Chapter 8
General discussion
General discussion

This chapter contains a summary, a general discussion, some general limitations of the methods that were used, and finally a general conclusion and ideas for future research.

Summary of results

Chapter 2. The Drug Information and Monitoring System (DIMS) in The Netherlands: implementation, results and international comparison.

In this chapter, a comprehensive overview of the DIMS was given in terms of history, organization, methodology, laboratory analysis and some of the main results of monitoring psychostimulants throughout the years. The ecstasy-, cocaine- and amphetamine markets proved to be very dynamic and often declines in purity of these substances coincided with the rise of novel pharmacological substances. In the case of amphetamine, declines in purity were quite simply counterbalanced with increases of caffeine content. For ecstasy and cocaine this was more complex with mCPP, mephedrone, 4-fluoroamphetamine or BZP emerging in street ecstasy over the years and procaine, lidocaine, phenacetin and levamisole appearing in street cocaine. However, the rationale behind these added substances probably differed in some instances. Whereas the novel substances in ecstasy tablets were very likely added to mimic the effects of MDMA, adulterants in cocaine may have simply been added to increase profit by selling a more diluted product. A rough international comparison with other drug monitoring systems was made to provide some insight into the different drug markets globally. Interestingly, the cocaine markets appeared similar over a wide geographical dispersion, whereas synthetic stimulant markets sometimes differed considerably between countries in close vicinity to each other. These differences are probably best explained in terms of export and local manufacturing of illicit drugs. Cocaine is exported from a similar source (Latin America) to all other countries, whereas synthetic stimulants can be locally produced. Finally, this chapter argued for combining illicit street drug data from different sources, such as
a consumer derived drug monitoring system like DIMS and forensic drug data. In conclusion, having accurate street drug data facilitates monitoring of the continuously changing markets and aids in making risk assessments for prevention and (international) drug policy.

Chapter 3. The relationship of quality and price of the psychostimulants cocaine and amphetamine with health care outcomes.

This chapter approached drug monitoring from a socioeconomic perspective of the drug market by relating the DIMS data on cocaine and amphetamine price and quality to regularly collected data on two different health outcomes of interest: addiction treatment and hospital admissions. There was a strong relationship throughout time (1992-2008) for purity, price and adulteration of cocaine in relation to both these health outcomes, whereby purity and price were inversely correlated and adulteration was positively correlated. In contrast, amphetamine purity, price and adulteration hardly showed any relationship, only price showed a moderate positive correlation with addiction treatment. This showed that illicit cocaine market variables probably influenced the consumption patterns and subsequently explain the increases in health care outcomes, along similar lines as regular market dynamics influence consumption and, thereby, health. Mechanisms other than pure market dynamics might underlie the difference that was found between cocaine and amphetamine, such as a higher desirability of cocaine and a greater population of problematic users in The Netherlands (Van Laar et al., 2010). This might have caused users to be more responsive to price decrements of cocaine for instance.

Chapter 4. An analysis of cocaine powder in The Netherlands: content and health hazards due to adulterants.

This chapter described aspects of the cocaine market in The Netherlands, such as purity and adulteration between 1999 and 2007. The data showed that cocaine was increasingly adulterated. The group of adulterants consisted of other psychostimulants, such as caffeine, local anaesthetics, such as lidocaine or procaine and various prescription medicines with
various applications, such as diltiazem or levamisole. Adulterated cocaine was associated with more adverse effects than unadulterated cocaine and might pose additional health hazards. Diltiazem, hydroxyzine and phenacetin were the main adulterants contributing to these adverse effects. Diltiazem was primarily associated with adverse cardiovascular effects, although it was probably added to counteract cocaine's cardiotoxicity (Rowbotham et al., 1987; Ansah et al., 1993). Hydroxyzine was associated with hallucinations, in line with its described side-effects (Sweetman, 2006). Phenacetin also showed an increased association with adverse effects, but this could not be attributed to a clear mechanism of action.

Chapter 5. Impact of a transient instability of the ecstasy market on health concerns and drug use patterns in The Netherlands.

This study described the transient shortage of MDMA on the ecstasy market in The Netherlands in 2008 and 2009 and its impact on health concerns and drug use patterns of ecstasy users. As it turned out, the shortage had a considerable impact on the number of users handing in ecstasy tablets at the DIMS for the reason of health concerns, whereas respondents, recruited at the testing facilities, reported no major changes in their ecstasy use. The finding that users did not adjust their use in the event of a shortage of their drug of choice was in contrast with other studies (Topp et al., 2003; Weatherburn et al., 2003; Roxburgh et al., 2004; Cunningham et al., 2008). However, these studies all involved highly addictive drugs and a marginalized and problematic group of users. This is the first study to demonstrate that well-integrated recreational ecstasy users show a different behavior: apparently, the reduction of available MDMA did not cause a major shift in drug use. Possible explanations could be confidence about their own networks of ecstasy supply or peer pressure or drug dependence preventing a change in drug use, for example. Actually, it has been described previously that ecstasy users were depending on their network of peers to obtain safe, good quality tablets, supporting the first reason (Korf, Benschop, & Brunt, 2003). As a drug use reduction intervention, the shortage of MDMA did not affect ecstasy use amongst this subset of users. However, drug users were more concerned
about their health and more often decided to use of a system for harm reduction (DIMS) to reduce possible health risks. This is an example of the typical balance between the policies of use reduction and harm reduction (Caulkins & Reuter, 1997; Weatherburn, 2009).

