för rättskemi och rättsgenetik genomförs de toxikologiska analyserna av de rättsmedicinskt undersökta dödsfallen.

Det förtydligas i rapporten att rättsmedicinska toxikologiska data visar på *förekomsten* av olika substanser bland avlidna utan hänsyn tagen till om substanserna orsakat dödsfallen. Därför bör indikatorer som baseras på dessa data kallas för narkotikadödsfall (och när det gäller exempelvis opioider som opioiddödsfall). Detta till skillnad från siffror som bygger på dödsorsaksregistret där orsakssambandet har utretts. Dödsfall baserade på dödsorsaksregistret och som bedöms som orsakade av narkotika, benämns i denna rapport som narkotikarelaterade dödsfall (och när det gäller opioider som opioidrelaterade dödsfall).

De skattningar som redovisas i denna rapport tyder på att det skett en faktisk ökning av antalet dödsfall med narkotikaförekomst och även, högst sannolikt, i antalet narkotika*relaterade* dödsfall men att tidigare redovisade ökningstrender varit kraftigt överskattade. Den huvudsakliga anledningen till denna överskattning är metodförändringar – metodförbättringar – inom RMV som lett till att man identifierar fler dödsfall över tid med narkotikaförekomst. Socialstyrelsen (2016) har sedan tidigare rapporterat om metodförändringar när det gäller kodning av dödsfall i dödsorsaksregistret.

Såvitt vi kan bedöma har vi tagit hänsyn till alla viktiga och större metodförändringar som skett inom RMV (på rättskemiska laboratoriet) under tidsperioden. Först och främst gäller det den stora ökningen av antalet rättsmedicinskt undersökta dödsfall som screenas för förekomst av olika narkotikapreparat. I tillägg, i mindre utsträckning, sänkta kvantifieringsgränser för att ett visst preparat ska räknas som ett positivt fall. Slutsatserna i denna rapport bygger på antagandet att inga andra större, för oss okända, metodförbättringar inträffat under tidsperioden.

Det är viktigt att poängtera att den ökning i narkotikadödsfall som framkommer under senare år efter kontroll för metodförändringar är betydande (från 2008 till 2014: + 33 % i absoluta antal; + 27 % per invånare 15 år och äldre) och beror på en ökning av antalet opioiddödsfall. Idag består de allra flesta narkotikadödsfall (och narkotikarelaterade dödsfall) av opioiddödsfall och flertalet av dessa är syntetiska opioider som metadon, buprenorfin, fentanyl och oxikodon. Det är också dessa preparat som svarar för i stort sett hela ökningen under de senaste åren. Den exakta ökningen i procent eller i absoluta tal ska dock tolkas med försiktighet.

Antalet narkotikadödsfall, och antalet narkotikarelaterade dödsfall, har ökat både bland män och kvinnor och i olika åldersgrupper. Det tycks som om det har skett en kollektiv förskjutning uppåt av antalet dödsfall på så sätt att fördelningen mellan män och kvinnor och mellan olika åldersgrupper ser ungefär densamma ut i dag som för 10–15 år sedan. Värt att notera är att uppgifterna för 2014 som redovisats till EMCDDA avseende underliggande dödsorsaker visade på en kraftig ökning bland unga vuxna (20–24-åringar), från 51 dödsfall 2013 till 102 dödsfall 2014. Det är viktigt att följa denna utveckling för att se om det rör sig om en tillfällig ökning eller om den högre nivån kvarstår även 2015.

Analyserna som redovisas av kombinerat bruk av opioider och alkohol och/eller bensodiazepiner visar att andelen opioiddödsfall med alkoholförekomst minskat under de senaste tio åren medan kombinationen opioider och bensodiazepiner snarare ökat som andel av samtliga opioiddödsfall. Resultaten indikerar att förändringar i alkoholbruket bland dödsfallen inte kan förklara ökningen i antalet opioiddödsfall medan bensodiazepiner däremot kan ha varit en bidragande faktor till ökningen. Det kombinerade bruket av opioider och bensodiazepiner är snarare regel än undantag bland opioiddödsfallen. Effekterna av det kombinerade bruket av opioider och bensodiazepiner bör utredas närmare.

De analyser som genomförts av dödssättet bland de narkotikarelaterade förgiftningsfallen visar att det endast är de oavsiktliga förgiftningsdödsfallen som ökat och inte de till följd av avsiktlig handling (suicid) och de med obestämd (oklar) avsikt. Detta kan tyda på att ökningen av antalet narkotikarelaterade dödsfall främst beror på en ökning av överdoser bland narkotikamissbrukare.

Det framkommer tydligt i denna rapport att den svenska statistiken över narkotikarelaterade dödsfall (och narkotikadödsfall), och framförallt rapporteringen av denna, har varit förvirrande. En viktig lärdom för framtiden är att man måste ha bättre kontroll på metodförändringar som sker på olika nivåer i de olika mätmetoderna som ligger till grund för de indikatorer som används för att spegla utvecklingen av narkotikarelaterad dödlighet.

Den bristande statistiken är faktiskt svår att förstå, inte minst i ljuset av att Sverige anses ha statistik och register av god internationell kvalitet. I stort sett alla dödsdata som behövs finns också framtagna i Sverige men dessa data är utspridda på olika huvudmän och sammanfogningen – länkning – av data är bristfällig eller saknas helt.

Rapporten nämner flera steg som kan tas för att avsevärt förbättra kvaliteten och därmed möjligheterna att dra bättre slutsatser av den pågående utvecklingen. Det kanske viktigaste steget är att underlätta en länkning på individnivå av rättsmedicinska toxikologiska data med data från dödsorsaksregistret. Detta har diskuterats i ca 20 år men steget har ännu inte tagits.

Socialstyrelsen utvecklar för närvarande sin narkotikastatistik som baseras på dödsorsaksregistret. Den utgör den officiella och viktigaste statistiken över narkotikarelaterade dödsfall.

CAN och RMV planerar att gemensamt utveckla den rättsmedicinska toxikologiska statistiken så att den kan användas för regelbunden monitorering över, först och främst, förekomsten av olika narkotikapreparat bland rättsmedicinskt undersökta dödsfall. Detta kan vara ett viktigt komplement till den officiella statistiken över narkotikarelaterade dödsfall och i linje med EMCDDA:s rekommendationer över selektionskriterier för ett specialregister.

De brister som denna studie visat på i den svenska statistiken över narkotikarelaterade dödsfall leder också till ett ifrågasättande av jämförbarheten av svenska siffror med siffror från andra europiska länder. Detta gäller både i omfattningen (nivåer) av narkotikarelaterad dödlighet för olika år och i jämförelser av trender mellan Sverige och andra länder. Dessutom kan det inte uteslutas att metodförändringar även genomförts i andra länder, vilket ytterligare skulle kunna försvåra jämförbarheten. Till detta ska läggas redan existerande skillnader mellan länder i de olika stegen från inträffat dödsfall till ett kodat narkotikarelaterat dödsfall. Detta gäller exempelvis i hur vanligt det är med rättsmedicinska undersökningar i olika länder och hur många substanser som screenas för.

Sammanfattningsvis bör man vara mycket försiktig i att dra långtgående slutsatser av redovisade skillnader mellan länder i narkotikarelaterad dödlighet. Slutsatserna i rapporten baseras endast på ingående analyser av data från ett land (Sverige). Mer långtgående slutsatser om jämförbarheten skulle vara möjliga att dra om liknande analyser genomförs i flera andra europeiska länder.

Summary

This report describes the situation of drug-related deaths in Sweden and constitutes a basis for the expert meeting in Stockholm in September 2016 as part of an EMCDDA project on drug-related deaths, which will focus on seven European countries with high or increasing drug-related deaths.

According to official mortality statistics, drug-related deaths have more than doubled in Sweden over the last 10 years or so, mainly due to a higher number of deaths with opioids. However, the reliability of these statistics has been questioned due to methodological changes in the different indicators of drug-related deaths. This is also the main matter dealt with in this report.

In order to get a better understanding of the trends in drug-related deaths, and of the comparability of the Swedish with the data from other European countries, detailed analyses of mainly toxicological forensic data have been conducted. The data cover all forensically investigated deaths in Sweden over the past 15-20 years. According to Swedish regulations, all certified or suspected unnatural deaths must be reported to the Police by the physician issuing the death certificate. The Police will then request a forensic investigation. Almost all drug-related deaths in Sweden are subjected to forensic investigations, including toxicological analyses, and thus constitute the basis for all drug-related death indicators in Sweden. Out of a total of 90,000 deaths every year, more than 5,000 deaths are forensically investigated. These numbers have remained stable for over 20 years. Several of the data analyses in this study have been conducted by CAN in dialogue with the National Board of Forensic Medicine (RMV).

It is made clear in this report that death data that is directly based on toxicological analyses, and nothing else, shows the presence of different substances among the forensically investigated deaths. Since this selection is not based on any consideration of causality, these deaths are referred to as *drug deaths* (or e.g. opioid deaths). Selections from the general mortality register (GMR) (also known as the Cause of Death Register, CDR) are instead based on causes of death and are therefore referred to as indicators of *drug-related deaths* (or e.g. opioid-related deaths).

The estimations made in this report suggest that a real increase in drug deaths, and most likely drug-related deaths, has occurred, but that the previously reported increasing trends have been greatly exaggerated. The main reason for this exaggerated picture is that the changes – or improvements – in methods of analyses within forensic investigations (more cases tested, and lower threshold for drug detection) have led to the detection of more deaths with positive findings of drugs. As reported by the National Board of Health and Welfare (NBHW, 2016), changes in coding practices have also contributed to a false rate of increase. To the best of our knowledge, all major changes in methods of analyses implemented at RMV from 2008 to 2014 have been taken into account in this report. The conclusions made are based on that important assumption. In any case, the results and the exact trends should be interpreted with caution.

The increase that remains after controlling for changes in methodology is still rather substantial and is due to an increase in the number of opioid deaths (from 2008 to 2014 with approximately 33% in absolute numbers and 27%, per inhabitants aged 15 or over). Today, most drug deaths, and drug-related deaths, are tied to opioids, usually synthetic opioids such as methadone, buprenorphine and fentanyl.

Interestingly, the increase in drug deaths, and drug-related deaths, is observed among both men and women and across several age groups. It appears as if there has been a more or less collective shift upward in death rates, so that the gender and age distributions look much the same today as they did 10-15 years ago. However, data for 2014 showed a dramatic increase in drug-related

poisoning deaths (underlying cause of death) among young adults (20-24 years of age), from 51 deaths in 2013 to 102 in 2014. Here, follow-up is important, to see if the levels remain as high in 2015.

Studies of the combined use of opioids with alcohol and/or benzodiazepines revealed that alcohol involvement in opioid deaths (and all drug deaths) has decreased (from about from about 36% of all opioid deaths in year 2000 to less than 25% in year 2014), whereas benzodiazepine involvement has increased at more or less the same pace as opioid deaths (in 2014: ~65% of all opioid deaths). Interestingly, of the four groups of opioid deaths, with or without alcohol or benzodiazepine involvement, it is only the group of opioid deaths combined with benzodiazepines that shows a clear and substantial rising trend since 2006. Opioid deaths with no benzodiazepines and no alcohol show a modest increase, whereas the two groups of opioid deaths including alcohol, one including and one not including benzodiazepines, show no increase during the entire study period (here 1994-2014). The same patterns and trends for combined use are revealed for all drug deaths, i.e., opioid deaths plus deaths with illicit drugs.

The results on polydrug use in opioid deaths suggest that alcohol use cannot explain the increase in opioid deaths, while the use of benzodiazepines may have contributed to the increase. As a matter of fact, the combined use of benzodiazepines and opioids is more rule than exception in opioid deaths. The effect of this combined use in opioid-related deaths needs to be investigated much more in the future, but this also requires measures of the use of benzodiazepines among opioid addicts in general.

Analyses of manner of death in poisoning cases show clearly that it is the number coded as unintentional poisoning deaths that has increased for the past 10 years or so, whereas intentional (suicides) and undetermined poisoning deaths have both remained rather stable. This may suggest that the increase is mainly due to overdoses among drug addicts.

It is obvious from this report that the Swedish drug-related deaths statistics, and especially the handling and reporting of data, have been confusing. An important lesson for the future is that one must keep track of changes in statistics that are related to case ascertainment, investigation and recording practices. This has certainly not been done in Sweden. The inconsistencies revealed in the statistics are difficult to comprehend, given that Sweden is generally known for high-quality statistics. More or less all death data that could be needed are compiled and available from certain sources. The problem is that these data are spread out and not linked together, making it difficult to achieve a reliable assessment of drug-related death trends.

This report mentions several steps that should be taken in order to improve the situation. Perhaps the most important step would be to facilitate a linkage of forensic toxicological data with cause of death data, something that has been discussed for many years, is recommended by the EMCDDA, and is in place in several European countries, in the form of national technical working groups (EMCDDA, 2015: Assessment of the implementation of the five Key Epidemiological Indicators).

The National Board of Health and Welfare is in the process of developing their statistics based on causes of death. These statistics constitute the official and most important statistics in this field. CAN and RMV are considering development of the forensic toxicology data further, in order to create a special register to be used for regular monitoring. This could be an important complement to the official statistics on drug-related deaths and would be rather similar to the EMCDDA recommendations of selection criteria for special registers.

The inconsistencies in the Swedish data on drug-related deaths also question the comparability of the Swedish statistics with other European countries, both in levels for specific years and in country-specific trends. In addition, it cannot be ruled out that also other countries have done methodological changes (improvements) in their statistics over time which may further hamper the comparability. To this should also be added already existing country differences in many of

the stages of the collection of the drug-related deaths statistics, such as in the degree of forensic investigations and in the number of substances included in toxicological analyses.

Altogether this implies that country comparisons in the rate of drug-related deaths should be done very cautiously also in comparisons of trends in drug-related deaths. This is the implication drawn from the Swedish case. Similar assessments of the possible impact of methodological changes also in other countries would be needed in order to draw more certain conclusions of the degree of comparability.

1. Introduction

According to official mortality statistics, drug-related deaths have doubled in Sweden over the last 10 years (NBHW, 2015). The increase is mainly due to a higher number of deaths with opioids (e.g., Fugelstad, 2016; NBHW, 2016, Wikner et al., 2014). Since the increase in number of opioid deaths has taken place simultaneously with a substantial expansion of opioid substitution treatment (OST) for heroin addiction, mainly with methadone and buprenorphine as substitute drugs, an intense debate about this form of treatment has taken place (for an overview of the debate, see e.g., Hasselgren, 2015 & Rickert & Johnson, 2013). Furthermore, Sweden ranks second among European countries in drug-related mortality (EMCDDA, 2016), a situation that calls into question the efficiency of the Swedish drug policy in terms of preventing drug abuse and drug-related deaths. Thus, the increase is used from different ideological positions, either to criticise the "restrictive" Swedish drug policy or to defend the old "traditional" policy.

However, the question has also been raised whether there has been such a dramatic increase as indicated by the different time series on drug-related deaths (e.g., Ledberg, 2015a; Hasselgren & Guttormsson, 2015). In a recent report from the Swedish authority responsible for the general mortality statistics, the National Board of Health and Welfare, it is stated that the increase to a significant extent is due to changes in coding practices and improvements in the forensic investigations of deaths, thus implying that the recent increase may be a statistical artefact (NBHW, 2016). Others argue for a dramatic, more or less 100 per cent increase since 2006 (e.g., Fugelstad et al., 2016). This report will focus on the basic question of whether or not there has been a dramatic increase in drug-related deaths in Sweden, and whether, and to which extent the increase is due to changes in surveillance. This will be done through detailed analyses of drug mortality data covering the past 15-20 years.

Data on drug-related deaths can fulfil several purposes, besides monitoring prevalence of deaths, in particular when these data are interpreted along with other drug indicators such as population surveys and in- and outpatient data. They can, for instance, help to identify new or more dangerous patterns of use, such as the use of different combinations of substances. They can also help to identify the characteristics of people with a higher risk of dying, and the particular circumstances surrounding deaths, in order to contribute to preventative work (see e.g., EMCDDA, 2009). Therefore, timely and accurate statistics on drug-related deaths are of vital importance.

Drug-related mortality is not a fully uniform or well-defined concept and measurements of drug-related deaths are therefore subject to various forms of trade-offs, such as which drugs should be taken into account and, ultimately, which deaths should be considered to be drug-related.

Differences in the levels and in the trends of drug-related deaths across Europe have triggered a research project from the EMCDDA. This project started in 2015 and focuses on seven countries, particularly in the north of Europe, where drug-related deaths mortality is higher than the EU average, and or increasing. The project aims to enhance the analysis of the drug-related deaths data (including their completeness and quality), question the caveats and possible comparability issues, and explore the contextual information that may explain the drug-related situation and trends (ref Slides – EMCDDA DRD projects 2015-2016– they will be available on the DRD web pages).

Sweden is one of the concerned countries, and this work constitutes a preparation to this European analysis.

Today, three different indicators are used in Sweden in order to monitor drug-related deaths or drug death trends. Two of them are selections from the general mortality register (GMR) (also known as the Cause of Death Register, CDR) based on causes of death and are therefore indicators of *drug-related deaths*. The third indicator is based on deaths where forensic toxicological analyses show the presence of illegal drugs or different pharmaceutical opioid drugs. Since this selection is not based on any consideration of causality, these deaths are referred to as *drug deaths*.

These three indicators will be presented in some detail in the next chapter, but it should be mentioned that since all three are entirely or largely based on toxicological findings reported from forensic investigations, detailed analyses of the toxicological data are crucial in order to better understand the trends in drug-related deaths over time. This report presents the results of such analyses. These analyses have been conducted by CAN, a national centre of competence with one of its main tasks to study drug trends in Sweden, in collaboration with the National Board of Forensic Medicine (Rättsmedicinalverket, abbreviated *RMV*)[1].

The data analyses are done for two main reasons. One is to assess to what extent, if any, improvements in forensic examinations, particularly toxicological analyses, have had an impact on the trends in drug-related deaths. The second reason is that these data include important information on drug use patterns among the deceased, information that cannot easily be obtained from the GMR.

The report has the following disposition. Chapter two provides a more detailed description of the drug-related deaths statistics in Sweden, with a closer presentation of the three indicators (time series) applied in Sweden, including the drug-related deaths trends according to these indicators. This chapter also presents some other relevant basic information, such as the number and proportion of deaths forensically examined and the proportion of drug-related deaths that undergo forensic examination.

Chapter three presents the main results from the analyses of toxicological data from forensic examinations. The main question at issue is thus if the increases shown in all three indicators mirror true changes or if recording practices, i.e. improvements in the forensic investigations, may have contributed to an exaggerated or even false increase in the reported number of drug-related deaths. The term recording practices is here used broadly and refers to both forensic methodology as well as coding rules, even though this study focuses on the first, in particular effects of increased screening and lower threshold values for drug detection.

Chapter four shows numbers and trends in drug-related deaths for men, women and different age groups, as well as different combinations of polydrug use among the deceased. Finally, Chapter five summarizes the main results and presents some conclusions and suggestions for improvements in the future monitoring of drug-related deaths trends in Sweden.

[1] The principal task of RMV is to produce reports required in legal cases. It has four different fields of operation – forensic medicine, forensic psychiatry, forensic toxicology and forensic genetics.

2. Statistics on drug-related deaths in Sweden

The basis for the classification of most deaths with drug involvement is the more than 5,000 forensic autopsies conducted in Sweden every year. This number has remained stable for several decades (in year 1994: 5,553; year 2000: 5,223; year 2005: 5,366; year 2010: 5,226; year 2014: 5,346), also in relation to the annual number of deaths in Sweden, which has amounted to approximately 90,000 for many years.

According to Swedish regulations, all certified or suspected unnatural deaths, obscure deaths (involving alcohol/drug addicts, subjects with no known diseases, decomposed bodies, subjects with unknown identity or suspected malpractice cases), must be reported to the Police by the physician issuing the death certificate. In these cases, the Police will request a forensic autopsy. Unnatural deaths are thus forensically examined, but there are some exceptions. One is accidental falls among the elderly, which are rarely examined forensically. There are also cases where patients are treated for poisoning and traffic accidents in hospitals, but not referred to a forensic examination after death. There are six forensic departments that conduct examinations, covering the whole Swedish territory and population (Umeå, Uppsala, Stockholm, Linköping, Gothenburg and Lund).

During an autopsy, femoral blood, urine and vitreous samples are collected, fluorinated, and submitted to the Department of Forensic Chemistry at RMV in Linköping, which constitutes a national laboratory, where all samples are routinely screened for pharmaceutical drugs and ethanol. Illicit drugs were previously only screened upon request from the responsible pathologist, i.e., when drug intake seemed likely based on circumstantial information and autopsy findings (Jönsson et al., 2007). The number of drugs screened and the extent of screening for several drugs, including illicit drugs, have increased over the past years and is today conducted routinely in almost all autopsy cases (see also Chapter 3).

Since 1992 the basic pathological results and results from toxicological screening are stored in the national forensic medicine database and the national forensic toxicology database, respectively. The latter database forms the basis for the analyses presented in Chapter 3.

The toxicological findings are considered when the forensic pathologist determines the cause of death mentioned on the death certificate. Death certificates are sent from RMV to the National Board of Health and Welfare, where causes of death are classified according to the English version of the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10), including the official updates published on the World Health Organization's (WHO) website. The data are entered into the general mortality register (GMR), kept by the same Board. As indicated by the report from the National Board of Health and Welfare (2016), not all substances mentioned on the death certificates are recorded in the GMR. This makes it very difficult to use the GMR in order to assess the extent of ante-mortem polydrug use among the deceased.

The National Board of Health and Welfare aims at including all deaths among Swedish residents, whether or not the deceased was a Swedish citizen and whether or not the death occurred in Sweden or abroad. However, a study showed that a death certificate was missing in about 1.1% of deaths in 2013 (NBHW, 2013). These incomplete cases are listed in the GMR, but without any medical information. Non-residents who die in Sweden are not included in the GMR.