Chapter 6. Instability of the ecstasy market and a new kid on the block: mephedrone.

The transient shortage of MDMA on the ecstasy market during 2008 and 2009 coincided with a worrisome phenomenon that has drawn considerable attention over the years: the introduction or rise of new substances on the synthetic drug market. The data strongly suggested that mephedrone was used as a substitute for MDMA in ecstasy tablets during the shortage. In the UK, mephedrone was perceived an important cause for health concerns and it was quickly banned under Misuse of Drugs Act 1971 (de Paoli et al., 2011; McElrath & O’Neill, 2011). In our study there was some support for this health concern with mephedrone proving a strong psychostimulant with properties similar to ecstasy, but also cocaine or methamphetamine. In comparison with MDMA, mephedrone appeared more addictive with many users reporting craving for the substance.

Chapter 7. Linking the pharmacological content of ecstasy tablets to the subjective effects of drug users.

This chapter aimed to address the discrepancy between tablets sold as ecstasy and the actual content with respect to subjective effects reported by drug users (Parrott, 2004). The DIMS database was utilized to link the chemical composition of the tablets to the effects that were reported beforehand by the users that handed in these tablets. A wide variety in the chemical content was present in these tablets and it was possible to discriminate between the effects with tablets containing MDMA alone and tablets containing other substances. MDMA alone showed the strongest association with desirable subjective effects, unparalleled by any other psychoactive substance present in ecstasy tablets. This association was dose-dependent, with higher doses of MDMA showing an increased
likelihood of desired effects, but very high doses to evoke adverse subjective effects. The piperazine derivates benzylpiperazine (BZP) and meta-chlorophenylpiperazine (mCPP) showed a high association with adverse subjective effects, whereas mephedrone and p-fluoroamphetamine showed relatively high associations with desirable subjective effects. This unique way of using the DIMS data showed that there is a strong rationale for the prolonged presence of MDMA as the key ingredient of the ecstasy market from the perspective of the users and, subsequently, the producers. It may further help to understand differences in subjective effects found between studies from different countries and/or different timeframes, when ecstasy tablets were of varying purity and/or composition.

General discussion

Results of this thesis will be discussed according to the main aims that were stated in the introduction.

1. The DIMS can be used for identifying risky substances in illicit street drugs.

Many studies in this thesis have touched upon this, either directly or indirectly. The function of DIMS as a surveillance tool to detect hazardous situations or substances has been discussed in chapter 2, illustrated by examples of many new substances that were detected over the years of monitoring and finally by warning campaigns that were orchestrated by the DIMS in the case of dangerous substances, including atropine in cocaine or PMA in ecstasy tablets (EMCDDA, 2007; Braida et al., 2008 and Felgate et al., 1998; Kraner et al., 2001; Dams et al., 2003). The study results in chapter 4 clearly demonstrate drug monitoring data as a means to identify potentially risky and hazardous adulterants in cocaine. By describing the increase of adulterated cocaine on the streets throughout the monitoring period and comparing the adverse subjective effects with those of unadulterated cocaine it was already clear that adulteration causes more adverse effects. By further describing the nature of the adulteration and the
specific relationships of the different adulterants with adverse effects, it appeared that certain adulterants were responsible for health problems in specific. In part, these adverse events could be explained by the well-known side-effects of these adulterants, such as atropine (Gyermek, 1998). But many adverse effects could probably be attributed to the interaction with cocaine itself or to the route of administration of cocaine.

Likewise, the results of chapter 6 were an effort to identify a new substance in the ecstasy street market with possible risks. Since no scientific information was available at the time for mephedrone, it was a preliminary effort in describing its effects and placing those in a context of possible harm indication. Mephedrone is a substituted cathinone and is part of a new wave of very diverse chemicals tentatively referred to as “legal highs” or “research chemicals” (EMCDDA, 2010; Brandt et al., 2010; Nichols, 2011). The term “legal high” is derived from the fact that most of these substances do not have a legally controlled status yet, which is of course an advantage from point of view of global commercial trade. However, in 2011 mephedrone was banned in the UK. These new chemicals are manufactured in laboratories worldwide, sometimes on demand by experimenters and users alike. But usually, the chemicals are shipped and meant for sale through commercial internet suppliers, often sold under false pretences with names that do not arouse suspension with the authorities, such as insect repellent or plant fertilizer (Evans-Brown et al., 2011). As the results showed, mephedrone could indeed pose an unknown health threat, because it seemed to be more addictive and was ingested by naive ecstasy users. The nature of this threat only starts to be unravelled in very recent pharmacology and toxicology journals (Motbey et al., 2011; Hadlock et al., 2011; Kelly, 2011).