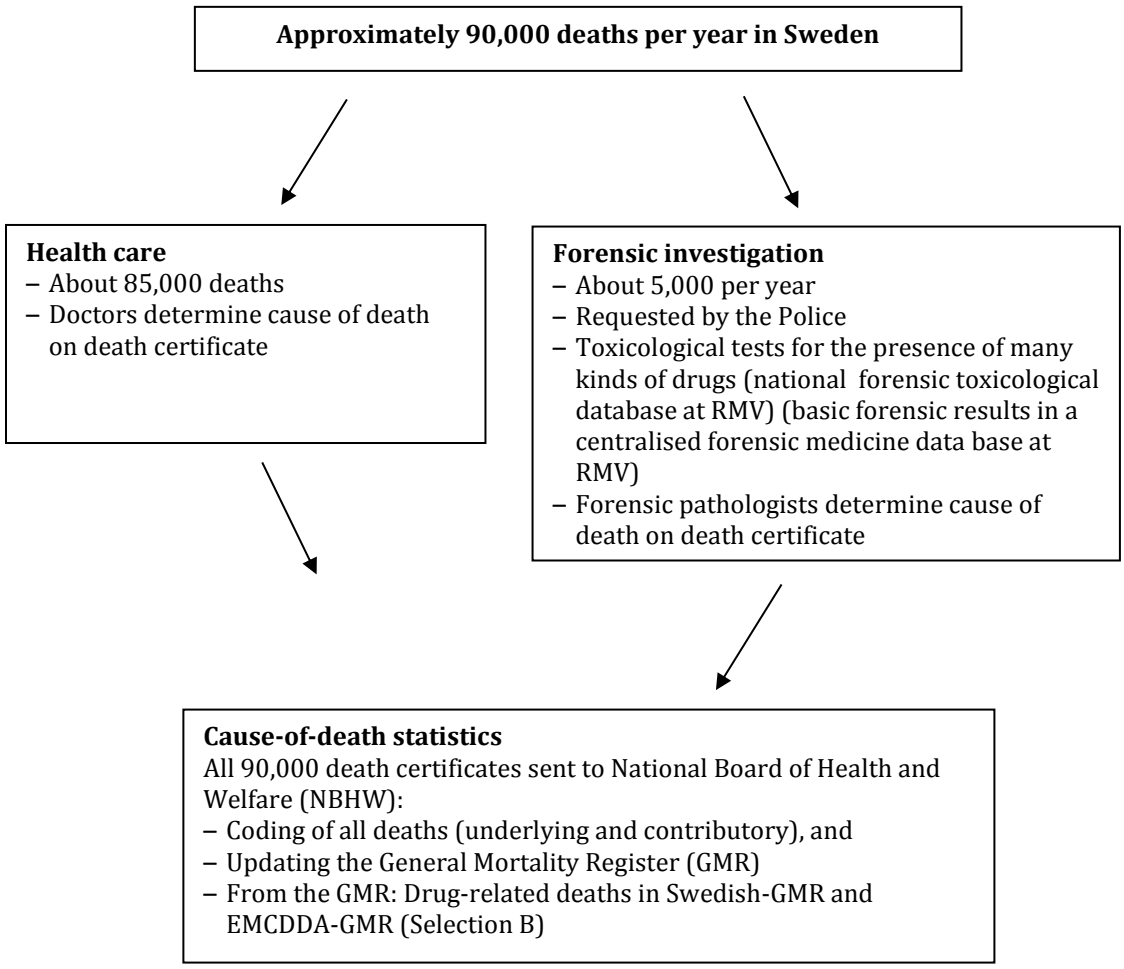

Figure 1. The chain from a death to statistics in the GMR.

The steps from a death to a recording in the GMR are shown in Figure 1. As shown, approximately 90,000 people die every year in Sweden (in 2014: 89,062) out of a population of 9.7 million (in 2014). Most deaths (approximately 85,000) are not the subject of a forensic investigation, but go through the health care system (hospitals). However, the majority of all acute drug-related deaths are forensically investigated (Fugelstad, 2016).

The three indicators on drug-related deaths an drug deaths

Two of the three indicators are selections of deaths from the Swedish official cause-of-death register, i.e., the GMR at the National Board of Health and Welfare. One is a selection originally developed in Sweden in 1987 (hereafter named the Swedish-GMR), and the other a selection defined by EMCDDA (often referred to as Selection B), first used in 1997 after the introduction of the ICD-10 (hereafter named the EMCDDA-GMR). Both selections are based on a set of ICD codes for drug-related conditions. In the Swedish-GMR, a death is considered drug-related if a drug-related condition appears anywhere on the death certificate, whereas the EMCDDA-GMR specification requires that a drug-related condition is stated as the underlying cause of death.

The EMCDDA-GMR (see EMCDDA, 2009) selection comprises deaths (from 1997) fulfilling one of the following criteria:

(1) Mental and behavioural disorder due to psychoactive substances use, harmful use, dependence and other mental and behavioural disorders due to opioids (F11), cannabinoids (F12), cocaine (F14), other stimulants (F15), hallucinogens (F16), or multiple drug use (F19) or

(2) Poisonings (X and Y codes) that are accidental (X41, X42), intentional (X61, X62) or of undetermined intent (Y11, Y12) due to substances under the headings narcotics (T40.0-T40.9, except dextropropoxyphene) or psychostimulants (T43.6). T-codes are thus selected in combination with the X- or Y-codes, respectively.

Following the update of the guidelines, codes X44 X64 and Y14, in combination with T-codes are also included but few countries have implemented this change (EMCDDA DRD protocol 2009). Sweden is not one of them where it is included.

The broader Swedish-GMR selection comprises deaths with any of the following ICD codes, either as underlying or contributory cause of death:

1994-1996 (ICD-9): 304, 965.0, 968.5, 969.6 or 969.7.

1997 onward (ICD-10): F11-F16, F18-F19, O35.5 (maternal care for (suspected) damage to foetus by drugs), P04.4 (foetus and new born affected by maternal use of drugs of addiction), T40.1-T40.3, T40.4 except dextropropoxyphene, T40.5-T40.9, T43.6, Z50.3 (drug rehabilitation) or Z71.5 (drug abuse counselling and surveillance).

More succinctly put, the Swedish-GMR , including a few additional, non-poisoning specific codes (within parenthesis above) compared to the EMCDDA-GMR, is based on underlying and/or contributory cause of death, whereas EMCDDA-GMR is based only on underlying cause of death.

The Swedish-GMR is now under revision by the NBHW and a new drug-related death indicator has been suggested including more pharmaceuticals then previously (as well as illicit drugs) and only poisoning deaths (NBHW, 2016)

The third indicator is a selection of deaths based solely on toxicological findings for certain drugs from the national toxicological data base at RMV. This indicator, often named Toxreg, comprises all deaths where a forensic toxicological analysis shows the presence of illegal drugs or of the opioids methadone, buprenorphine or fentanyl in the body. There is thus no requirement that the death was certified or assessed as due to poisoning; toxicological analysis results alone determine if a death should be included. If several drugs are found the drug considered primarily responsible for the event is identified based on a predefined standard with the following priority order: 1) heroin or morphine; 2) methadone; 3) buprenorphine; 4) fentanyl; 5) amphetamine; 6) cocaine; 7) other drugs except THC, and last on the order of priority, 8) THC. Group 7, other drugs, contains less common drugs, such as methamphetamine, GHB and ecstasy. To exclude suicides or accidental poisoning by morphine or other opioid drugs prescribed for pain relief, only deaths in the age range up to 60 years of age are included. However, if both morphine and the heroine metabolite 6-monoacetylmorphine are found the death is included in the Toxreg irrespective of age, since this particular combination indicates intake of illegal heroin (Fugelstad, 2016).

Toxreg is thus solely based on toxicological findings and not on cause of death, whereas the two GMR-based drug-related deaths series depart to a substantial degree from the toxicological findings obtained in the forensic investigations. Both GMR selections are based on the information specified on death certificates and most of the death certificates that include drugs as cause of death are the result of forensic investigations.

In 2014, 14% of the death certificates for drug-related deaths in the Swedish-GMR lacked information on drugs, but included reports of previous drug abuse (most of them given ICD-10 code F11). Almost all of them were reported from health care, not from RMV (NBHW, 2016). As

for the EMCDDA-GMR (Selection B), 609 cases were reported in 2014 and only 12 of them (2%) had unknown toxicology (see also Table 1 below). It should be added that not all deaths with known toxicology will necessarily have passed through a forensic investigation, but that deviating cases are very few.

In summary, there is a considerable degree of overlap between the three indicators. However, there are also significant differences, namely:

- Toxreg is based only on the presence of different drugs in forensically investigated deaths and is therefore in practice not a directly drug-related deaths indicator. The Swedish-GMR and the EMCDDA-GMR are based on cause of death.
- The Swedish-GMR includes both underlying and contributory causes of death, the EMCDDA-GMR only underlying (but combinations of codes are required).
- Toxreg is based only on toxicological data from forensic investigations (selected from the previously mentioned national toxicological forensic data base). The Swedish-GMR and the EMCDDA-GMR include all deaths with drug-related diagnoses, forensically investigated or not, and with or without known toxicology.
- Toxreg includes a smaller number of opioid drugs than the Swedish-GMR and the EMCDDA-GMR.
- Toxreg has an age limit of 60 years for including pharmaceutical opioids.

The selection criteria thus differ between the three indicators and none of the three captures all "true" drug-related deaths during a year.

Previously reported trends in drug-related deaths and drug deaths, according to the three indicators

Figures 2a-b show the trends according to the three indicators in absolute numbers of deaths and per capita (per 100,000 inhabitants aged 15 or more). As mentioned, the three selections differ on the total number of deaths, but show similar trends with stable levels in the late 1990s and early 2000s, with increasing numbers after year 2006. The Swedish selections (Swedish-GMR and Toxreg) show higher numbers than the EMCDDA-GMR and are closer to each other than to the EMCDDA-GMR.

In 2014, the number of drug-related deaths reached 765 for the Swedish-GMR, 686 for Toxreg and 609 for the EMCDDA-GMR. The increase since 2006 is dramatic. When taking population growth into consideration, the increase from 2006 to 2014 is 117% for the Swedish-GMR, 114% for Toxreg and 185% according to the EMCDDA-GMR. For all three indicators, the increase has accelerated over the past few years, especially between 2013 and 2014. According to the EMCDDA-GMR, the number of drug-related deaths (age 15-64) in Sweden amounts to 93 per million population. This compares with and EU average of 19 cases per million population in 2014 (EMCDDA European Drug Report, 2016). If this reflects an actual difference between Sweden and other EU-countries, is another matter and, at least indirectly dealt with in this report by scrutinising the validity of Swedish data.

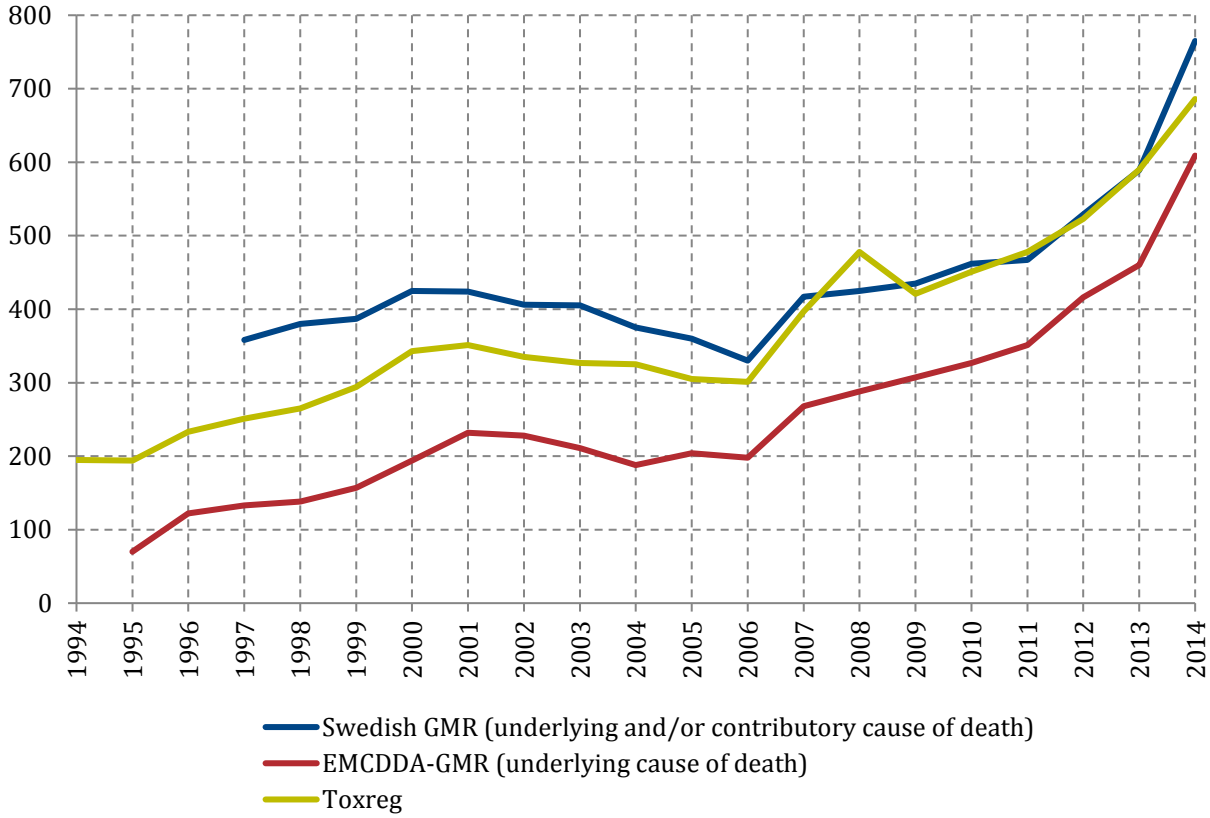

Figure 2a. Drug-related deaths (or drug deaths) according to the three indicators, 1994/1997-2014, in absolute numbers.

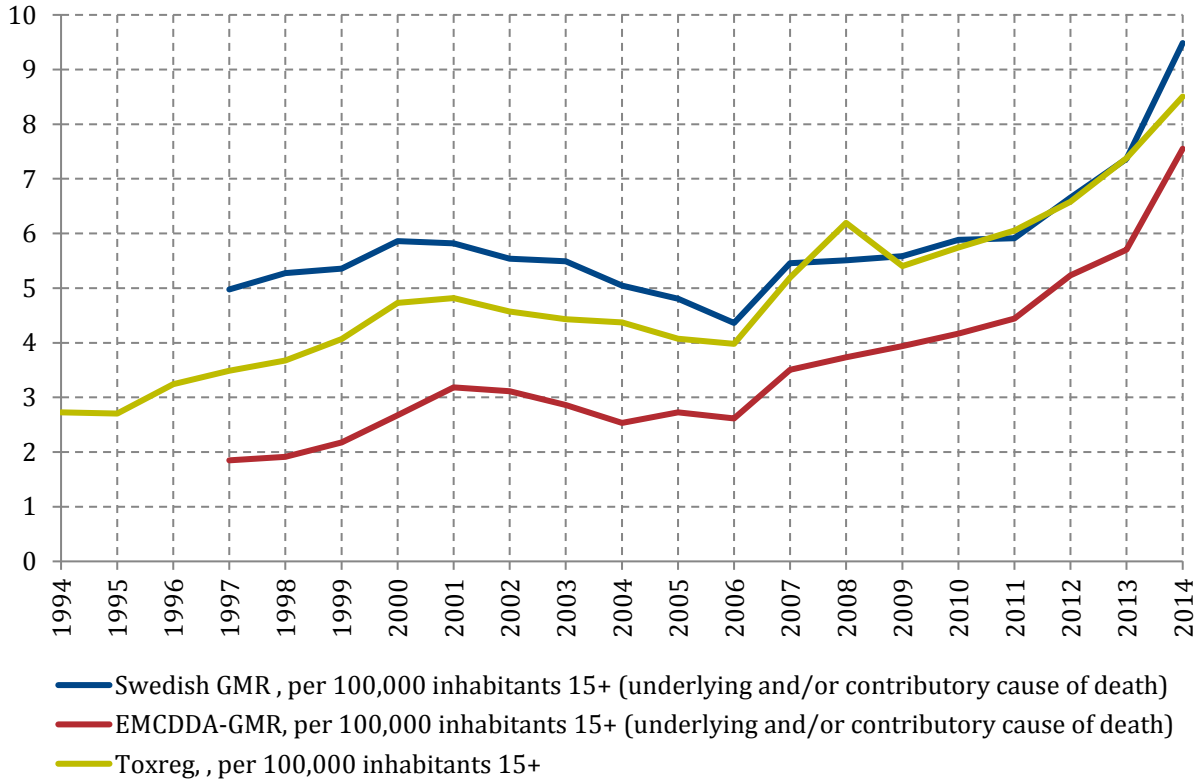

Figure 2b. Number of drug-related deaths (or drug deaths) according to the three indicators 1994/1997-2014, per 100.000 inhabitants aged 15 or over.

It should be mentioned that the degree of overall overlap is not as high as the rather similar total estimates shown in Figures 2a-b. For the period 1997-2012, 34% of Toxreg deaths were not present in the Swedish-GMR. Also, 43% of the deaths in the Swedish-GMR were not present in Toxreg. However, the degree of overlap differs between different drugs. Heroin deaths in Toxreg (as reflected by the 6-monoacetylmorphine metabolite) are very well captured by both GMR selections (90-95%). Most morphine, methadone, buprenorphine, and fentanyl cases in Toxreg are also captured (60-80%) (Fugelstad, 2016). The remaining drugs in Toxreg show a lesser degree of overall capture within both GMR selections, from a few percent for THC, to 40% for cocaine and 60% for amphetamine, in relation to the Swedish-GMR. The corresponding proportions in relation to the EMCDDA-GMR are lower (cocaine: 16%, amphetamine: 22%) (Leifman et al., 2015, unpublished data).

Since the number of opioid deaths contributes an increasingly large proportion of all drug deaths over the past 10 years or so, it is likely that the overall overlap between the three indicators has increased. However, this has not been possible to test.

Opioids are today the most commonly mentioned drugs on death certificates (see, e.g., NBHW, 2016) and account for most or almost all of the increase since the year 2006, according to all three indicators. Toxreg reports an increase in opioid deaths from 152 deaths in 2006 to 494 deaths in 2014. In 2006, opioid deaths accounted for 50% of all drug deaths in Toxreg. In 2014, the proportion reached 72%.

Table 1 shows the number of drug-related deaths and the number of such deaths with opioids from 2004-2014, according to the EMCDDA-GMR (Selection B). In 2014, opioids were found in 86% of 597 drug-related deaths. In 2004, the corresponding proportion was 67%. The number of deaths with any drug tested for other than opioids has increased from 50 to 90 deaths between 2004 and 2014. As mentioned above, almost all drug-related deaths found in the EMCDDA-GMR, which is based on the underlying cause of death, include information about drugs on death certificates and almost all of them have passed through a forensic investigation. The number with known toxicology over time is shown in Table 1.

Table 1. Number of drug-related deaths according to EMCDDA-GMR (EMCDDA, selection B, ST6), number of cases with known toxicology and number with and without opioids.

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Number of drug-related deaths	188	204	198	268	288	307	327	351	419	460	609
Number of cases with known toxicology	152	187	184	259	273	285	306	341	407	451	597
Number with opioids (+ any drug)	102	130	145	220	240	255	259	318	350	415	507
Number with any drug without opioids	50	57	39	39	33	30	47	23	57	36	90

3. The impact of changes in recording practices on reported statistics

In the previously mentioned report from the National Board of Health and Welfare (NBHW, 2016), it is stated that the increase in drug-related deaths to a significant extent is due to changes in coding practices and improvements in the forensic investigations of deaths. This chapter will first describe the more important changes that have occurred and then assess whether or not the changes (improvements) within forensic investigations may have had an effect on the number of positive cases detected.

It has not been possible to assess the direct impact of the changes in coding practices, since we do not have access to all necessary data on causes of death. However, this assessment has already been done by the NBHW (2016). Instead, the focus here will be on changes (improvements) in the toxicological analyses performed at the Department of Forensic Chemistry and our analysis will be based on individual-level data from the national forensic toxicology database. The possible downside to this is that we are not studying drug-related deaths, but deaths with positive toxicology. However, this also has its advantage, as these forensic toxicology data are not affected by errors or changes over time in the coding practices of drug-related deaths. As shown in Figure 1, coding takes place a later stage. The toxicological data can thus reveal trends for specific substances or groups of substances, irrespective of whether their ICD codes have changed over time and whether or not the substances are included in the drug-related deaths (drug deaths) indicators presented in Chapter 2.

The main questions in this chapter are thus (1) if changes in recording practices, in this case improvements in forensic examinations, have had an effect on the number of detected cases with positive toxicology, and (2) the trends in drug deaths and drug-related deaths after controlling for such an effect.

Coding practices

The National Board of Health and Welfare (2016) reports several changes in coding practices that have had an impact on the drug-related deaths statistics (both GMR selections).

One is that the information on the death certificates for poisoning cases became more specific in 2007, which made it possible to more often use codes included in the GMR selections of drug-related deaths, instead of codes not included (T50.9, others, non-specified drugs/medicines). This could have an effect in 2007 compared with 2006 (see, e.g., the increase 2007 compared with 2006 in Table 1).

Another change was that the opioid tramadol was coded as T39.3 until 2012, but after that as T40.8. The T39.3 code is not included in the drug-related deaths statistics, whereas the T40.8 code is.

A third change is that a previously common opioid substance, dextropropoxyphene (DXP), is not included in the drug-related deaths indicators. Toxreg also does not include DXP. DXP gradually became less common in the 2000s and was removed from the market in March 2011. Other opioid substances that possibly replaced DXP are included in the drug-related deaths statistics, however. As DXP related cases are systematically omitted, the Swedish DRD data have for several years not been strictly comparable with the data from the other European countries who apply fully the European DRD (drug-related deaths) protocol.

The controls of these coding changes were done by including T50.9, tramadol and DXP one by one and then all together in the original Swedish-GMR. The result of these controls was that the coding changes have driven the drug-related deaths statistics upward. The most conservative test, controlling for all three factors, showed an increase from 2000 to 2014 with approximately 18% and from 2006 to 2014 with almost 50%. This should be compared with the most 'liberal' uncontrolled estimate shown in Figures 2a-b: a 60% increase from 2000 to 2014 and a more than 100% increase from 2006 to 2014.

All these tests were thus done on the Swedish-GMR, including both underlying and contributory causes of death. It is not certain that the effects of changes in coding would be similar if they were done on the EMCDDA-GMR (selection B), comprising only underlying causes of death.

Forensic investigations and toxicological improvements

As mentioned in Chapter 2, more than 5,000 (5,200-5,500) forensic autopsies are conducted every year and this number has been stable for several decades.

Screening for pharmaceutical drugs and ethanol has been done on almost all forensic autopsy samples for many years. However, the number of pharmaceutical drugs screened for, including different opioids, has increased. Also, the number of screening tests has increased for several of these drugs, such as fentanyl and buprenorphine. In addition, the limits of detection and quantification have changed for certain substances over the years. Methadone has been screened for routinely in more or less all samples from the deceased for several decades and this has not changed during the period for this study.

For many years, illicit drugs were screened for only upon request by the responsible pathologist, i.e. when intake seemed likely based on circumstantial information and autopsy findings. Over time, screening of illicit drugs has increased. In September 2011, a new analytical method, based on mass spectrometry (Time of Flight), was introduced for screening of both pharmaceuticals and several illicit drugs. The new method has made it possible to identify new types of psychoactive substances and has increased the sensitivity in analyses for low concentrations of known substances; among the opioids especially morphine and oxycodone. Furthermore, most illicit drugs, THC excepted, are also captured in this new screening method, which means that most illicit drugs are screened for in essentially all samples from the year 2012 onward.

The analyses conducted in this study, presented below, use data from the national forensic toxicology database. First, the presence over time of various drugs (positive toxicology) in forensically examined deaths will be presented. Special attention will be paid to opioids, since these substances account for almost the entire increase in drug-related deaths. Thereafter, different methodological issues will be looked into more closely, here too with special focus on opioids.

The presence of different drugs in forensically investigated deaths

Of all substances classified as narcotics today in Sweden according to the Swedish Medical Products Agency (Läkemedelsverket), approximately 200 (in July 2016: 202) are tested for by the RMV. However, not all of them have been included in the drug deaths statistics. The most common of these more than 200 substances detected in the forensic investigations are shown in Tables 2a-b. The two columns to the right include all substances. A list of all these substances is shown in Appendix 1. The numbers in the two tables should be seen as crude information (raw data), which forms the basis for all drug-related deaths statistics in Sweden.

The data show that many of the substances have become more prevalent in the forensic autopsy samples, especially during the second half of the period. This also means that the sum of the

number of drugs detected among the deceased has increased. For all the fully 200 substances, there were 4,898 cases of positive toxicology in 2014 distributed over 1,863 deaths, which gives a ratio of 2.6 positive substances per death in 2014. The ratio for the past few years is higher than in earlier years, when it often reached somewhere around 1.9-2.0. Benzodiazepines, which are not included in any of the three indicators on drug-related deaths or drug deaths, also show an increasing trend, more or less doubling over the last 10 years. The number of deaths with positive tests for one or several of these substances has also increased; from about 1,100 per year during the first part of the period (1994-2006) to 1,863 in 2014. Worth noting is the large increase in the total number of substances and in the number of benzodiazepines detected from 2011 onward, from 2,659 in 2010 to 4,898 in 2014. This dramatic shift, especially from 2010 to 2012, coincides with the introduction of the new analysis method at RMV, mentioned above, which made it possible to detect lower concentrations for several of the substances.

In Table 3, the same substances are shown, but only for subjects aged 60 or younger. This was done in order to test if the same trends occur also among younger subjects, who generally use fewer medicines than elderly people. Approximately the same trends are revealed as in Table 2. For methadone, buprenorphine, fentanyl and illicit drugs, the differences in numbers are small, but for other pharmaceutical drugs the differences are substantial. This is particularly true for benzodiazepines, morphine, oxycodone, tramadol and codeine. Until year 2006, the number of deaths varied between 700 and 800, and then increased to more than 900 per year for 2007-2010. The number has increased every year after 2010 and reached 1,241 in year 2014. For subjects under 60 years of age, the number of substances per death has also increased, from roughly 1.8-1.9 in the first half of the period to roughly 2.1-2.2 in 2007-2010. As for all ages (Table 2), a dramatic change occurred *after* 2010 with much more substances found. In 2012 the number of substances reached 2.8 per death and in 2014 it exceeded 3.0 per death.

The two tables also reveal that several of the opioids show rather dramatic increases over the past 8-10 years and only one, DXP, shows a very clear decrease.

Some of the opioids show a clear increase from 2010 to 2012, i.e., before and after the change in analysis method. Other opioids, however, show a more gradual increase over the past 8-10 years. Illegal drugs, with the exception of cannabis (THC) and amphetamine, show rather small numbers and changes in absolute terms over the study period. Amphetamine increased until 2006/2007, and has since then varied somewhat over the years but with no clear trend. Cannabis shows a gradual increase throughout the entire study period.

A large but overlooked increase is shown by the pharmaceutical pregabalin, from no cases during the first half of the period to 245 (Table 2) in 2014. Pregabalin is an antiepileptic medicine used against, e.g., epilepsy, anxiety and nerve pain.

Table 2. The presence of different substances in forensically investigated deaths and number of deaths, 1994–2014, all ages Source: national forensic toxicology database.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)	(19)	(20)	(21)	(22)	(23)
	Hero-in[5]	Only morp-hine	Code-ine	Metha-done	Bupre-nor-phine[1]	Fen-ta-nyl	Oxy-cod-one	Tram-adol	DXP	Amp-heta-mine	Met-amp-heta-mine	Coca-ine	MD-MA	MDA	MD-EA	GHB	THC	Prega-balin	Methyl-phen-idate	Benzo-diaze-pines [2]	Total benz. sub-stances [3]	Total number of sub-stances[4]	Number of deaths incl. at least one of the subst.
1994	71	44	72	11		4			369	79	0[1]	4	1	0	0	0	59			798	1,266	1,867	1,057
1995	72	43	81	16		5			392	71	2	3	0	0	0	0	46			857	1,382	1,952	1,090
1996	82	48	86	15		0			444	95	3	2	3	2	0	4	51			824	1,307	1,975	1,112
1997	105	42	86	20		2		27	450	88	6	6	2	2	0	3	60			813	1,299	2,059	1,107
1998	101	51	84	10		1		32	405	92	1	5	0	0	0	1	90			754	1,163	1,930	1,109
1999	114	41	76	19		1		66	402	124	7	14	4	5	0	3	75			755	1,188	2,025	1,137
2000	143	62	90	13		2		77	325	112	10	18	14	11	0	5	123			731	1,184	2,072	1,126
2001	132	79	73	20		1		117	249	127	24	7	14	6	0	7	111			780	1,220	2,222	1,208
2002	106	57	81	32		1	1	117	207	133	11	15	9	6	0	4	100			705	1,083	2,030	1,095
2003	93	50	84	34	3	15	7	125	162	120	16	25	10	3	0	6	99			710	1,070	2,046	1,116
2004	85	57	90	30	13	9	6	151	138	128	9	20	1	1	0	8	117			626	989	1,978	1,062
2005	97	54	98	33	24	9	15	178	130	109	13	16	3	2	1	7	85			699	1,033	2,132	1,169
2006	69	65	103	30	20	5	18	174	92	130	21	17	3	2	0	3	101			678	1,020	2,121	1,146
2007	102	58	96	56	42	15	32	171	89	159	28	16	10	5	0	5	112	2		828	1,263	2,555	1,308
2008	78	78	108	91	65	22	33	193	93	158	47	24	4	2	0	15	151	18	4	794	1,244	2,728	1,321
2009	74	89	106	93	67	22	50	223	95	124	53	15	3	2	0	5	139	37	4	808	1,223	2,640	1,318
2010	54	91	115	106	74	27	48	196	84	136	31	13	5	3	0	6	137	39	10	833	1,221	2,659	1,338
2011	57	131	127	104	85	49	62	187	36	111	28	11	5	4	0	4	139	107	35	967	1,606	3,203	1,466
2012	60	170	141	136	107	86	101	163	21	97	15	22	2	4	0	3	135	198	71	1,196	2,186	4,028	1,672
2013	97	169	136	136	119	82	135	172	17	132	7	38	4	2	0	7	168	239	84	1,288	2,332	4,159	1,725
2014	106	201	152	138	154	111	168	169	11	177	16	36	25	16	0	7	187	245	108	1,282	2,509	4,898	1,863

[1] Empty cells for all substances means that no tests were done. The number 0 in a cell means that no test showed positive toxicology but could sometimes mean that no tests were done (It is sometimes not possible to separate the two). However, small numbers (0, 1, 2) most likely indicate a low presence of these drugs among the deceased and hence there were few cases suspected and tested.

[2] Number of deaths with the detection of at least one positive finding of a benzodiazepine substance.

[3] Includes the sum of all detected benzodiazepine substances, see list in Appendix 1. Each positive test of a benzodiazepine is counted. A death incl. both diazepam and lorazepam is thus given a value of 2.

[4] According to the list of substances classified as narcotics shown in Appendix 1.

[5] 6-monoacetylmorphine and morphine concentration > codeine concentration (see Druid & Holmgren, 1999).

Table 3. The presence of different substances in forensically investigated deaths and number of deaths, 1994-2014, in the age group up to 60 years. Source: national forensic toxicology database.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)	(19)	(20)	(21)	(22)	(23)
	Hero-in[5]	Only morp-hine	Code-ine	Meth-adone	Bupre-nor-phine[1]	Fent-anyl	Oxy-cod-one	Tram-adol	DXP	Amp-heta-mine	Met-amp-het-amine	Coca-ine	MD-MA	MDA	MD-EA	GHB	THC	Preg-abalin	Methyl-pheni-date	Benzo-diaze-pines [2]	Total benz. sub-stances [3]	Total number of sub-stances[4]	Number of deaths incl. at least one of the subst.
1994	71	29	64	10		4			214	78	0[1]	4	1	0	0	0	59			517	874	1,366	719
1995	72	37	68	16		5			238	70	2	3	0	0	0	0	46			568	956	1,439	749
1996	79	39	64	14		0			275	94	2	2	3	2	0	4	50			530	870	1,414	760
1997	105	30	76	18		2		17	269	87	6	6	2	2	0	3	60			566	968	1,602	788
1998	100	41	65	9		1		15	251	91	1	5	0	0	0	1	90			515	830	1,434	776
1999	114	37	62	17		0		27	258	124	7	14	4	5	0	3	75			522	875	1,555	802
2000	143	50	66	13		2		36	224	109	9	18	14	11	0	5	123			519	868	1,608	822
2001	132	66	54	20		1		68	171	123	24	7	14	6	0	7	110			563	922	1,726	882
2002	106	40	63	32		0		59	133	128	11	15	9	6	0	4	100			506	822	1,595	794
2003	91	42	65	34	3	15	6	76	95	117	16	24	10	3	0	6	99			501	798	1,606	811
2004	83	43	66	29	13	9	3	85	94	123	9	20	1	1	0	8	115			448	740	1,520	759
2005	93	44	69	30	23	6	10	102	81	106	13	16	3	2	1	7	85			464	734	1,567	782
2006	65	45	68	29	20	5	7	88	56	125	20	17	3	2	0	3	100			439	703	1,526	752
2007	100	39	70	55	40	14	23	101	59	150	26	16	10	5	0	5	110	2		588	927	1,942	922
2008	77	66	81	84	63	16	25	125	58	155	47	24	4	2	0	15	146	16	4	575	930	2,148	970
2009	74	63	73	88	67	16	33	154	61	120	52	15	3	2	0	5	135	34	4	570	989	2,043	925
2010	50	69	77	101	71	21	31	118	58	127	31	13	5	3	0	6	132	34	10	582	895	2,022	919
2011	52	87	77	96	83	40	42	126	29	105	27	11	5	4	0	4	135	98	34	692	1,220	2,491	1,025
2012	57	99	82	132	103	58	61	102	16	89	15	21	2	4	0	3	129	176	68	798	1,595	2,973	1,076
2013	86	91	89	126	112	57	81	112	13	123	7	37	4	2	0	7	159	212	80	858	1,655	3,039	1,107
2014	101	100	89	129	145	78	99	120	5	167	16	36	25	16	0	7	180	219	105	890	1,888	3,763	1,241

[1-5]: see table 2

Trends in different opioids

There are several different opioids. Most of them are included in the two GMR selections, but DXP is not (in Toxreg, neither tramadol, oxycodone nor codeine are included). A problem with not including all opioids could be that different opioids are substituted for each other, which may give rise to incorrect trends.

This will be illustrated with the opioid DXP. Most EU countries include DXP in the EMCDDA selection B, as indicated in the DRD protocol (EMCDDA, 2009), but Sweden does not. Sweden has argued that DXP is seldom abused, but is used as pharmaceutical drug, and should therefore not be included. In Sweden, DXP was a popular opioid analgesic (painkiller) for everyday pains in the early 1990s, but it was later found to have a strong toxic effect in combination with alcohol. Studies showed that DXP caused up to 200 deaths annually in the 1990s (see Jonasson & Jonasson, 2001, 2004). This lead to a lower number of prescriptions and fewer deaths related to DXP. In March 2011, the substance was removed from the market. The question, however, is if people who previously used DXP were given other 'similar' opioids, such as tramadol. That tramadol may work as a substitute for DXP has, for instance, been shown in a Finnish forensic study (Häkkinen et al., 2012).

Thus, the question is if DXP, which is not included in the statistics, has been substituted with other opioids included in the statistics of drug-related deaths. If this is the case, a second question is if this has inflated the trend in drug-related deaths.

DXP has for many years been part of the routine screening for pharmaceutical drugs and we can therefore follow the trends for this, as well as for other opioids. As was shown in Table 2, the level was high in the 1990s, declined in the early 2000s and there have been very few cases after it was removed from the market.

To give a better idea of any possible substitution effect, Figure 3 presents the development of the number of DXP deaths together with the number of opioid deaths[2], both including and excluding DXP and deaths with tramadol and/or oxycodone. The latter could possibly be used as substitution substances for DXP. The number of opioid deaths, excluding DXP, shows a sharply increasing trend during the entire period. The number of opioid deaths, including DXP, is on a much higher and rather stable level during the first 10 years, but shows an increase 1994-1997 and a decrease 2000-2006. Thus, opioid deaths including DXP show more or less the same degree of increase as opioid deaths excluding DXP, but with an increasingly smaller gap in numbers between them. As also shown, the decrease in DXP occurs simultaneously with an increase in oxycodone and tramadol. During the second half of the period, DXP was already at a rather low level and the number of deaths including other opioids increased much more than the continued decline in DXP.

Thus, the increase in opioids excluding DXP during the first half of the period could possibly be the result of a substitution effect, where DXP has been replaced by other opioids included in this time series, such as tramadol and oxycodone. However, it cannot more than marginally explain the increase in the total number of opioid deaths from 2006 to 2014.

The same pattern is revealed by comparing the total number of drug-related deaths (not only opioids) according to the Swedish-GMR with and without the inclusion of DXP (Figure 4), i.e., a

[2] The following opioids are included here and in analyses that follow in Chapters 3-4: heroin, morphine, methadone, buprenorphine, fentanyl, oxycodone, tramadol, DXP, and codeine. For the past years, these opioids have constituted approx. 97% of all deaths with findings of opioids. The reason why the remaining 3% are not included is that information regarding number of screening tests or threshold values of positive cases is missing. However, the trends are not changed by including or excluding these other opioids.

large gap in the late 1990s, but then a gradually smaller gap and with almost no difference since 2011.

Figure 3 also shows that DXP constituted almost two thirds of all opioid deaths in the mid-1990s and less than 1% in 2014. It is unrealistic to assume that none of these DXP users have turned to other opioids. However, if they have not, the increase becomes much more explosive and must involve a large portion of 'new' opioid users. Thus, in all subsequent analyses on opioid deaths and drug deaths in this and the next chapter, DXP will be included.

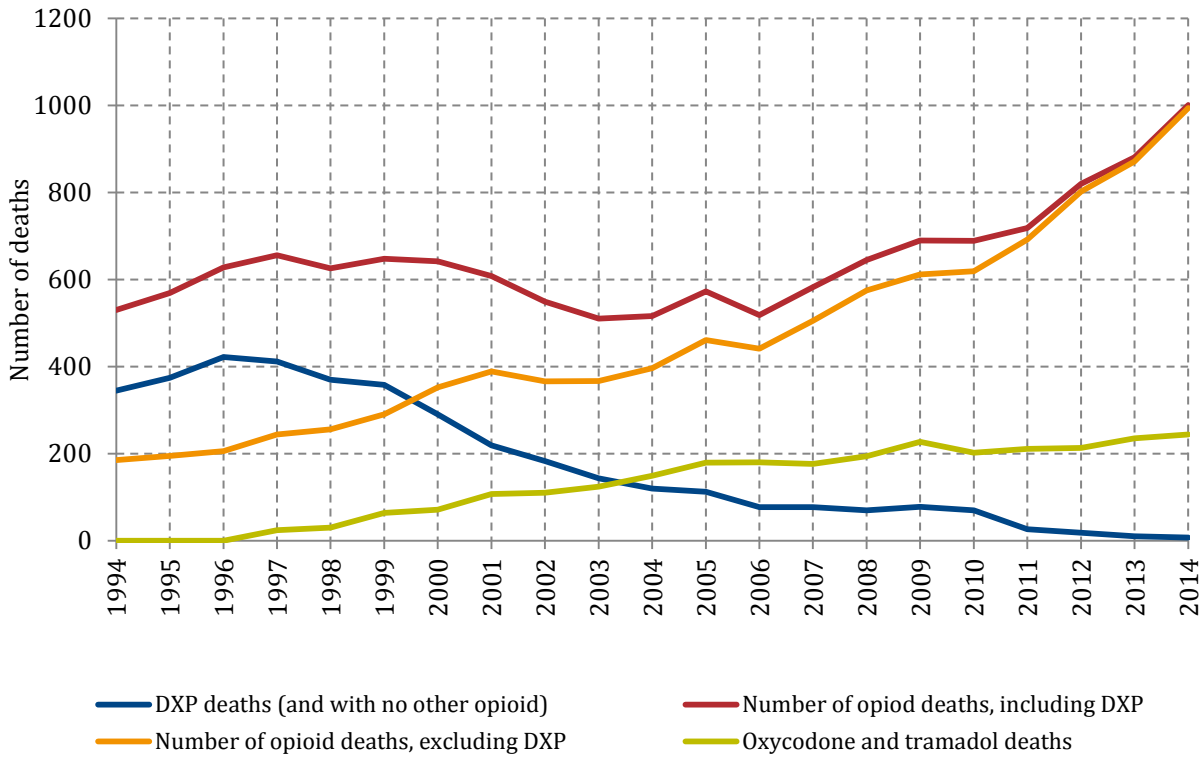

Figure 3. Number of forensically investigated deaths with positive toxicology for different opioids Source: national forensic toxicology database.

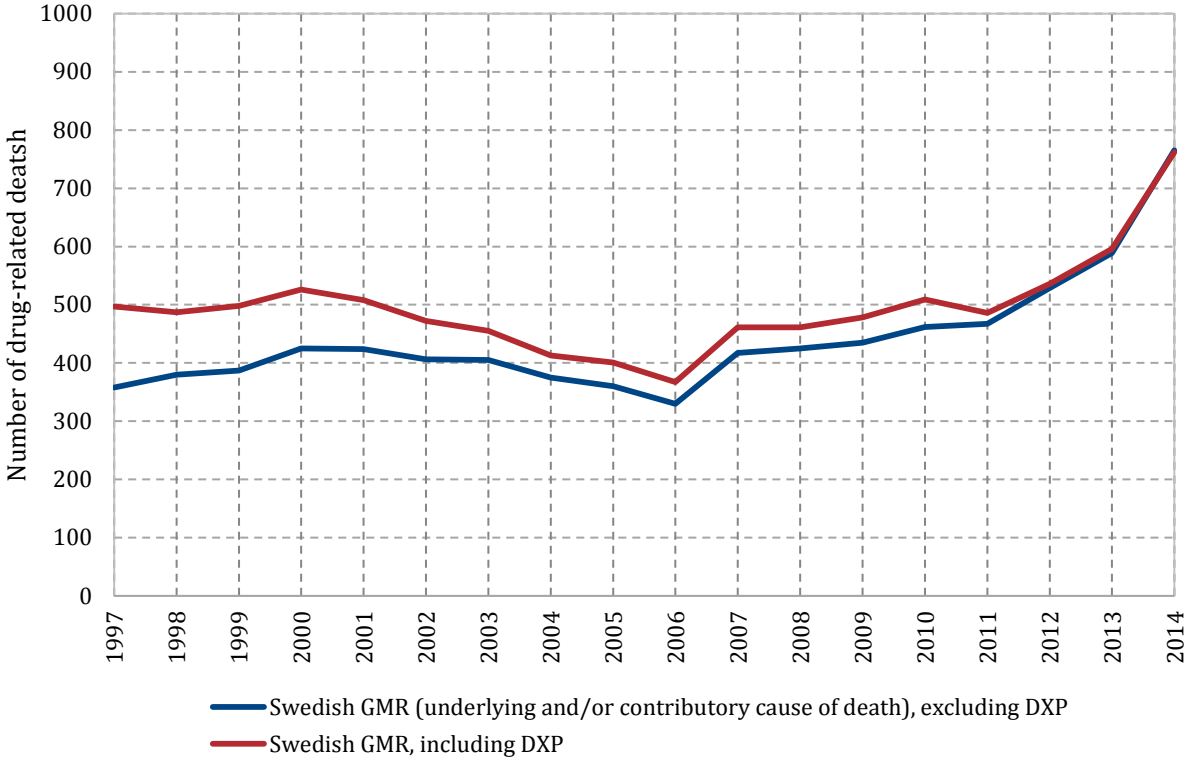

Figure 4. Total number of drug-related deaths (not only opioids) according to the Swedish-GMR and Swedish-GMR including DXP (note that tramadol is not included until 2013). Source: National Board of Health and Welfare.

Figure 5 gives a rather clear summary of what has been found so far. The interpretation of the trends in Figure 5 is as follows. The number of opioids found in forensic examinations has increased and parallels an increase in the number of opioid deaths. The increase in number of opioid deaths parallels the increase in number of opioid-*related* deaths. Since opioids account for the lion's share of all drug-related deaths, the total number of drug-related deaths has also increased.

However, the question of changes in recording practices within forensics has not yet been answered. Is it possible that improved technology with more screening and the possibility to detect lower concentrations have contributed to these upward trends? The remainder of this chapter will address this issue.

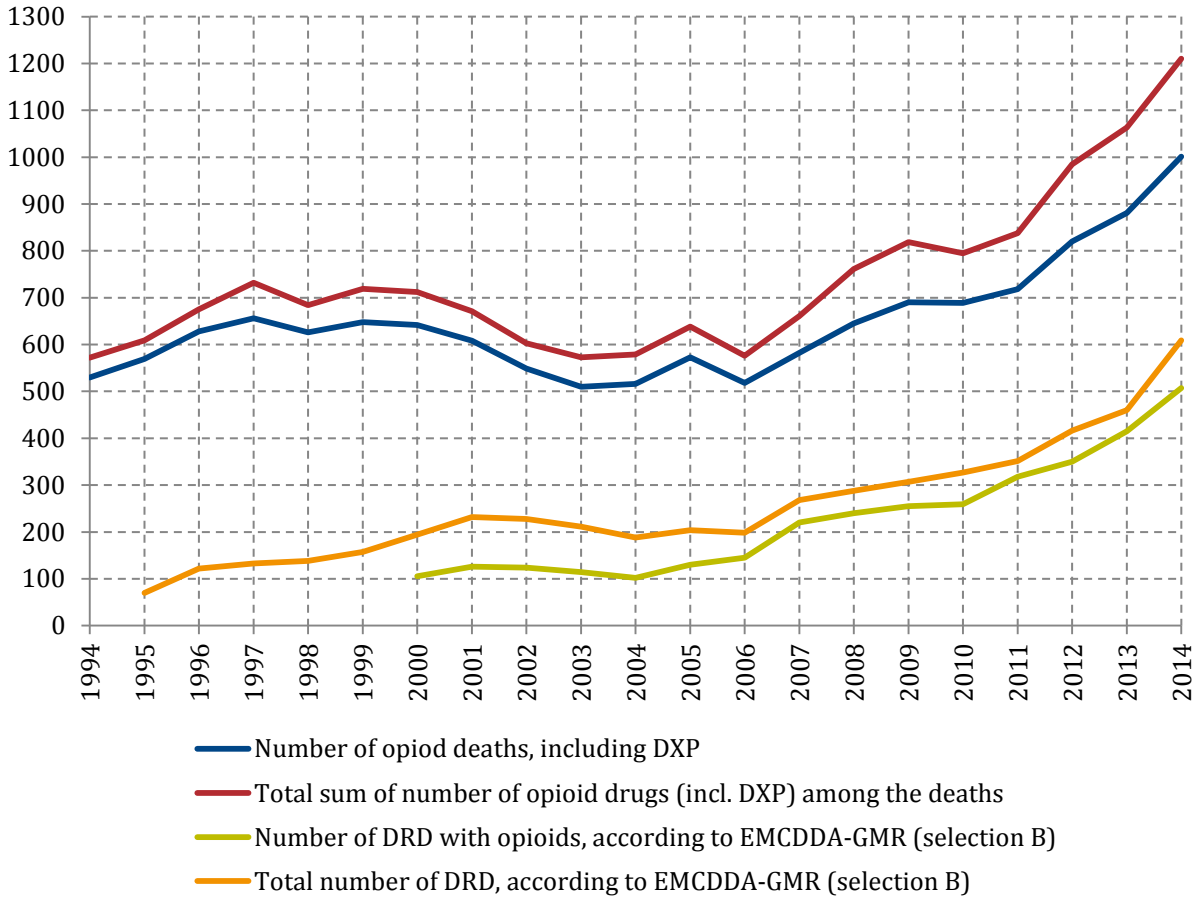

Figure 5. The presence of opioids (positive toxicology) in forensically investigated deaths (sum of number of opioids found and number of opioid deaths) according to forensic data, and number of opioid-related and drug-related deaths according to EMCDDA-GMR.
(The following opioids are included: heroin, morphine, codeine, methadone, buprenorphine, fentanyl, oxycodone, tramadol and DXP. These constitute the absolute majority of all opioid deaths, approx. 97% during the past years.) Sources: national forensic toxicology database, EMCDDA-Selection B, standard Table 6 for Sweden.

The effects of lowering the threshold values for positive toxicology

Improved analytical methods have been implemented over time at RMV, not the least during the past few years. As a consequence, lower substance concentrations could be detected in the quantification analyses (or verification tests) and as a result, the threshold value for positive cases was lowered for methadone (in June 11, 2012; from 0.1 to 0.05 µg/g in blood), oxycodone (in December 2010; from 0.05 to 0.005 µg/g in blood) and DXP (in June 11, 2012; from 0.1 to 0.05 µg/g in blood).

Since there are data on the concentrations for each positive case (above the threshold value in verification test), it is possible to compare the trend using the old threshold value with the trend using the new lower threshold value. Quarterly data will be used instead of yearly data, in order to get a better and more precise assessment of possible changes and the effects of these changes on the number of detected positive cases.

The report by the National Board of Health and Welfare interpreted the increase in methadone-related deaths, from about 100 in 2011 to 140 in 2012, as an effect of a lowered threshold value. Figure 6 shows that the increase in number of methadone deaths actually started in the fourth quarter of 2011 and the first quarter of 2012, thus already before the lowering of the threshold

value. Moreover, the two lines in the graphs after the change show only small differences in level. Thus, the lower threshold value did not affect the number of methadone deaths. It should also be mentioned that the number of screening tests has not changed for methadone for many years, since it is included in the routine screening for pharmaceutical drugs. The increase in late 2011 and during 2012 must therefore have other causes. Figure 6 also reveals another period with sharp rise in numbers, namely from 2006 to 2008. This increase cannot be explained by methodological changes in forensic practices.

The corresponding trends for oxycodone are shown in Figure 7. The lowering of the threshold value for a positive case in December 2010 resulted in a clear (roughly 50%) increase in numbers, on average 48 more cases for the period 2012 to 2014. This is important to take into consideration if one wants to study trends in drug prevalence among the deceased. However, it should be kept in mind that most of these new cases with concentrations in the interval 0.005-0.05 µg/g most likely did not die of oxycodone intoxication, and therefore have little impact on the number of drug-related deaths.

The effects of the lowered threshold value for DXP in June 2012 (not shown in any graph) was an increase in one positive case in 2012 (below 0.05-0.1 µg/g in blood) (21 instead of 20 DXP deaths), three in 2013 (17 instead of 14) and, again, one extra case in 2014 (11 instead of 10).

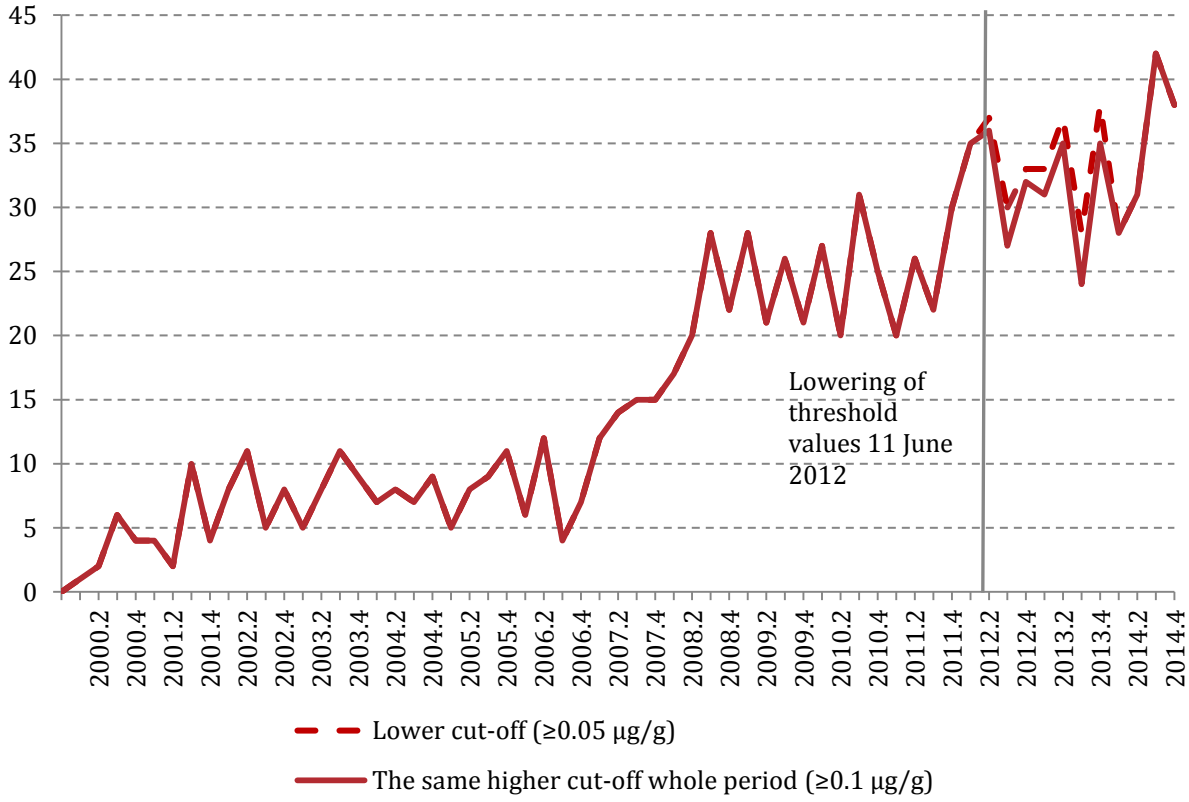

Figure 6. Number of methadone deaths with the old (0.1 µg/g) and the new threshold values (0.05 µg/g), quarterly data 2000.1-2014.4. Source: national forensic toxicology database.

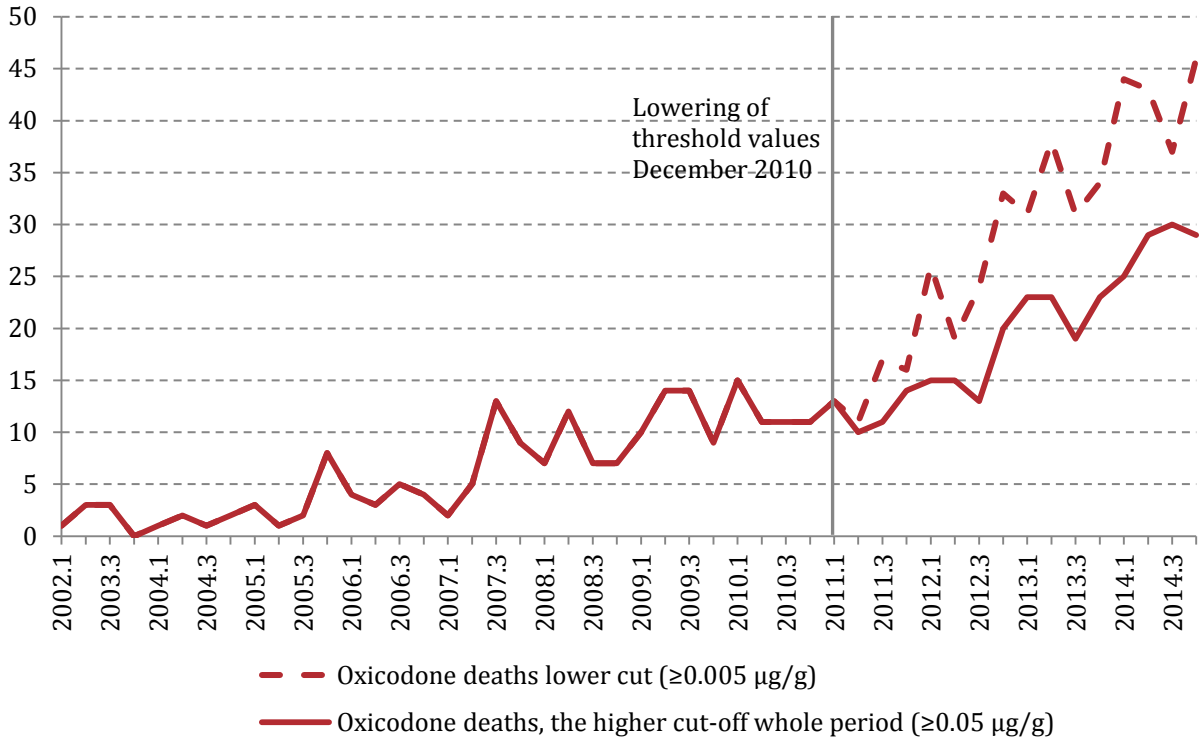

Figure 7. Number of oxycodone deaths with the old (0.05 µg/g) and the new threshold values (0.005 µg/g), quarterly data 2002.1-2014.4. Source: national forensic toxicology database.

In order to see if the concentrations have changed over time for all the opioids, even though no specific lowering of threshold has been implemented for other opioids besides methadone and oxycodone, the median concentration has been calculated for most opioids per year from 2000 (or first available year) until 2014. This is shown for some substances in Table 4. The lowered threshold value for oxycodone also lowered the median concentration, but the lowered threshold value for methadone did not. There are no clear indications of lower concentrations over time for any opioids other than oxycodone.

Table 4. Median concentration per year of different opioids in forensically investigated deaths with positive toxicology (µg/g in blood).

	Oxycodone		Fentanyl	Methadone		Tramadol	Morphine	Codeine	Bupre-norphine
	(≥0.05 µg/g)[1]	(≥0.005 µg/g)	(≥0.05 µg/g)	(≥0.1 µg/g)	(≥0.05 µg/g)	(≥0.05 µg/g)	(≥0.005 µg/g)	≥0.005 µg/g)	(≥0000.2 µg/g)
2000				0.400	..	0.500	0.1300	0.0300	
2001				0.200	..	0.400	0.1100	0.0200	
2002				0.300	..	0.500	0.1300	0.0400	
2003				0.200	..	0.600	0.1100	0.0500	-
2004				0.400	..	0.600	0.0900	0.0600	-
2005	0.300	..		0.300	..	0.900	0.1200	0.0500	0.0020
2006	0.400	..		0.300	..	0.750	0.1000	0.0700	0.0010
2007	0.300	..		0.300	..	0.700	0.1100	0.0500	0.0010
2008	0.300	..	0.0057	0.300	..	1.100	0.1100	0.0400	0.0090
2009	0.300	..	0.0039	0.500	..	0.800	0.0900	0.0700	0.0007
2010	0.200	..	0.0062	0.400	..	1.000	0.0600	0.0900	0.0010
2011	0.295	0.200	0.0064	0.400	..	0.900	0.1000	0.0700	0.0011
2012	0.200	0.100	0.0055	0.365	0.360	0.850	0.0700	0.0600	0.0009
2013	0.200	0.070	0.0055	0.380	0.360	0.920	0.0700	0.0400	0.0009
2014	0.200	0.100	0.0052	0.400	0.400	0.890	0.1200	0.0400	0.0010

Grey area: change in threshold value for a positive case. Source: national forensic toxicology database.
- = Too few cases;
Empty cells means that no tests were done.
.. = Not applicable
[1] Threshold value in the quantification analyses for a positive case

The effects of increased screening

The number of screening tests has increased during the past years for several drugs. Has this had an effect on the number of detected cases with positive toxicology? The number of screening tests is shown in Table 5, together with the number of positive cases. Methadone, oxycodone and tramadol show no change in the number of screening tests; all forensically investigated deaths are screened. For the other opioids, however, the number of screening tests has increased over the years.

For fentanyl, routine screening was implemented in September 2011 and, after that, everyone is screened. For buprenorphine, the number screened has increased gradually, but the substance is still not included in routine screening (2,294 out of 5,363 were screened in 2014). For codeine and morphine, about 40% were screened in 2008 (2,369 out of 5,111), but this number has increased and as of September 2011, all samples are screened.

Table 5. Number of screening tests and number with positive toxicology for different opioids.

	Fentanyl		Methadone		Buprenorphine		Morphine		Codeine		Oxycodone		Tramadol	
Year	Number of screening tests	Number positive cases	Number of screening tests	Number positive cases	Number of screening tests	Number positive cases	Number of screening tests	Number positive cases	Number of screening tests	Number positive cases	Number of screening tests	Number positive cases	Number of screening tests	Number positive cases
2008	72[1]	22	5,111	87	460	65	2,369	114	2,369	97	5,111	33	5,111	191
2009	59	20	5,248	96	601	53	2,262	118	2,262	100	5,248	50	5,248	227
2010	52	26	5,223	103	1,169	72	1,988	112	1,988	106	5,223	50	5,223	197
2011	1,670	49	5,015	98	1,656	84	2,926	146	2,926	116	5,015	56	5,015	180
2012	4,992	84	4,992	135	1,783	106	4,992	189	4,992	124	4,992	102	4,992	192
2013	5,143	81	5,143	135	2,023	113	5,143	186	5,143	130	5,143	135	5,143	202
2014	5,363	113	5,363	139	2,294	160	5,363	219	5,363	147	5,363	170	5,363	176

[1] The numbers for 2008-2010, do not refer to screening tests but verification tests done by the request of responsible pathologist.
Source: national forensic toxicology database

Fentanyl

Fentanyl, which has a definite date of change, makes it possible to test the effect of the change from 0% screening to 100% after September 2011. The number of positive fentanyl cases together with a marked time for the change is shown in Figure 8. As can be seen, the number of positive fentanyl cases is rather stable during the quarters before the change (2010.1-2011.2), it starts to increase in Q3 2011 (with September as the first screening month) and it increases further during Q4 2011, the first quarter with full screening. After that, the number has been rather stable, with a modest increasing trend. The increase from one level before screening to a new higher level after full screening is clearly seen in Figure 8.

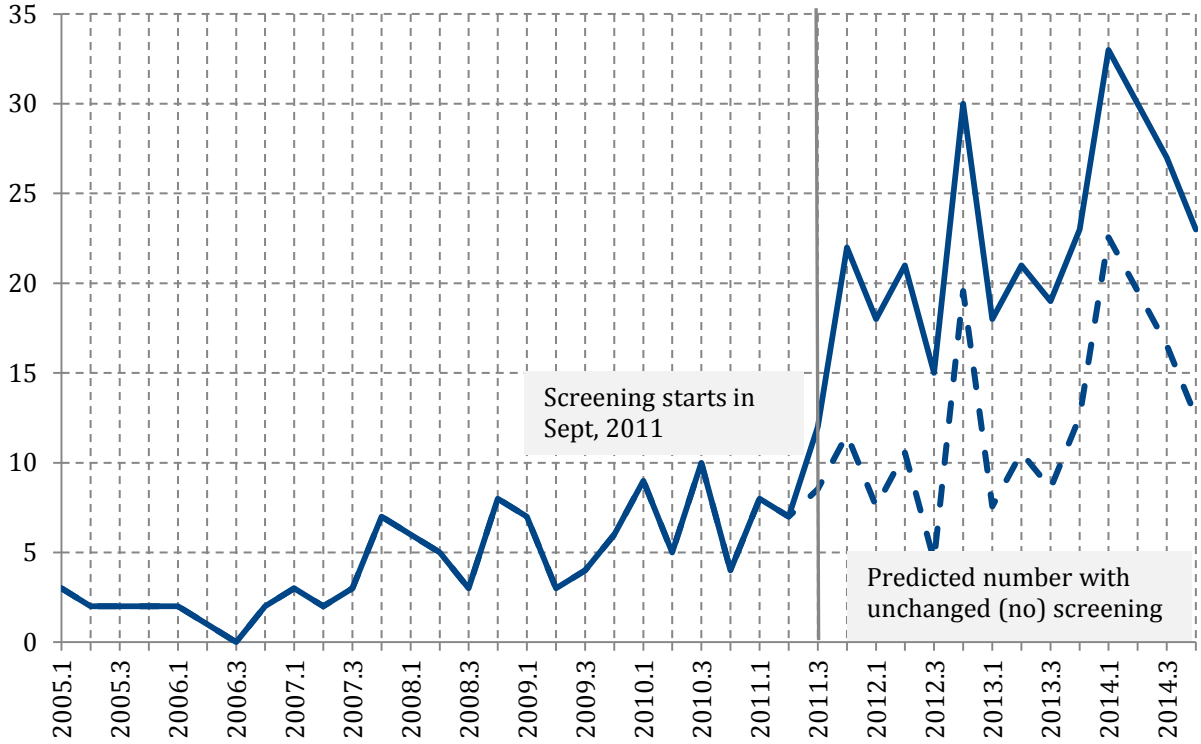

Figure 8. Number of fentanyl cases with positive toxicology, per quarter, before and after the implementation of routine screening in September 2011. Dashed line = predicted number with no screening. Source: national forensic toxicology database.

This screening effect can also be estimated through time series analysis. One of the complications often encountered in statistical analyses of time series data is that the series are trending, which is also the case here. This may give rise to spurious relationships since two series may evolve in the same, or the opposite, direction without being causally related to each other. Another complication is the structure of the error term; the error term includes, among other things, causal factors that are not included in the analysis. One of the prerequisites in ordinary regression analysis is that the error term does not have any structure. In time series analysis this assumption is not realistic, since explanatory variables that are left out can be expected to be auto-correlated – that is, to have a structure. In the present case, there is the additional complication of seasonal variation found in quarterly data.

These complications are taken into consideration in the technique for time series analysis that was developed by Box & Jenkins (1976), often referred to as ARIMA-modelling. By means of differencing, the series are made stationary. This means that rather than analysing the relationship between the raw series, we analyse the relationship between the changes. The

differencing reduces the risk for spurious relationships, though it is not eliminated. Another feature of ARIMA-modelling is that the error term (noise) structure is estimated and incorporated into the model. This increases the reliability of the model estimates.

Here, quarterly data will be used (with more observations than yearly data) and with a dummy variable representing the intervention (screening) with the value 0 for the period with no screening and 1 for the period with screening. Quarter three 2011 includes one month (September) with screening out of three in total, and therefore the dummy variable gets the value 0.33 for that period.

The results of the time series analyses are presented in Table 6. The estimate indicates an increase due to the implementation of screening of 10.4 more positive fentanyl cases per quarter, i.e., 42 more substance-positive deaths detected during one year, or in percentage, a doubling of positive cases. As shown in Figure 8, the number has increased also after 2012. This increase cannot be explained by increased screening, since everyone is screened from September 2011 onward. Thus, the predicted number of positive cases, after controlling for the screening effect (dashed line in Figure 8), still shows an increase from 2010 to 2014, but at a much lower level than that observed. The observed increase from 2010 to 2014 is from 26 to 113 fentanyl deaths. Controlling for the screening effect, the increase should be from 26 to 71.

Table 6. Estimated effects of routine screening on all samples for fentanyl in September 2011. Data for the period Q1 2005 to Q4 2014 (ARIMA time series analysis).

	Estimate (Dummy variable)	SE	Model	Q	P
Fentanyl deaths	10.4	2.53	ARIMA (1,1,0) SARIMA (0,1,0,4)	4.47 (lag 4)	0.00

Buprenorphine

As was shown in Table 5, the number of screening tests for buprenorphine has increased gradually, albeit with no clear before and after date for screening as was the case for fentanyl. Still, we want to estimate the possible effect of the increased screening on buprenorphine data as well. For this purpose, the fentanyl estimate will be used but applied to buprenorphine, starting from 2008 with 460 screening tests, through 2014 with 2,294 tests. By assuming the same relative effect (a doubling of the number of positive cases when going from 0 to 100% screening), the predicted number of positive cases for buprenorphine due to increased screening can be estimated roughly.

In 2008, the 460 screening tests, out of 5,111 deaths (9%), detected 65 positive cases in the final verification test. In 2014, the number of screening tests had increased to 2,294, out of 5,363 deaths in total, (43%) and the number of positive cases reached 156. With the same number of screening tests in 2014 as in 2008 (i.e., 9%) the number would be reduced by an estimated 18 positive cases, i.e., 138 instead of 156. Thus, even after controlling for increased screening, there is an increase but it is somewhat less pronounced. The estimations were done for every year after 2008.

In addition to increased screening, there have also been other changes in the testing procedures for buprenorphine. From January 2003 (the first year of testing for buprenorphine) to February 2008, tests were only done at the request of the responsible pathologist, i.e. when the presence of buprenorphine was suspected.

During this period, however, some changes were made. In January 2003, tests were introduced on urine (threshold value 2 ng/mL urine). In May 2004, screening tests were introduced for urine (5 ng/mL) and in July 2005 blood tests were introduced (0.2 ng/g blood).

The twelve months after February 2008 (March 2008-February 2009) was a trial period, during which buprenorphine was part of the screening for all illegal drugs (and was done in all cases where urine was available). From March 2009 to May 2010, the procedure went back to the way it was before March 2008.

From June 2010 onwards, buprenorphine again became part of the screening for illegal drugs, i.e. one of several drugs routinely tested for when screening for illegal drugs was requested. During that period, a new chromatography and detection technique was introduced for blood testing (November 2010) and urine testing was updated with a new chromatography and detection technique (June 2011). Finally, from September 2011 when the new screening method was introduced (Time of Flight), also blood screening were introduced and made on all forensically investigated deaths but with a much higher threshold value (10 ng/g in blood) compared to the verification test (0.2 ng/g in blood).

It is difficult, if not impossible, to assess the effect of all these changes on the number of detected positive cases. It is likely that at least part of the effect of these changes is captured by the estimated effect of increased screening, but it is possible that there are additional effects of these changes in the testing procedure. Actually, this is what the quarterly data of the number of positive tests for buprenorphine indicates in Figure 9a. The different main periods (1-5) are clearly marked in the figure. The second period (2008.3-2009.2) does not really show any sign of an effect of the changed testing procedure (with no increased growth rate compared with the pre-test years 2006-2008), but the next period (3) does: when testing went back to the old (pre-trial) procedure, the number of positive cases dropped, but then increased again in period 4, when it became part of the illegal drug screening.

Thus, it is period 3 (March 2009-May 2010) that deviates from periods 2, 4 and 5 during 2008.2-2014.4, with a lower number probably due to a less effective testing procedure. Assuming the same rate of increase per quarter for period 2 as for the other periods, approximately 2.2 extra positive cases per quarter are missing for period 3. The net predicted number of positive cases from these two effects (increased screening and a less effective testing procedure in March 2009-May 2010) is shown in Figure 9b.

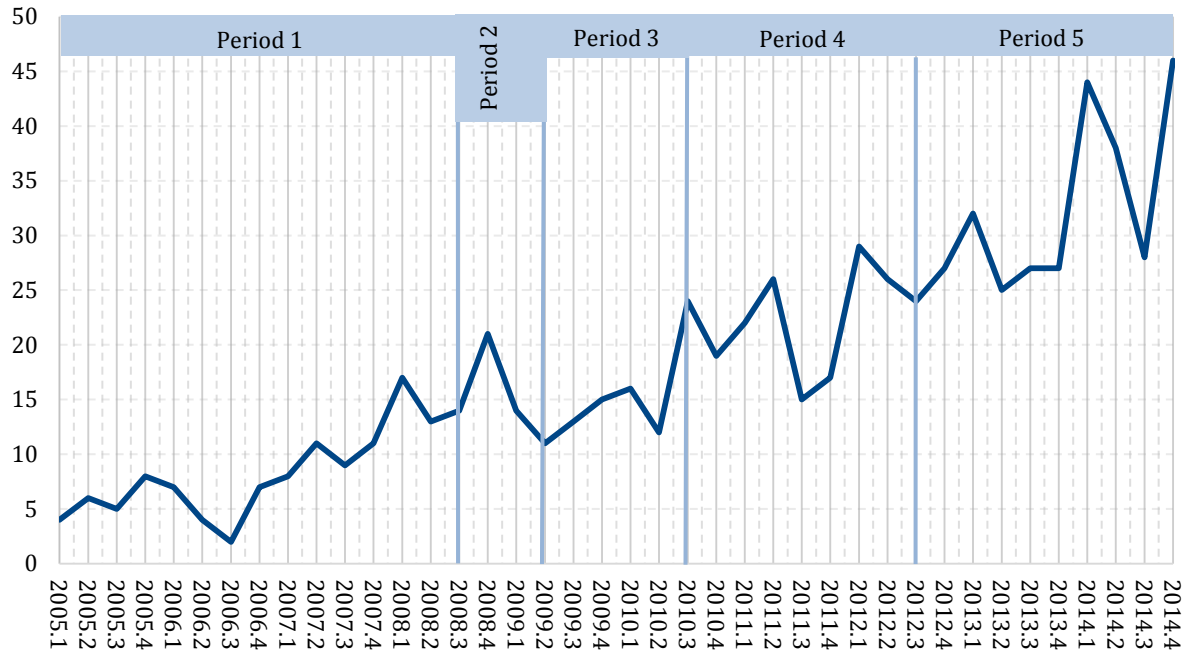

Figure 9a. Quarterly number of buprenorphine cases with positive toxicology.
Period 1: Screened for at the request of responsible pathologist; Period 2: Part of screening **for all illegal drugs done** in all cases where urine was available; Period 3: Screened for only at the request of responsible pathologist; Period 4: Part of screening **for all illegal drugs** done at the request of responsible pathologist; Period 5: Par of Time of flight: screening on everyone but with high threshold value but with lower on the verification test. Source: national forensic toxicology database.

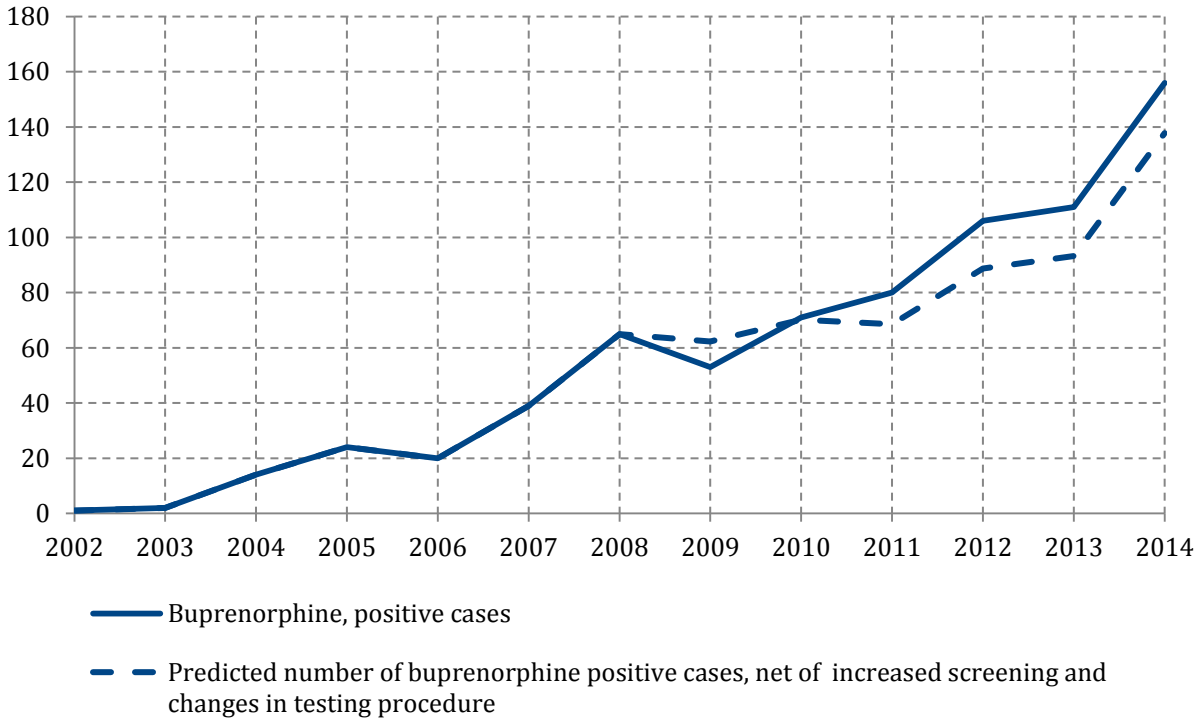

Figure 9b. Number of buprenorphine cases with positive toxicology per year, with and without control for increased screening and changes in testing procedures (from part of illegal drug screening requests to specific buprenorphine screening requests and back again). Source: national forensic toxicology database.

Morphine and codeine also show an increased number of screening tests, but as shown in Table 5, already in 2008 tests for both substances were done on 46% of all forensically investigated deaths. The number of screening tests remained at more or less the same level until 2010. In 2011, the number increased with an extra 1,000 tests (+ 47%) and as of the calendar year 2012, tests were done for all forensically investigated deaths. The number is exactly the same for both substances (for exact numbers, see Table 5).

The high level already in 2008 makes it unlikely that the relative increase caused by increased screening tests would be the same as for fentanyl and buprenorphine, both starting from much lower levels in 2008. Instead, we will compare the number of positive cases 2008-2010, before the change started, with 2012, when the change in screening was completed.

This will be illustrated with morphine. The number of positive cases remained at approximately the same level during the years 2008-2010 (around 115), during a period with a rather stable number of screenings, but increased with 74 positive cases in 2012, when all forensically investigated deaths were screened. Assuming that this difference (74 extra positive cases) is the effect of going from about 38% (in 2010) to 100% screening (in 2012), it is easy to calculate the numbers, net of increased screening.

The results of these calculations are shown in Figure 10 for both substances. The effect is stronger for morphine than for codeine and only morphine shows any further increase after 2012, which cannot be explained by increased screening.

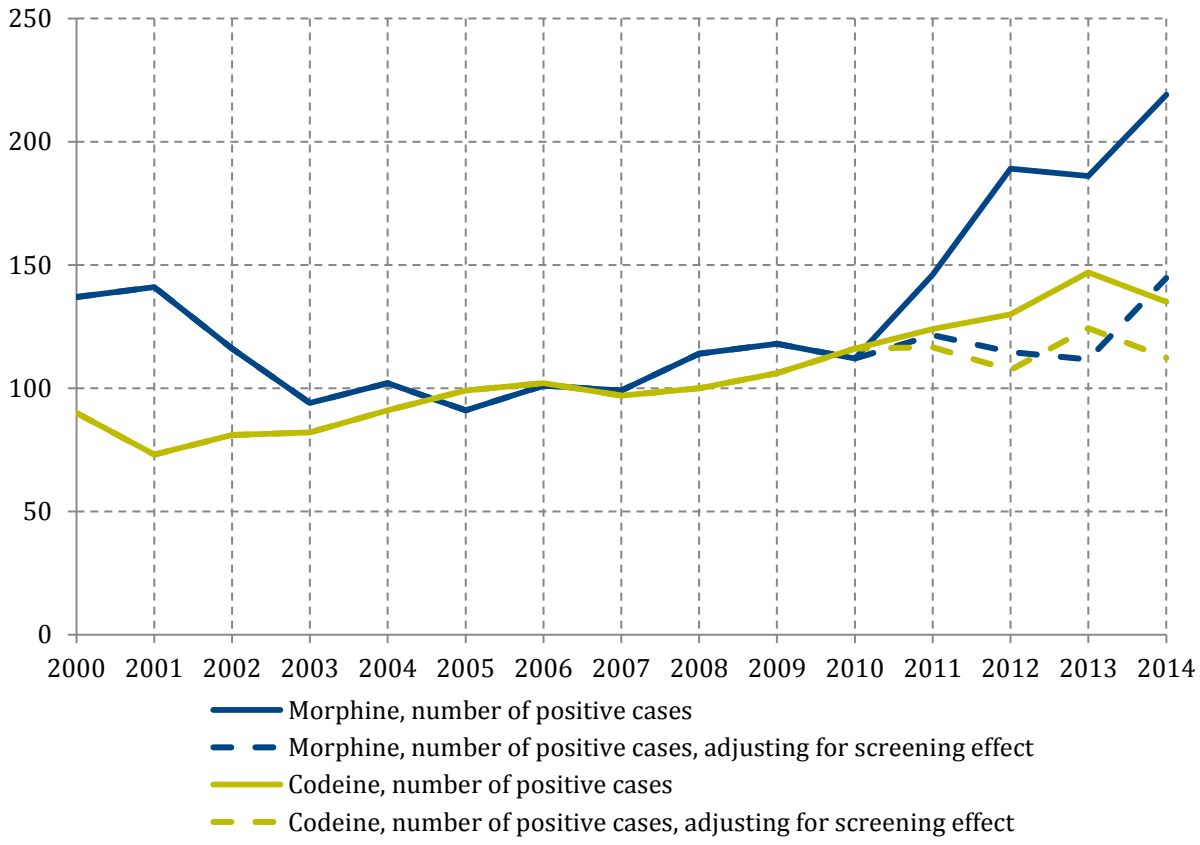

Figure 10. Number of morphine and codeine cases with positive toxicology, per year, with and without control for increased screening, per 100,000 inhabitants. Source: national forensic toxicology database.

In summary, the estimates show clearly that increased screening (and a changed testing procedure for buprenorphine) has had effects on the number of detected positive cases for all four opioid substances, with an increased number of screening tests from 2008 to2014. The effect appears, in relative terms, to be strongest for fentanyl, going from no screening to full screening from one month to another, and weakest for buprenorphine and codeine. The results also show that even after taken into account the effects of increased screening, the numbers are still increasing for fentanyl and buprenorphine and probably also for morphine, but not for codeine. Thus, increased screening does explain a substantial part of the increased number of positive cases of the tested opioids, but it does not explain the entire increase.

Other changes in toxicological testing practices

A limitation of the analyses shown above is that data on the number of screening tests before 2008 are missing, which makes it impossible to conduct similar tests for a longer time period. However, fentanyl and buprenorphine cases were relatively few in number before 2005-2006 (not tests were done on buprenorphine before 2003) and both morphine and codeine cases were at rather stable levels from the mid-1990s to 2007. Morphine, codeine, DXP, heroin, methadone and tramadol have been part of the screening for pharmaceutical drugs for the whole period (1994-2014) and oxycodone since 2005. Still, one should be particularly cautious in making comparisons back in time before 2008.

Moreover, no analyses have been done on heroin (6-monoacetylmorphine), since we do not have the yearly number of screening tests. However, there was no significant increase from the period before the new technology was implemented (2008-2010) to 2012, after the new technology was implemented, in the number of heroin deaths, i.e., positive for 6-monoacetylmorphine (2008: 47, 2009: 51, 2010: 34, 2011: 39, 2012: 40).

Increasingly, more drugs are screened for routinely in all forensically investigated deaths. Formerly, particularly before 2011, most illegal drugs were screened for only at the request of the responsible pathologist, i.e., when intake was suspected. These requests were based on circumstantial information and autopsy findings, but screening was requested quite often. However, it cannot be ruled out that that the suspicion would vary somewhat between pathologists and over time, which might have had an effect on the time series. This is difficult to test empirically.

During the period April 2008 to March 2009, RMV conducted total testing of the occurrence of illegal drugs in all forensically investigated deaths. This may shed some light on the degree of underestimation of the number of “true” deaths with findings of illegal drugs. This total screening resulted in a temporary increase in the number of positive cases for illegal drugs in 2008 compared with 2007 and 2009. This temporary increase in 2008 is visible in Figures 2a-b for the Toxreg forensic data, with 81 more drug deaths than in 2007 (from 397 in 2007 to 478 in 2008) and 56 more than in 2009. This increase in 2008 consisted of more positive cases of THC, GHB, amphetamine and cocaine. No similar peak was found in the GMR selections (see Figure 2a).

Thus, this effect of the extra screening efforts suggests that the presence of a number of illegal drugs in forensically investigated deaths has been underestimated to some extent, at least during the years when illegal drugs were screened for only when intake was suspected. It does not, however, necessarily indicate that the trends for the other years have been incorrect, since it still is possible that the degree of underestimation and underreporting has been at a rather stable level.

Since no similar peak was found in any of the two GMR selections in 2008, it may also indicate that the extra illegal drugs found were of little importance for actual deaths (Fugelstad et al., 2016). On the other hand, this was not unexpected, since the effect of total screening of illegal drugs seemed to have had the strongest effect on the number of detected positive findings of

cannabis (THC) and the risk of a fatal cannabis overdose is extremely small compared with the risks of opioid and stimulant drug overdoses (Gable, 2004). There are actually no reports of fatal overdoses of cannabis in the epidemiological literature (Calabria et al., 2010).

Furthermore, this absence of an effect of increased screening on the number of illegal drug-related deaths cannot easily be generalised to apply to other substances, such as the opioids studied above.

Additional important changes in testing procedures from the year 2000 onward have not come to our attention. However, the example of buprenorphine above illustrates quite well that several changes in testing procedures have occurred over the years. Consequently, it cannot be ruled out that other changes have occurred over time for different substances. Still, given the information available of no further major changes, the data points to an increase in opioid deaths.

Estimated total effects of all changes in toxicological forensic analyses

This chapter will end with rough assessments of the total effects of the methodological improvements presented above and an equally rough estimation of the trends in drug deaths (forensic data) and drug-*related* deaths after controlling for these changes. The time period 2000-2014 will be used and most focus will be on the trends from 2008 onward. As we are mainly using toxicological forensic data, the changes in coding practices for tramadol and for the code T50.9 are not relevant. However, the inclusion or exclusion of DXP is, and will therefore be considered. Again, it should be stressed that no corrections of screenings, or of anything else, have been made to data for the period before 2008.

The number of detected opioids in the deaths, with and without corrections, is presented in Figure 11. All three series include DXP and all three thus have exactly the same numbers for the years 2000-2008. All three series show increases from 2006 onward with sharper increases during the past 3-4 years. The slope of last year's increase, however, becomes less dramatic when the lowered threshold values (methadone, oxycodone, DXP) and, particularly, increased screening are considered. For the period 2000-2006, the number of opioids found in forensically examined deceased seems to decrease.

Figure 12 shows the same indicators as in Figure 11, but based on the *number of deaths* (number of individuals) with positive toxicology for opioids (opioid deaths). As shown, the same trends appear as in Figure 11 but, naturally, at lower levels. Thus, the number of opioid deaths, according to forensic toxicological data, has increased over the period, especially since 2011, but the increase is much smaller than what has previously been reported based on toxicological data (e.g., Fugelstad, 2016).

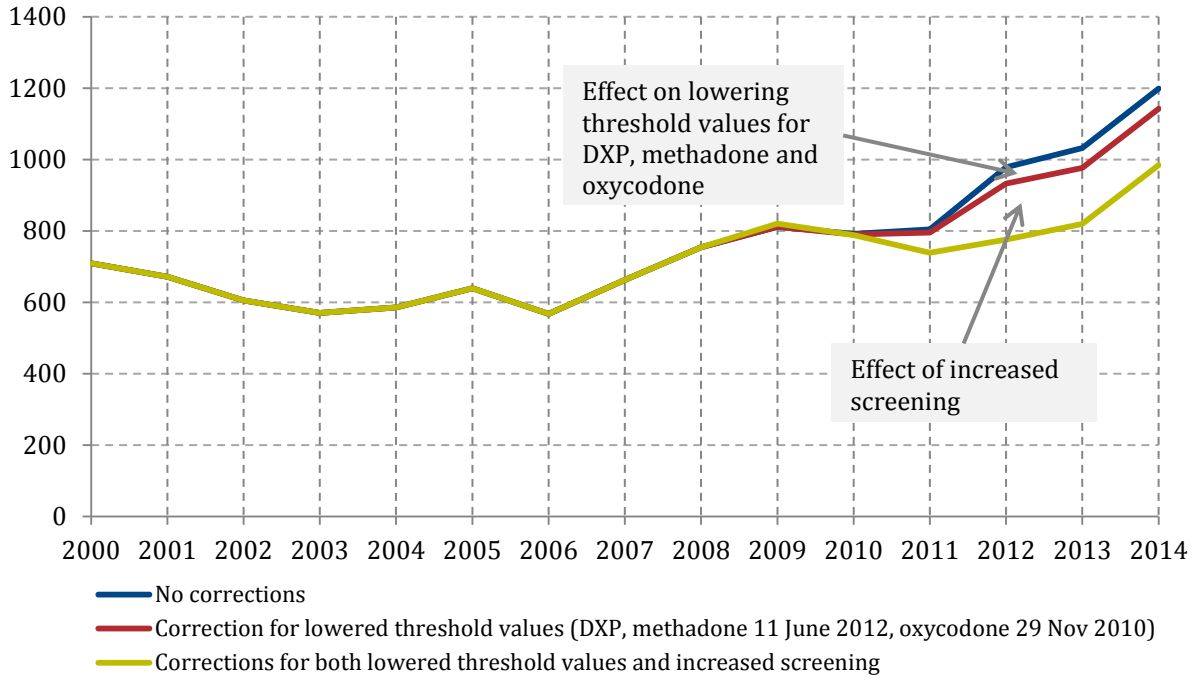

Figure 11. Number of detected opioids in forensically examined deaths before and after corrections for increased screening, changes in testing procedure for buprenorphine March 2009-May 2010 and lowering of threshold values for methadone and oxycodone. Source: national forensic toxicology database

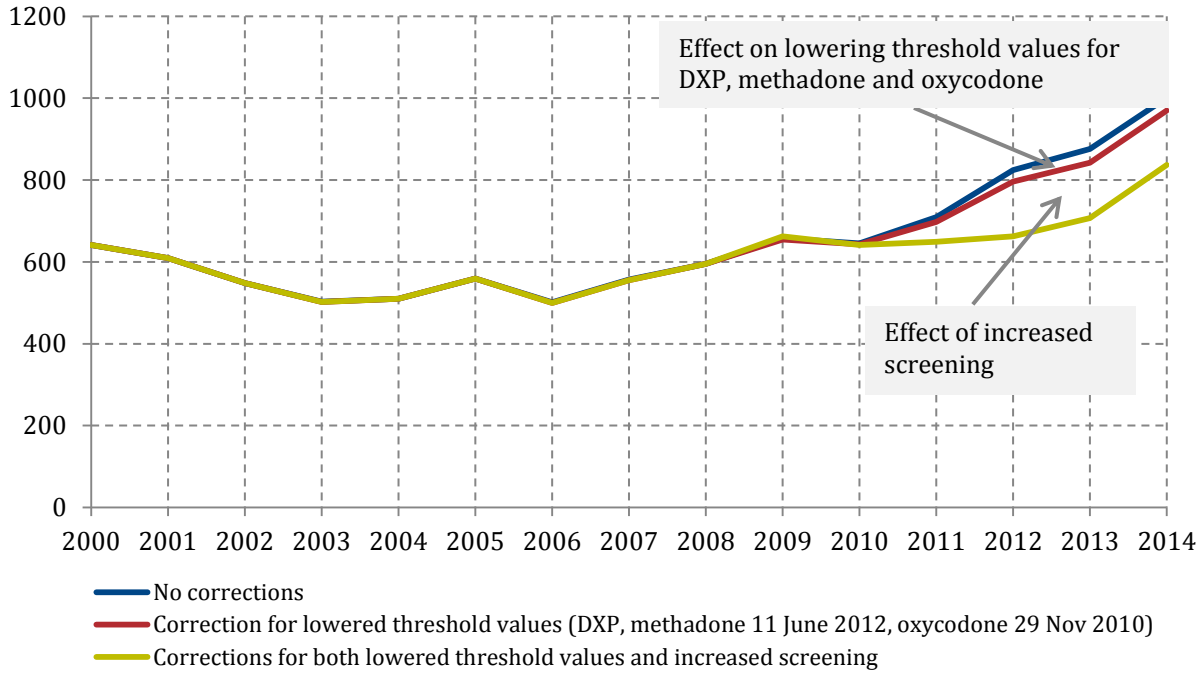

Figure 12. Number of forensically examined deaths with positive finding of opioids before and after corrections for increased screening, , changes in testing procedure for buprenorphine March 2009-May 2010, and lowering of threshold values for methadone, oxycodone and DXP. Source: national forensic toxicology database.

Figures 11-12 are trend indicators for opioid deaths, but not necessarily for opioid-*related* deaths. However, as can be seen in Figure 13, the trends in the number of opioids found in forensically examined deaths, the number of opioid deaths and the number of opioid-*related* deaths (according to the EMCDDA-GMR and including DXP) are similar, but at different levels. The correlations between the three over time are strong. Thus, when the number of opioids detected and number of opioid deaths increases, the prediction is that the number of opioid-*related* deaths also increases.

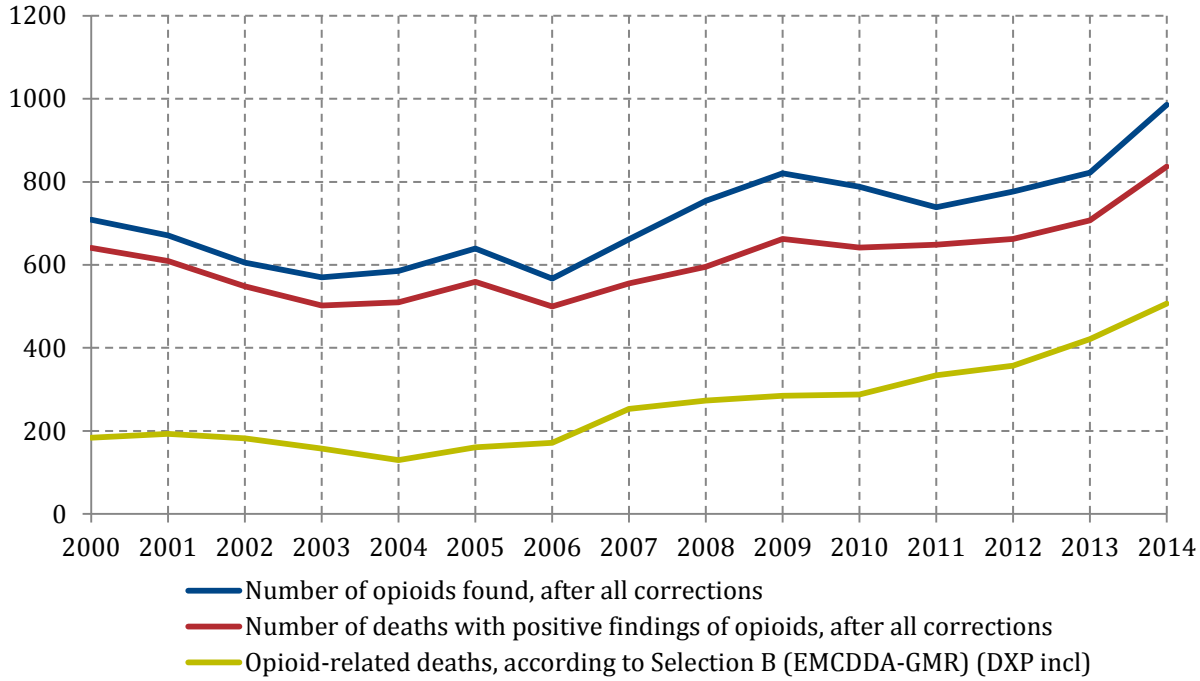

Figure 13. Number of opioids found in forensically examined deaths, number of deaths with a positive finding of opioids (opioid deaths) and number of opioid-*related* deaths (according to EMCDDA-GMR, Selection B including an estimate of number of DXP deaths).

The final graph (Figure 14) shows estimations of the total number of drug deaths based on forensic data, one dataset including cannabis (THC), another excluding cannabis, and drug-*related* deaths (DRD) based on the EMCDDA-GMR and the Swedish-GMR. For the two GMR selections, *crude* adjustments for increased screening and lowered threshold values for opioids (as shown above) have been applied based on the ratio between adjusted and non-adjusted opioid deaths obtained using forensic data. All of the indicators in Figure 14 include opioids *and* illicit drugs (amphetamine, cocaine, ecstasy etc.; basically columns 1-17 in table 2), but one of the forensic time series excludes cannabis (THC, column 17 in table 2). The reason for excluding cannabis, despite being an illicit drug, is that cannabis use is very rarely a cause of death, with no reports of fatal overdoses of cannabis in the epidemiological literature (Calabria et al., 2010). In Sweden 2014, there were four deaths with the code T40.7 (poisoning by, adverse effect of and underdosing of cannabis (derivatives), all four related to intake of spice, according to information from the National Board of Health and Welfare) compared with 72 cannabis deaths (not spice deaths) according to Toxreg (Fugelstad, 2016).

DXP is included in the forensic data (both lines), while one GMR series includes and the other excludes DXP. As shown, all six time series show increases since 2006. As for the two GMR selections, the slope becomes less sharp if DXP is included and the adjustments mentioned above are applied.

Also here, the correlations between the three indicators (dashed or solid lines) are strong. Thus, when the number of drug deaths increases, the prediction is that the number of drug-*related* deaths also increases (Pearson's r = 0.8-0.9).

Broadly speaking, based on the reliable trends (the dashed lines in Figure 14), the number of drug deaths according to forensic data is, for the past few years, approximately 60% higher than the EMCDDA-GMR numbers and 27% higher than the Swedish-GMR numbers. (The latter is not adjusted for not including tramadol before 2013 or for the effects of the T50.9 code.) The increase in the number of drug deaths from 2006 to 2014 according to toxicological data is now estimated at approximately 56%, which can be compared with the estimated 114% according to Toxreg, as shown in Figure 2a. Since information on number of screening tests is missing before 2008, the most comparable years are for the period 2008-2014. During that period, the corresponding increases amount to 33% and 44%, respectively. When taking into consideration the population growth, the increase in the adjusted time series are reduced from 33% (in absolute number) to 27% (per inhabitants aged 15 or over).

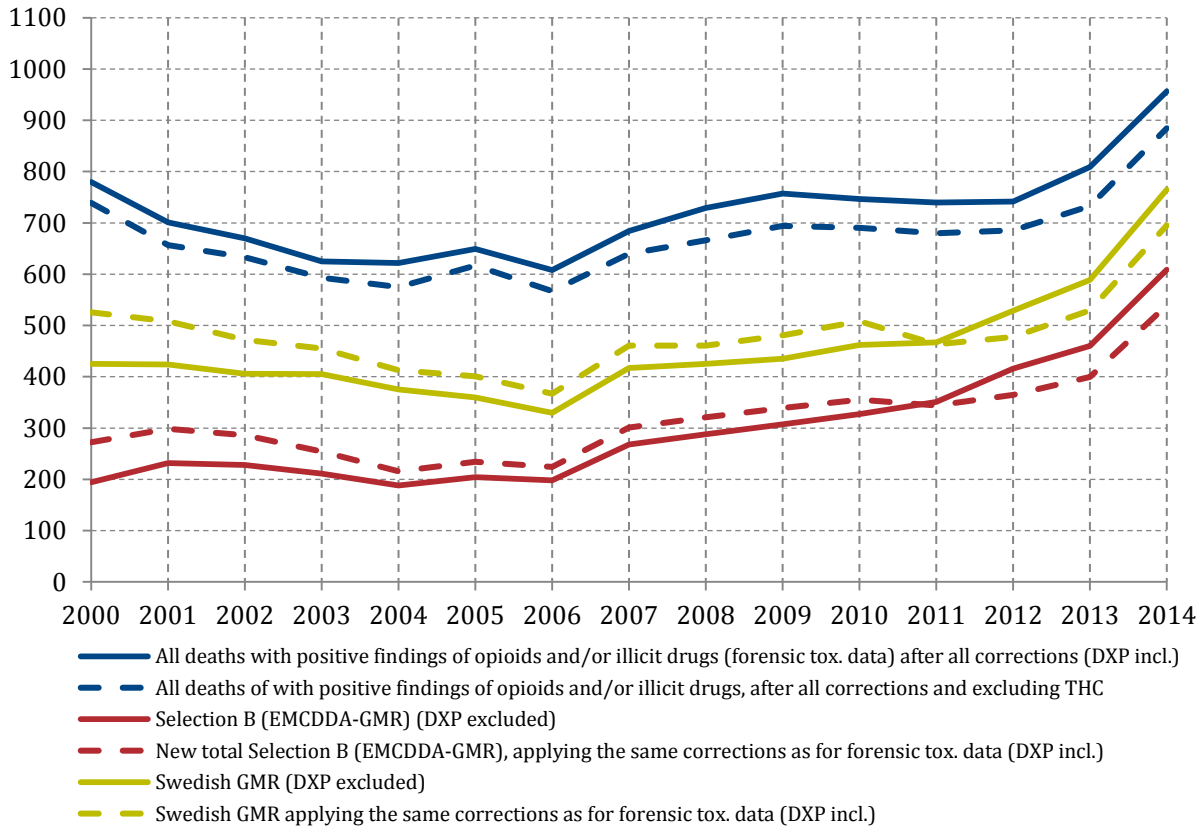

Figure 14. Number of drug deaths (opioids and/or illicit drugs in forensically examined deaths, including and excluding THC) and number of drug-related deaths (according to Swedish-GMR and EMCDDA-GMR, with and without corrections).

Summary

Most of the analyses conducted in this chapter were done on forensic toxicological data. We do not have access to individual-level data for any of the GMR selections and even if we did, they do not contain as detailed information on type of substance as the toxicological data.

The forensic toxicological data show the presence of drugs in forensically investigated deaths, and that is why the terms drug deaths or opioid deaths are used (not drug-*related* deaths). However, our comparison of drug deaths data with drug-*related* deaths data shows clearly that the trends are very similar, albeit at different levels.

Even after taking into consideration changes in the number of screening tests and lowered threshold values for a positive case, there is an increase in the number of opioid deaths and therefore also in the number of drug deaths and, most likely, in drug-*related* deaths. This increase is almost entirely due to an increase in pharmaceutical opioids. Nowadays, these substances are behind approximately 70-75% of all drug deaths and probably also of all drug-related deaths. Thus, illicit drugs only cause a minority of these deaths.

The data analysed in this chapter do not include new psychoactive substances (NPS). According to RMV, they are still very few in numbers (e.g. spice) and would therefore not more than very marginally change the rates and trends presented above.

The analyses also show that it is of great importance not only to be aware of changes in recording practices, but also to assess the effects of these changes and to present trends as a *net* of these effects. Once again, it should be repeated that the conclusion that there has been an increase is valid under the premise that there have not been any other major changes in testing procedures than the ones controlled for in the analyses above.

4. Drug deaths patterns – gender and age differences, polydrug use and manners of death

In order to provide better understanding of the development of drug-related deaths, this section will present changes over time among men, women and in different age groups. Also, the combinations of different drugs in drug deaths will be studied with a focus on alcohol and benzodiazepines. The chapter ends with a short description of manners of death in poisoning cases for different opioids.

Men and women

Tables 7-9 show the number (and different proportions) of deaths by gender and age. Table 7 is based on the Swedish-GMR, Table 8 on the EMCDDA-GMR and Table 9 on toxicological data.

According to the Swedish-GMR, women account for approximately one fourth of all drug-related deaths and this ratio has been rather stable for the entire period 1997-2014 (Table 7). The EMCDDA-GMR also shows a rather stable proportion of women among all deaths, about 25% for the past 10 years (Table 8). The proportion of women is higher in the forensic data, about 30% per year (Table 9). This higher proportion is probably due to the inclusion of opioids regardless of if a death was drug-related or not. (In Toxreg, the age limit is 60 years for all opioids except heroin, e.g., methadone, buprenorphine and fentanyl.)

Age groups

In a recent report from Ledberg (2015b) it was shown that the mortality in different cohorts of drug addicts was high but not increasing over time. Given an actual increase in drug-related deaths, and a stable and not increased mortality among known drug addicts, one possibility for the increase in drug-related deaths could be a higher influx of relatively unknown drug users. Possibly, this group could to a higher extent consist of rather young people without previous known drug history.

The average (mean) age could be retrieved from the EMCDDA-GMR and from the toxicological data, but not from the Swedish-GMR, excepting in 2014. According to EMCDDA-GMR (Table 9), the average age at death was 39.6 years in 2014. Ten years earlier (2005), it was 39.3. (In the Swedish-GMR, the median age in 2014 was 37 years for men and 48 years for women) However, the mean age may not give a full comprehensive overview of the age pattern over time, since some ages may show increases while others show decreases, with the mean age remaining more or less the same.

Tables 7-9 show the proportion of drug-related deaths (and drug deaths) accounted for by different age groups. The youngest group (< 30 years of age) showed an increased proportion for the first years until 2000 (Tables 7 and 9), but has since then been rather stable: roughly 25% in the Swedish-GMR and 20% according to toxicological data. Since the numbers of drug deaths and drug-related deaths have increased over the past eight years this also means that the numbers have increased quite significantly among young people. This is apparent in all three tables, e.g., among those aged 20-24 and 25-29 years according to the EMCDDA-GMR, as seen in Table 8. That table also shows clearly that the numbers fluctuate quite a lot between years. In 2014, the

number of deaths among 20-24-year-olds was 102, the year before 51. It remains to be seen if the increase in 2014 was temporary or not. According to RMV it cannot be explained by an increase in the new psychoactive substances (NPS) but is, as for other age groups, most likely explained by an increase in opioid-related deaths. This is verified by the toxicological data analysed in this chapter.

In the older age groups, the proportions have also been rather stable over the years. There may possibly have been an increase among those aged 50 or older from about 26% in 2000 to 34% in 2014, according to the Swedish-GMR (Table 7). Some indicators of such an increase are also visible in the EMCDDA-GMR data (Table 8), but not in the toxicological data (Table 9).

The toxicological data also makes it possible to study the average age at death in regards to different substances. As can be seen in Table 9, the mean (average) age varies substantially between different substances with the lowest mean age for methadone and buprenorphine (m=38 years of age) and highest for DXP, morphine and oxycodone (m = 52-60 years of age; although very few cases of DXP are from the last years). For the illicit drugs heroin and amphetamine, there is a tendency toward a higher mean age at the end of the study period, but the change is rather small. Not for any of the opioids is there a clear trend toward a lower mean age over time; if anything the trend is rather the opposite.

Consequently, the increase in the number of drug-related deaths is not linked only to young people. The overall pattern is that the relative increase is rather similar across age groups, so that age distribution is much the same today as it was 10 years ago. Thus, the average age at a drug death in Sweden has been almost constant for many years. The increase in deaths could still consist of people unknown to the authorities and with rather short drug abuse careers, but they are not younger than before, at least not until the year 2013.

Table 7. Drug-related deaths by sex and age group 1997-2014, according to the Swedish-GMR.

	Age groups							Men		Women			
Year	–19	20–29	30–39	40–49	50–	Prop. –29 years of age	Prop. ≥ 50 years of age	Number	Age standardised death rate	Num-ber	Age standardised death rate	Total	Prop. women
1997	6	46	114	96	96	15	27	269	6.1	89	2.0	358	25
1998	6	57	98	104	115	17	30	284	6.4	96	2.2	380	25
1999	5	72	113	94	103	20	27	287	6.4	100	2.2	387	26
2000	13	101	109	92	110	27	26	332	7.4	93	2.1	425	22
2001	12	90	105	105	112	24	26	327	7.3	97	2.1	424	23
2002	9	79	97	105	116	22	29	319	7.1	87	1.9	406	21
2003	12	75	73	110	135	21	33	300	6.7	105	2.3	405	26
2004	11	94	64	81	125	28	33	297	6.7	78	1.7	375	21
2005	11	81	73	81	114	26	32	269	5.9	91	2.0	360	25
2006	5	66	49	94	116	22	35	258	5.7	72	1.6	330	22
2007	9	94	78	105	131	25	31	318	7.0	99	2.2	417	24
2008	9	100	87	92	137	26	32	327	7.2	98	2.1	425	23
2009	11	94	81	93	156	24	36	333	7.2	102	2.2	435	23
2010	6	109	113	85	149	25	32	356	7.7	106	2.3	462	23
2011	14	111	86	74	182	27	39	342	7.2	125	2.6	467	27
2012	6	119	117	97	190	24	36	395	8.3	134	2.8	529	25
2013	15	145	115	105	209	27	35	434	8.9	155	3.2	589	26
2014	12	182	176	132	263	25	34	563	11.5	202	4.2	765	26

Table 8. Drug-related deaths by sex and age group 1997-2014, according to the EMCDDA-GMR.

Age groups	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
< 15					1						
15-19	8	6	4	5	5	10	5	11	6	13	9
20-24	27	25	24	37	30	43	39	47	47	51	102
25-29	40	36	27	34	51	40	56	54	64	77	70
30-34	19	23	16	34	41	32	59	42	55	55	96
35-39	18	24	22	20	25	33	36	37	56	48	63
40-44	20	28	24	37	33	35	21	27	38	44	50
45-49	12	14	29	38	25	31	33	28	41	43	51
50-54	21	13	19	25	29	34	26	38	38	46	67
55-59	12	12	6	11	19	15	19	25	35	27	37
60-64	5	9	12	8	10	14	14	17	10	22	24
≥ 65	6	14	15	19	19	20	19	25	29	34	40
Total number	188	204	198	268	287	307	327	351	419	460	609
Prop. 15-19	4%	3%	2%	2%	2%	3%	2%	3%	1%	3%	1%
Prop. 20-24	14%	12%	12%	14%	10%	14%	12%	13%	11%	11%	17%
Prop. 20-29	36%	30%	26%	26%	28%	27%	29%	29%	26%	28%	28%
Prop. 30-39	20%	23%	19%	20%	23%	21%	29%	23%	26%	22%	26%
Prop. 40-49	17%	21%	27%	28%	20%	21%	17%	16%	19%	19%	17%
Prop. 50-59	18%	12%	13%	13%	17%	16%	14%	18%	17%	16%	17%
Prop. 60+	6%	11%	14%	10%	10%	11%	10%	12%	9%	12%	11%
Average (mean) age	37.2	39.3	41.4	40.4	39.9	40	39.1	40	40.4	40.3	39.6

Table 9. Number of drug deaths per sex, age group and mean age at death in total and for different drugs. Forensic toxicological data 1997-2014.

		Sex		Age				Average age at death									
Year	Number of deaths	Prop. Wom-en	Prop. Men	Prop. below 30	Prop. 30-39	Prop. 40-49	Prop. ≥ 50	All drug deaths[1]	Ampheta mine	Heroin	Mor-phine	Metha-done	Bupre-norphine	Fentanyl	Oxy-codone	Trama-dol	DXP
1997	720	32	68	12	25	21	42	49.4	36.6	36.2	40.3	42.8				55.7	54.3
1998	723	34	66	15	20	19	46	49.3	37.6	34.9	41.4	40.6				60.0	54.1
1999	754	33	67	17	20	18	44	48.4	36.9	35.9	38.2	40.9				63.5	53.4
2000	752	30	70	21	21	19	40	46.5	37.6	34.9	39.0	32.8				60.4	52.6
2001	726	30	70	19	22	21	39	46.7	38.1	33.8	38.5	40.7				56.4	52.9
2002	679	26	74	18	19	20	43	48.0	39.3	35.1	42.5	34.7				58.1	54.7
2003	628	28	72	20	18	23	39	47,2	38,7	35,8	41,7	38,1		35,5		56,2	57,5
2004	664	29	71	22	15	21	42	47.0	38.5	36.1	43.9	38.5	32.9	40.7		55.8	51.9
2005	667	31	69	19	16	19	47	48.3	36.8	35.0	41.1	38.7	31.3	54.3	54.4	55.2	55.2
2006	635	28	72	15	14	20	50	50.2	39.5	37.6	47.3	40.8	30.6	31.0	56.3	58.8	55.4
2007	722	26	74	21	16	23	39	45.9	38.6	36.7	43.1	35.2	35.4	37.0	48.9	53.6	53.7
2008	803	26	74	21	20	19	41	45.3	40.2	35.0	43.3	38.7	30.8	45.9	46.6	52.3	54.2
2009	816	28	72	21	16	21	42	46.7	38.8	33.7	45.3	38.7	30.9	45.1	50.7	50.0	54.1
2010	816	28	72	20	18	18	43	46.6	39.4	36.9	46.8	38.7	34.2	46.3	49.1	54.1	51.9
2011	812	26	74	22	18	17	43	46.2	40.1	36.9	49.5	38.2	35.8	43.8	51.4	49.9	46.6
2012	929	29	71	20	15	16	49	49.0	40.6	38.0	52.0	39.7	37.0	50.4	50.3	52.6	48.0
2013	1,026	26	74	21	18	16	46	47.5	39.7	35.8	50.7	40.3	37.1	49.8	49.8	50.5	46.8
2014	1,161	30	70	20	19	16	45	47.9	39.8	37.3	52.4	38.4	37.7	46.8	51.8	48.2	60.5

[1] Includes opioids (see footnote, page 21) and illicit drugs.

Polydrug use

This section gives an overview of polydrug use over time, specifically use of different opioids in combination with alcohol and/or benzodiazepines. Changes in polydrug use could, perhaps, also be a contributory factor behind the increase in opioid-related deaths. There is plenty of evidence that polydrug use, or multiple substance use, is common in general population samples and in treatment samples (e.g., Hakkarainen & Metso, 2009; Smith et al., 2011; Hönhe et al., 2014; Midanik et al., 2007). Studies have also shown that polydrug use is common among drug addicts in Sweden (see e.g., Leifman, 2015) and that multiple drugs are often found in poisoning deaths (e.g., Wikner et al., 2014; Fugelstad et al., 2010).

A widespread polydrug use was also indicated in Tables 2-3: the number of substances found in the forensic investigations exceeded the number of investigated deaths by far. As for only different opioid substances, the number of opioids per death has been found to be stable at about 1.2 for the past 10 years. Here, we want to study the combined use of opioids with two other commonly used substances, namely benzodiazepines and alcohol (ethanol). The forensic toxicological data contain information on the presence of different benzodiazepines and ethanol for each death.

The presence of alcohol in forensically investigated deaths for different threshold values (blood alcohol concentrations of ≥ 0.2, ≥ 0.5, ≥ 1.0 per mille) is shown in Figure 15. The numbers have been rather stable, excepting for the lowest cut-off (0.2 per mille), with a tendency toward an increase both in numbers and in proportions; from about 1,700-1,800 deaths during the first half of the period (1994-2005) to 1,850-1,890 in the years 2006-2010. The numbers may have decreased after 2010, but this should be interpreted cautiously since this change (drop) coincides with the introduction of the new analysis method for screening. Also, the *proportion* of alcohol-positive deaths (not shown) has been rather stable, but with a tendency toward an increase, from about 30% with an alcohol concentration of ≥ 0.2 per mille during the first years to about 33% in the last years.

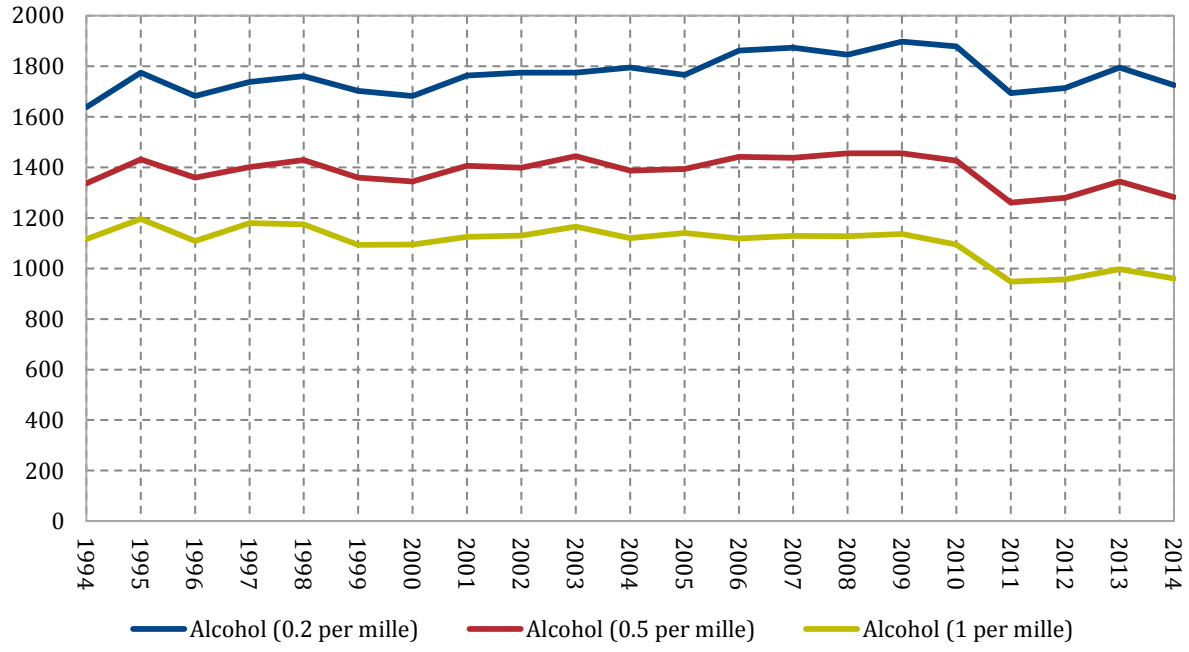

Figure 15. The number of forensically investigations deaths positive for alcohol (≥ 0.2, ≥ 0.5, ≥ 1.0 per mille) per year.

The number of deaths with an alcohol concentration of at least 1.0 per mille has for all years reached between 1,100-1,200 deaths (≥ 0.5 per mille alc. conc.: 1,300-1,400) or around 20% (≥ 0.5 per mille: 25%) of all deaths.

Table 10 shows the number of detected benzodiazepines, the number of deaths with at least one benzodiazepine detected, and the proportion of all forensically investigated deaths with positive toxicology for benzodiazepines. The number of detected benzodiazepines (also shown in Table 2) was rather stable from the mid-1990s to 2010, but somewhat lower in 2003-2006. From 2011, the number has increased, but as exemplified with diazepam in the table, this is likely to be the result of lowering threshold values for several of the benzodiazepines (not only diazepam) from October 2011. (In this report, we have not had the possibility to assess the effects of lowering the threshold values for several benzodiazepines. This could, however, be done at a later stage.) More or less the same trends are found for number of deaths and the proportion of benzodiazepine deaths in relation to all forensically examined deaths.

Thus, since almost all of the increase in numbers and proportions occurred between 2010 and 2012, it was probably due to the change in recording practices and the presence of benzodiazepines in forensically investigated deaths has most likely been rather stable for many years.

Table 10. The presence of benzodiazepines[1] in forensically examined deaths.

Year	Number of positive findings of benzodia-zepines	Number of deaths with at least one detected benzodiazepine	Prop. benzodiazepine deaths of all forensically examined deaths	Diazepam	
				Old higher threshold (0.05 µg/g)	Lower threshold (0.025 µg/g)
1994	1,268	799	14.3	284	
1995	1,397	871	15.7	300	
1996	1,360	851	15.6	280	
1997	1,354	850	15.7	282	
1998	1,225	789	14.5	301	
1999	1,238	794	14.6	305	
2000	1,233	765	14.6	348	
2001	1,295	828	14.6	338	
2002	1,174	758	13.3	275	
2003	1,140	759	13.1	268	
2004	1,059	678	12.1	278	
2005	1,134	765	14.0	243	
2006	1,131	754	12.4	251	
2007	1,388	904	16.8	301	
2008	1,339	855	16.5	279	
2009	1,331	873	17.0	282	
2010	1,317	891	16.9	253	
2011[2]	1,682	1,024	20.7	297	308
2012	2,156	1,248	25.1	263	321
2013	2,211	1,281	25.0	290	349
2014	2,418	1,315	25.5	309	366

[1] Including zolpidem and zopiclone.
[2] Grey area marks years (Oct 2011-Dec 2014) when the lowering of threshold values may have contributed to an increased number compared with the years before.

The main question remains, namely how the trends of positive findings of alcohol and benzodiazepines have evolved among drug deaths. For this purpose, some basic analyses have been conducted which could, perhaps, be elaborated further at a later stage. The analyses are based on toxicological data, but the increase in screening and the lowering of threshold values for positive benzodiazepine cases are not controlled for.

Different combinations of drugs present have been studied. The main results are shown in the detailed Table 11 and in Figures 7-8. They show involvement levels for alcohol and/or benzodiazepines in all drug deaths (i.e., opioids and illicit drugs), as well as in opioid deaths. We have also looked at specific groups of opioids, but the results turned out to be similar to the ones presented below.

Alcohol involvement (alone or together with benzodiazepines) has been rather stable in absolute numbers during all years from 1994-2014, but with some yearly variations. However, since drug deaths (or opioid deaths) have increased, alcohol involvement relative to all drug deaths (or opioid deaths) has declined.

Benzodiazepines have increased about as much in absolute terms as opioids up to 2014. Since the number of benzodiazepine deaths is lower than the number of opioid deaths, the increase in relative terms is larger for benzodiazepines, especially after 2010. This means that the proportion of positive findings of benzodiazepines among opioid deaths and drug deaths was rather stable or increased somewhat from the mid-1990s to 2010 (from about 47% to 53% of all opioid deaths), but increased very much after 2010 (from 53% in 2010 to 65% in 2014 of the opioid deaths). As shown in Figures 16-17, the subgroups of positive findings of opioids and benzodiazepines (Figure 16), or drug deaths and benzodiazepines (Figure 17) with no alcohol involvement, show particularly large increases over the past four years.

However, as was indicated in Table 10, the most likely explanation of this dramatic shift after 2010 is the lowering of the threshold values for several benzodiazepines in October 2011. Therefore, the most reasonable interpretation of the data is that benzodiazepine involvement in opioid deaths (or in drug deaths) has been rather stable in relative terms, but has increased in absolute numbers over the years, e.g., from 2006-2014.

Taken together, the results indicate that alcohol cannot explain the *increase* in opioid (drug) deaths, whereas benzodiazepine could be a contributory factor. This needs to be investigated more closely in the future.

Table 11. Combinations of alcohol and/or benzodiazepine findings in drug deaths (opioids and illicit drugs) and opioid deaths in forensically investigated deaths. Data in absolute numbers and in relation (%) to all deaths in that category.

	Opioids and all illicit drug deaths									Opioid deaths								
	All (with or without benzodia-zepines and alcohol)	No benzo-diazepines, no alcohol		Benzo-diazepines and alcohol		Benzo-diazepines, no alcohol		Alcohol, no benzodia-zepines		All (with or without benzodia-zepines and alcohol)	No benzo-diazepines, no alcohol		Benzo-diazepines and alcohol		Benzo-diazepines, no alcohol		Alcohol, no benzodia-zepines	
	Number	Num-ber	% of all	Num-ber	% of all	Num-ber	% of all	Num-ber	% of all	Number	Num-ber	% of all	Num-ber	% of all	Num-ber	% of all	Num-ber	% of all
1994	561	183	32.6	95	16.9	164	29.2	119	21.2	505	165	32.7	81	16.0	154	30.5	105	20.8
1995	591	173	29.3	118	20.0	168	28.4	132	22.3	537	155	28.9	107	19.9	156	29.1	119	22.2
1996	657	199	30.3	101	15.4	208	31.7	149	22.7	589	178	30.2	85	14.4	195	33.1	131	22.2
1997	688	228	33.1	138	20.1	193	28.1	129	18.8	630	209	33.2	124	19.7	178	28.3	119	18.9
1998	671	236	35.2	89	13.3	190	28.3	156	23.2	607	215	35.4	81	13.3	176	29.0	135	22.2
1999	699	253	36.2	120	17.2	187	26.8	139	19.9	620	217	35.0	113	18.2	176	28.4	114	18.4
2000	719	264	36.7	101	14.0	204	28.4	150	20.9	618	217	35.1	89	14.4	178	28.8	134	21.7
2001	689	226	32.8	99	14.4	209	30.3	155	22.5	585	189	32.3	86	14.7	184	31.5	126	21.5
2002	624	193	30.9	108	17.3	184	29.5	139	22.3	520	149	28.7	86	16.5	166	31.9	119	22.9
2003	597	228	38.2	93	15.6	182	30.5	94	15.7	478	172	36.0	74	15.5	162	33.9	70	14.6
2004	603	218	36.2	94	15.6	159	26.4	132	21.9	492	173	35.2	72	14.6	140	28.5	107	21.7
2005	627	240	38.3	88	14.0	182	29.0	117	18.7	534	190	35.6	73	13.7	168	31.5	103	19.3
2006	589	207	35.1	91	15.4	164	27.8	127	21.6	471	151	32.1	79	16.8	147	31.2	94	20.0
2007	658	202	30.7	98	14.9	231	35.1	127	19.3	528	157	29.7	79	15.0	203	38.4	89	16.9
2008	733	230	31.4	94	12.8	264	36.0	145	19.8	569	172	30.2	76	13.4	223	39.2	98	17.2
2009	755	264	35.0	114	15.1	259	34.3	118	15.6	620	208	33.5	95	15.3	224	36.1	93	15.0
2010	753	239	31.7	111	14.7	267	35.5	136	18.1	620	188	30.3	92	14.8	238	38.4	102	16.5
2011	797	257	32.2	116	14.6	315	39.5	109	13.7	654	205	31.3	98	15.0	279	42.7	72	11.0
2012	886	230	26.0	165	18.6	394	44.5	97	10.9	732	173	23.6	139	19.0	350	47.8	70	9.6
2013	925	273	29.5	161	17.4	394	42.6	97	10.5	747	208	27.8	117	15.7	352	47.1	70	9.4
2014	1,103	317	28.7	171	15.5	498	45.1	117	10.6	909	239	26.3	145	16.0	448	49.3	77	8.5

[1] Grey area marks years where the increased screening of opioids and the lowering of threshold for benzodiazepines values may have contributed to an increased number compared with the years before. Lowering of threshold values for opioids is controlled for by using the same higher threshold values for all the years. Increased screening for opioids is not controlled for here.

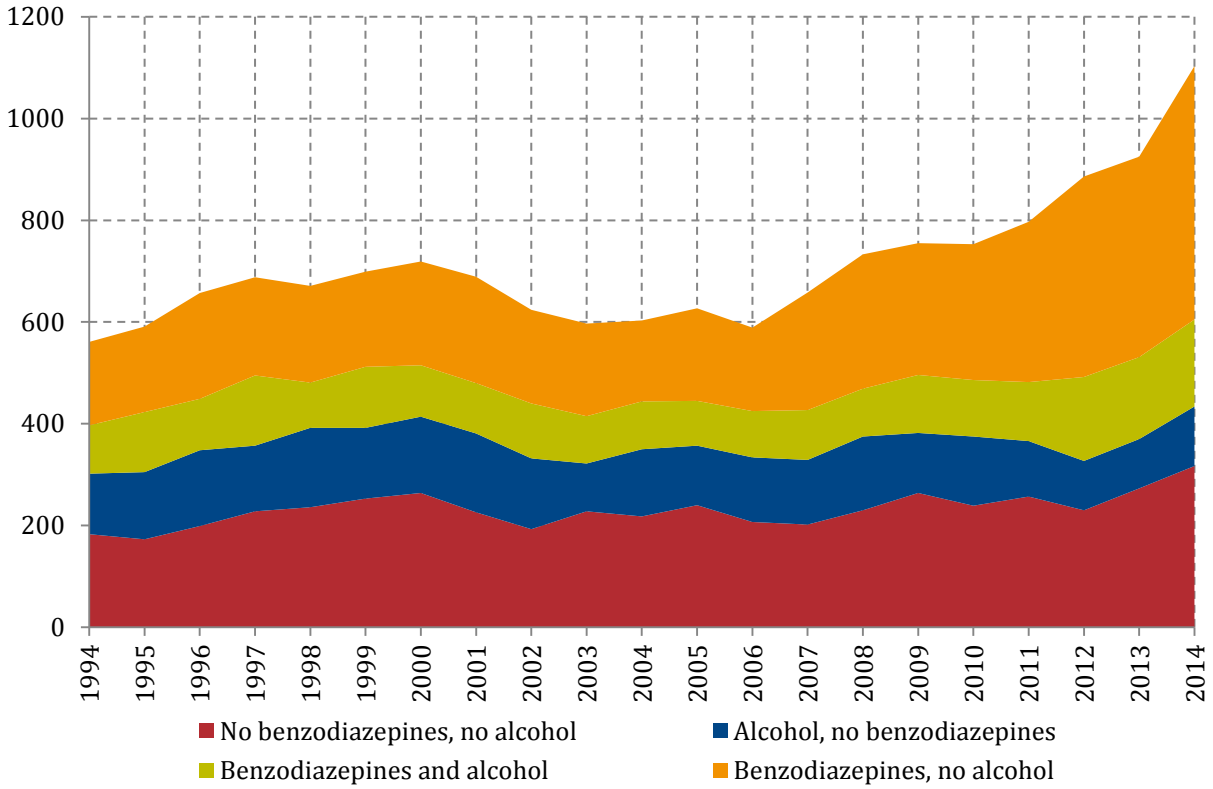

Figure 16. Different combinations of alcohol and/or benzodiazepine findings in all forensically investigated drug deaths (opioids and illicit drugs). The four time series are mutually exclusive. Data in number of deaths.

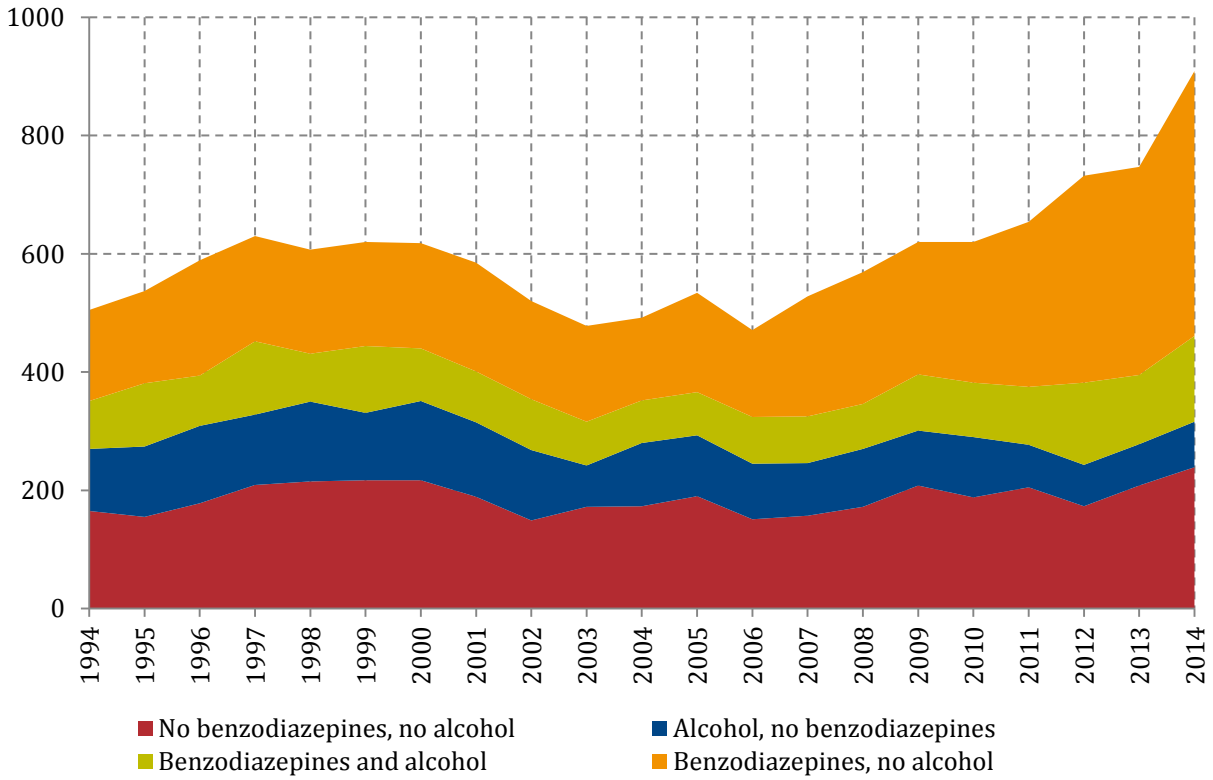

Figure 17. Different combinations of alcohol and/or benzodiazepine findings in all forensically investigated opioid deaths. The four time series are mutually exclusive. Data in number of deaths.

Manners of death in poisoning cases

Most of the deaths studied above are poisonings. In 2014, poisonings constituted 96% of all drug-related deaths according to the EMCDDA-GRM and the number of poisoning deaths has increased substantially over the past eight years or so.

Poisoning deaths consist of three main groups, namely unintentional deaths (accidental), intentional deaths (suicides) and undetermined deaths (unclear). It is importance to look more closely at how these three groups have changed over time, since that may improve our understanding of the changes in the past years. Since opioids are behind more or less all of the increase, the focus will be on this group of substances.

Data from the GMR show that both the number of intentional drug-related poisoning deaths (X61, X62) and the number of undetermined drug-related poisoning deaths (Y111, Y12) have remained rather stable for many years, whereas the number of unintentional drug-related poisoning deaths (X41, X42, X44) has increased. This is shown in Figure 18.

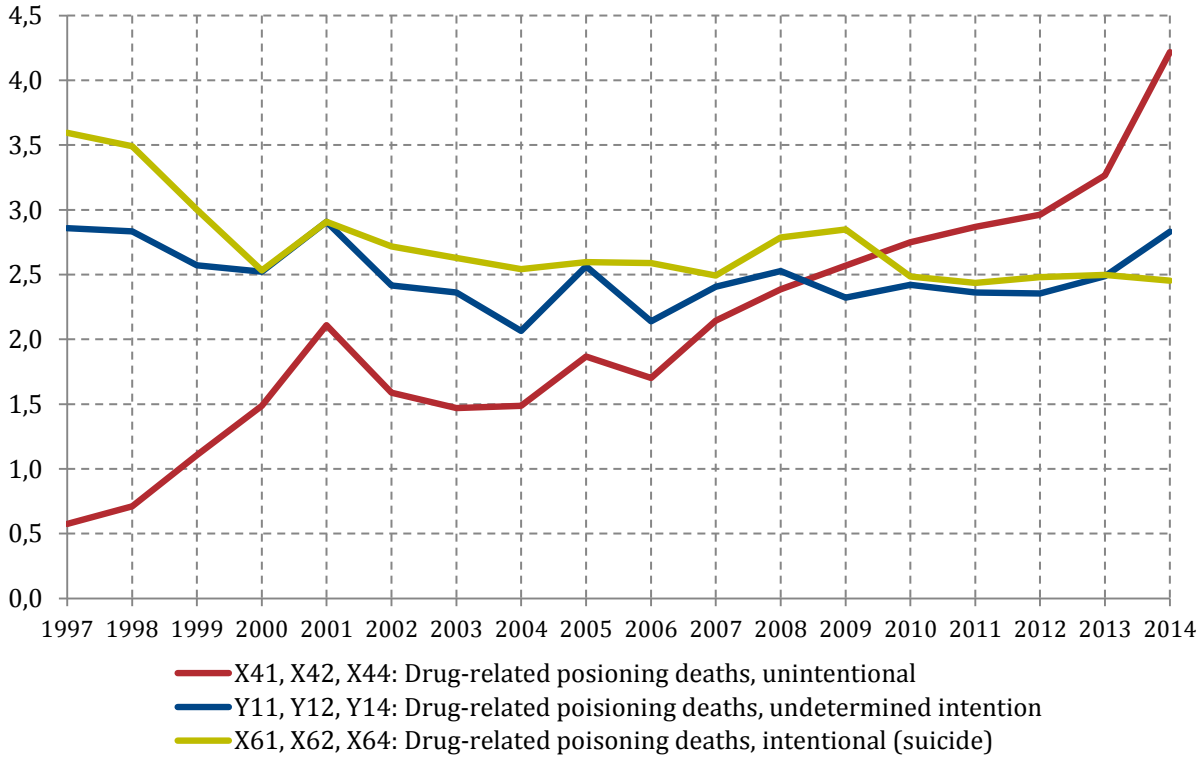

Figure 18. Subgroups of poisoning deaths according to the General Mortality Register (cause-of-death statistics). Data in number of deaths per 100,000 inhabitants.

The national forensic medicine database and the national forensic toxicology database make it possible to study the distribution of manners of death for different substances, such as different opioids. For each opioid and each year 2002-2013, the distribution between the three manners of death has been compiled. The distribution per opioid shows small changes over time, but the distributions for the substances differ markedly.

Figure 19 shows these distributions for all years collapsed into one period (here: 2002-2013). The opioids with the largest increases since the mid-2000s are the ones with the highest proportion of unintentional deaths, namely methadone, buprenorphine and fentanyl. Heroin and morphine also have relatively high numbers of unintentional deaths. The very opposite is the case for DXP, with few unintentional but many intentional deaths. Oxycodone and tramadol have a rather even distribution between the manners of deaths. The rather high proportion of undetermined deaths is also noteworthy.

The different distributions of manners of death between the opioids could be the result of different categories of users for the opioids; there is probably a higher proportion of drug users and drug addicts for the substitution drugs methadone and buprenorphine as well as for heroin and possibly fentanyl. The others may have a more mixed or broader group of users, not least elderly people who are often given these drugs as pain medication. Some may abuse these opioids too, but the high proportion of suicide might indicate that they are used to shorten a life at the very end of a fatal, painful disease.

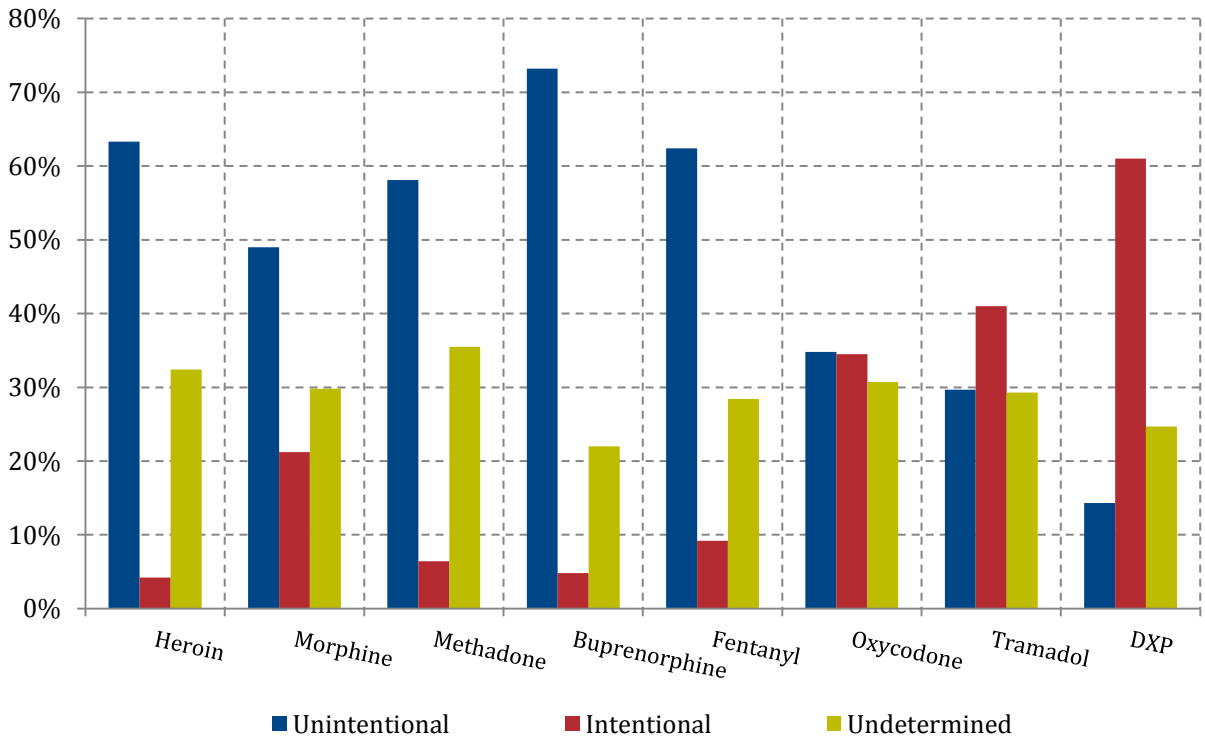

Figure 19. Distribution of manner of death (unintentional, intentional, unclear) among poisoning deaths of different opioids (forensic data) for the period 2002-2013.

5. Discussion

It is obvious from this report that the Swedish drug-related deaths statistics, and especially the handling and the reporting of these data, have been rather confusing. Some argue for a very large increase in drug-related mortality (Fugelstad et al., 2016), whereas others argue for a small increase or no increase at all (NBHW, 2016). Some have argued that the increase in drug-related deaths is a clear sign of the failure of the Swedish drug policy (e.g., Linton, 2015), others that it is caused by increasing elements of a more relaxed policy and particularly by less control over opioid substitution treatment (e.g., Fugelstad, 2015). Correct information about the trends in drug-related deaths is thus crucial in order to get a balanced debate and solid grounds for future decisions and actions.

The estimations reported in Chapter 3 suggest that a real increase in drug deaths *and* in drug-*related* deaths has occurred due to an increase in opioid-related deaths, but that the previously reported increasing trends have been exaggerated. The main reason for this is that the changes – or improvements – in recording practices in forensic investigations have led to the detection of more deaths with positive findings of drugs. As reported by the National Board of Health and Welfare (NBHW, 2016), changes in coding practices have also contributed to a false rate of increase.

The inconsistencies in the Swedish data on drug-related deaths also question the comparability of the Swedish statistics with other European countries, both in levels for specific years and in country-specific trends. In addition, it cannot be ruled out that other countries have done similar or other methodological changes (improvements) in their statistics over time which may further hamper the comparability. To this should be added already existing country differences in many of the stages of the collection of the drug-related deaths statistics, such as in the degree of forensic investigations and in the number of substances included in toxicological analyses.

Altogether this implies that country comparisons in the rate of drug-related deaths should be done very cautiously also in comparisons of trends. This is the implication drawn from the Swedish case. Similar assessments of the possible impact of methodological changes also in other countries would be needed in order to draw more certain conclusions of the degree of comparability.

The increase in drug deaths that remains after controlling for changes in recording practices is still substantial. As far as we know, all major changes implemented at RMV have been taken into account: an increased number of screening tests and lowering of threshold values. Still, it is not possible to exclude that other changes may have taken place. In any case, one should be cautious in interpreting the presented trends as measures of the exact increase in percentage or in absolute terms.

Interestingly, the increase in drug-related deaths is apparent for both men and women and in different age groups. It appears as if there has been a more or less collective shift upward in drug-related deaths, so that the gender and age distributions are roughly the same today as 10-15 years ago. However, data for 2014 showed a dramatic increase in drug-related poisoning deaths (underlying cause of deaths) among young adults (20-24 years of age), from 51 deaths in 2013 to 102 in 2014. This is important to follow-up, to see if it remains at the same high level in 2015.

Studies of the combined use of opioids with alcohol and/or benzodiazepines revealed that alcohol involvement in opioid deaths (and all drug deaths) has been at a rather stable level for all years since 1994, whereas benzodiazepines have increased at more or less the same pace as opioid deaths. Interestingly, out of the four groups of opioid deaths with or without alcohol and

benzodiazepine involvement, it is only the group of opioid deaths combined with benzodiazepines that shows a clear upward trend since 2006. Opioid deaths with no benzodiazepines and no alcohol show a modest increase, whereas the two groups of opioid deaths including alcohol (one including and one not including benzodiazepines) show no increase during the study period (here 1994-2014). The same patterns and trends for combined use are revealed for all drug deaths, i.e., opioid deaths plus deaths with illicit drugs.

The combined use of benzodiazepines and opioids is more rule than exception in opioid deaths. The effect of this combined use in opioid-related deaths needs to be investigated in much more detail in the future.

Analyses of manners of death in poisoning cases show clearly that it is the number of unintentional poisoning deaths that has increased over the past 10 years or so, whereas intentional (suicides) and undetermined poisoning deaths have both remained at rather stable levels. This may suggest that the increase is mainly due to overdoses among drug addicts.

An important lesson for the future, shown clearly in this report, is that one must keep track of changes in statistics that are related to recording practices. This has certainly not been done in Sweden. The inconsistencies revealed in the statistics are actually difficult to comprehend, given that Sweden is generally known for high-quality statistics. More or less all death data that could be needed are compiled and available from certain sources. The problem is that these data are spread out and not linked together, making it very difficult to achieve a reliable assessment of drug trends.

The following factors in particular seem to have contributed to the current confusing situation:

1. None of the three major governmental authorities responsible for parts of the drug statistics has the whole picture. This might not be a problem if there was well-functioning coordination between the three, but no such coordination seems to exist. In particular, there is a need for linking of forensic toxicological data with cause-of-death data, something that has been discussed for the past 20 years but is still not realised, whereas it is in place in several European countries.

2. The drug issue, including the statistics, has not been given sufficient priority. As a consequence, the statistics have been compiled rather mechanically, which is always problematic, especially when changes in recording practices take place. The European DRD protocol has not been applied fully, limiting the comparability of the Swedish statistics with the statistics from other European countries.

3. Toxreg statistics have been disseminated in Sweden, despite the fact that the selection criteria have not been drawn up through any consensus among a broader group of experts. The statistics are often incorrectly presented as the number of drug-related deaths, when they in fact only measure the number of forensically investigated deaths with positive toxicology for selected groups of substances and with no control for changes in recording practices. Furthermore, the usual way of presenting Toxreg in a hierarchy of drugs had distorted the picture and hidden the scale and trend of the polydrug use aspect of drug deaths.

The National Board of Health and Welfare is in the process of developing their statistics based on cause of death. These statistics constitute the official and most important statistics in this field. CAN and RMV will develop the forensic toxicology data further in order to create a special register to be used for regular monitoring. This could be an important complement to the official statistics of drug-related deaths and would be rather similar to the EMCDDA recommendations on selection criteria for special registers.

One important question is which substances should be selected for inclusion in drug-related deaths statistics. Approximately 200 substances classified as narcotics according to the Swedish Medical Products Agency (Läkemedelsverket) are tested for at RMV and not all of them are included in the drug deaths statistics. Today, most drug-related deaths are due to poisoning from legal pharmaceutical drugs, perhaps illegally used by opioid-dependent persons outside any maintenance programme. In any case, a sharp division between legal and illegal substances is difficult to establish. Furthermore, some substances are more common among drug addicts and are more often abused, but it is still difficult to make a clear distinction between different substances and to decide which should be included in the statistics. This was illustrated in Chapter 3 with the opioid DXP, which is not included in the Swedish statistics, but is included in the statistics of many other countries.

This is also a limitation of this study. Not all narcotic substances are included, not even all opioids, but the overwhelming majority of the number of opioid deaths are included. Roughly speaking, if all other opioids were included (e.g., MT-45 and hydrocodone), the number of deaths including opioids would increase by 2-3% and the number of opioid-*related* death probably by even less. In future, it makes sense to include them all, at least as a starting point (see below).

As concerns forensic data, our suggestion (from CAN and RMV) is to compile and report these data in the following four steps.

1. Select the number of detected substances classified as narcotics according to the Swedish Medical Products Agency (Läkemedelsverket) in forensically examined deaths. This includes both total number of deaths and number of deaths per substance or group of substances, e.g., opioids, benzodiazepines and amphetamines. These numbers can be monitored over time and give a good idea of the magnitude of drug involvement in groups at high risk of premature death.

2. Select the number of poisoning deaths in step 1, regardless of substance, in all forensically examined deaths. Here too, the total number of deaths and number of deaths per substance or group of substances can be monitored over time.

3. Select the number of poisoning deaths where opioids are considered to be the immediate cause of death. Here, all opioid deaths will have to be assessed at RMV. This will give us a good idea of the development of opioid-related deaths and the results could be reported within a rather short period of time.

4. Divide the opioid-related deaths from step 3 into the main subgroups of manner of death: unintentional, suicide, unclear. This will be an important indication of whether the changes observed relate mostly to overdoses among drug addicts or suicides among other opioid users. This is important for tailoring prevention measures.

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Appendix 1

Substances classified as narcotics according to the Swedish Medical Products Agency (Läkemedelsverket) and tested for at RMV.

Substances	Opioids	Amphetamine or similar	Cathinones	Phenethylamines	Cocaine	Cannabis	Hallucinogens	LSD	Others (NPS, pharmaceuticals, spice, GHB)	Benzodiazepines	Spice	NPS
Alprazolam									1	1		
Amphetamine		1										
Amobarbital									1			
Aprobarbital									1			
Barbital									1			
Brallobarbital									1			
Cyclobarbital									1			
Dextrometorphan							1					
Diazepam									1	1		
Nordazepam									1	1		
Dextropropoxyphene	1											
Ethylmorphine	1											
Fentanyl	1											
Phencyclidine							1					
Phenobarbital									1			
Phentermine		1										
Flunitrazepam									1	1		
Phenmetrazine		1										
Flurazepam									1	1		
GHB									1			
Heptabarbital									1			
6-acetylmorphine	1											
Hexapropymate									1			
Hexobarbital									1			
Cathine		1										
Carisoprodol									1			
Ketamine									1			
Ketobemidone	1											
Clomethiazole									1			
Clonazepam									1	1		
Chloral hydrate									1			
Chlordiazepoxide									1	1		
Codeine	1											
Cocaine					1							
Ecgonine					1							
Lorazepam									1	1		
LSD							1					
MDMA		1										
Meprobamate									1			
Mescaline							1					
Methadone	1											

Substances	Opioids	Amphetamine or similar	Cathinones	Phenethylamines	Cocaine	Cannabis	Hallucinogens	LSD	Others (NPS, pharmaceuticals, spice, GHB)	Benzodiazepines	Spice	NPS
Methaqualone									1			
Methamphetamine		1										
Methylphenidate									1			
Methyprylon									1			
Midazolam									1	1		
Morphine	1											
Methohexital									1			
Nitrazepam									1	1		
Oxazepam									1	1		
Oxycodone	1											
Pentazocine	1											
Pentobarbital									1			
Pethidine	1											
Pyrithyldione									1			
Pemoline									1			
Secobarbital									1			
Temazepam									1	1		
Tetrahydrocannabinol						1						
Triazolam									1	1		
Buphrenorphine	1											
Vinbarbital									1			
Zopiclone[1]									1	(1)		
Zolpidem[1]									1	(1)		
Cathinone		1	1									
Pholcodine	1											
Estazolam									1	1		
Psilocin							1					
Clobazam									1	1		
Tramadol	1											
O-Desmethyltramadol	1											
DOB		1		1								
2C-B		1		1								
A2		1										
Hydromorphone	1											
DOM		1		1								
DMA		1		1								
DOC		1		1								
Para-methoxy-amphetamine PMA		1										
4-mta		1										
Para-methoxymeth-amphetamine PMMA		1										
Bromazepam									1	1		
Phenazepam									1	1		

Substances	Opioids	Amphe-tamine or similar	Cathi-nones	Phene-thyl-amines	Cocaine	Cannabis	Hallu-cinogens	LSD	Others (NPS, pharma-ceuticals, spice, GHB)	Benzo-diaze-pines	Spice	NPS
Hydrocodone	1											
Dihydrocodeine	1											
Alfentanil	1											
Remifentanil	1											
Sufentanil	1											
2C-I		1		1								
Lormetazepam									1	1		
Methylone		1	1									
Modafinil									1			
Bromo-DragonFLY							1					
DOI		1		1								
Tetrazepam									1	1		
Pregabalin									1			
DMT									1			1
Mephedrone			1									
n-Ethylcathinone			1									
Mitragynine									1			
4-fluoroamphetamine		1										
Prazepam									1	1		
MDPV		1	1									
Methedrone		1	1									
Butylone		1	1									
4-HO-MET									1			1
Flephedrone		1	1									
2-oxo-3-hydroxy-LSD							1	1				
2-DPMP									1			1
MDAI		1		1								
Methcathinone		1	1									
4-MEC		1	1									
Buphedrone		1	1									
JWH-018									1		1	
JWH-081									1		1	
JWH-073									1		1	
JWH-200									1		1	
JWH-250									1		1	
JWH-398									1		1	
4-methylamphetamine		1										
1-3-methylbenzyl-piperazine		1										
JWH-122									1		1	
JWH-203									1		1	
JWH-210									1		1	
AM-694									1		1	

Substances	Opioids	Amphe-tamine or similar	Cathi-nones	Phene-thyl-amines	Cocaine	Cannabis	Hallu-cinogens	LSD	Others (NPS, pharma-ceuticals, spice, GHB)	Benzo-diaze-pines	Spice	NPS
AM-2201									1		1	
Ethylone		1	1									
Medazepam									1	1		
Pentylone		1	1									
3,4-DMMC		1	1									
Alpha-PVP		1	1									
Beta-ethylmeth-cathinone		1	1									
Methoxetamine							1					
2-fluoroamphetamine		1										
4-APB		1		1								
Etizolam									1	1		
2-fluorometh-amphetamine		1										
4-fluorometh-amphetamine		1										
Ethylphenidate									1			1
5-APB		1		1								
3-fluoroamphetamine		1										
RCS-4 ortho-isomer									1		1	
5-IT	1											
2-MMC		1	1									
3-MMC		1	1									
Tapentadol	1											
AM-1220									1		1	
AM-2233									1		1	
MAM-2201									1		1	
AH-7921	1											
Methiopropamine		1										
MDPPP		1	1									
MPPP		1	1									
Pyrazolam									1	1		
5-MAPB		1		1								
4-methylmethcathinone		1	1									
25C-NBOMe							1					
1-phenyl-2-butylamine		1										
n-Ethylnorketamine							1					
Flubromazepam									1	1		
2-aminoindane		1		1								
Alpha-PPP		1	1									
5-MeO-MiPT									1			1
Diklazepam									1	1		
n-Ethylbuphedrone		1	1									
MT-45	1											
Alpha-PEP		1	1									

Substances	Opioids	Amphe-tamine or similar	Cathi-nones	Phene-thyl-amines	Cocaine	Cannabis	Hallu-cinogens	LSD	Others (NPS, pharma-ceuticals, spice, GHB)	Benzo-diaze-pines	Spice	NPS
5-APDB		1		1								
5-EAPB		1		1								
6-APDB		1		1								
3-methoxymeth-cathinone		1	1									
25B-NBOMe							1					
3,4-dikloro metyl-fenidat									1			1
EAM-2201									1		1	
3-MeO-PCP							1					
3-MEC		1	1									
6-MAPB		1		1								
Alpha-PVT		1	1									
25H-NBOMe							1					
Diphenidine							1					
Butyrfentanyl	1											
2-MeO-Diphenidine							1					
n-Ethyl-4-methyl-norpentedrone		1	1									
4f-alpha-PVP		1	1									
Alpha-PHP		1	1									
25I-NBOMe							1					
MDPHP		1	1									
Flubromazolam									1	1		
Meclonazepam									1	1		
3-fluorophenmetrazine		1										
Acetylfentanyl	1											
4cl-alpha-PPP		1	1									
Isopropylphenidate									1			1
4.4-Dimethylaminorex		1		1								
Nimetazepam									1	1		
2,4-DMMC		1	1									
25B-NBF							1					
u-47700	1											
Delorazepam									1	1		
Dibuylon		1	1									
Propylphenidate									1			1
Clonazolam									1	1		

[1] Zopiclone and Zolpidem are included in the benzodiazepine group in the analyses in Chapters 3-4.