2. The DIMS can be used to resolve some basic health issues that are very difficult or impossible with more traditional techniques used in pharmacological science.

An important aim of this thesis was to show that drug monitoring can be more than a mere toxico-chemical data collection tool over time. For example, the information on the street market for psychostimulants could
be coupled to other information sources to shed light on larger dynamic processes, as was done in chapter 3 where DIMS data were coupled with health outcomes. This provided a useful way of handling drug monitoring data and results seemed consistent with similar efforts by others (Hyatt, Jr. and Rhodes, 1995; Caulkins, 2001, 2007; Smithson et al., 2004; Dave, 2006). Moreover, frequent sampling allows for a more reliable and accurate prediction and the relationship between relevant time-dependent phenomena can only be studied with a detailed monitoring system (Brownstein & Taylor, 2007).

Combining the toxico-chemical data of the DIMS with the information provided by drug users that handed in their drug samples made it possible to investigate the pharmacodynamics and health consequences of (combinations of) illicit street drugs. For example, in chapter 4 this strategy provided information on the health effects of many different pharmacological adulterants in cocaine powder; something that would have been impossible with the use of regular psychopharmacological research methods, such as questionnaires or experimental laboratory settings. This strategy was also used in chapter 7 to study the pharmacodynamic profile of pure MDMA compared to its substitutes or its combination with different additives. This would have been virtually impossible with conventional ways of measuring subjective effects in the interview setting, when there is no way of confirming actual intake of a substance, let alone the nature of the substance (Liechti et al., 2001; Verheyden et al., 2002; Huxster et al., 2006; Baylen and Rosenberg, 2006; Sumnall et al., 2006). In the experimental laboratory setting it would be very difficult, because all substances and mixtures would have to be prepared and tested on the participants separately, which would have been dismissed on ethical grounds alone (Tancer and Johanson, 2003; Jan et al., 2010; Lin et al., 2011). This way of adapting the DIMS data provided a unique way of understanding the rationale for the prolonged presence of MDMA as a key ingredient of ecstasy in the dynamic illicit drug market. It also provided unique information on the relationship between the chemical composition of ecstasy tablets and desirable or adverse effects and their possible relevance to health risks.
3. The value of drug monitoring for harm reduction and prevention.

How could the DIMS aid in harm reduction or prevention? Classical prevention involves the government investing in encouraging young people not to take drugs, by mass media campaigns or school programs for example (Derzon & Lipsey, 2002; Cuijpers et al., 2002). However, evidence for the effectiveness of this kind of approach is limited. The recognition that drug use is unavoidable, harm reduction is a much more active approach of offering prevention care to drug users, as exemplified by the famous syringe-exchange program with injecting drug users (Hartgers et al., 1989). In chapter 2, two arguments were given in favour of a drug analysis and testing system as a worthwhile prevention tool. First, individual harm-reduction advice might serve the needs of existing users better than promoting full abstention (Gamma et al., 2005). The DIMS provides this individual approach. Secondly, regulatory efforts by the government, either by law enforcement or prevention scaring tactics are often considered as tendentious and untrustworthy and conflicts with the individual’s idea of self-regulation (Ritter, 2010). Drug users might be better persuaded by personal contacts with well-informed peers or professionals of the DIMS (Allott et al., 1999; Falck et al., 2004; Toumbourou et al., 2007). Moreover, drug testing has been suggested as a useful tool to change drug use during a situation where drugs contain chemical compounds that are unwanted or unknown (Johnston et al., 2006).

The results presented in chapter 5 show that the shortage of MDMA on the ecstasy market increasingly led many more Dutch ecstasy users to have their drugs tested at the DIMS, mainly for reasons of health concern. This led to a rapid increase in awareness about the situation on the ecstasy market, which in turn led to a greater knowledge about the possibility of drug testing possibly through friends or internet (Benschop et al., 2002; Boyer et al., 2005; Gordon et al., 2006). Also, many drug testing facilities of the DIMS made their activities known through internet and certain test results may be have been circulated by means of internet as well. Taken together, this study showed that DIMS had an effective reach as a harm reduction tool, even though the information of shortage of MDMA provided
by the DIMS did no appaear to change drug use or drug use patterns of ecstasy users frequenting the testing facilities. At least, this showed that Dutch ecstasy users were responsive to harm reduction strategies and unwilling to take too many risks with their health. On the other hand, it could be argued that a system like the DIMS might also contribute to a mistaken feeling of safety about the drugs these users were taking. The absence of acute toxicological substances is in no way a guarantee that drugs are safe to be used. In fact, every form of drug use is potentially hazardous. However, a system like DIMS acknowledges this and tries to transfer prevention based on scientific information and gives education about general drug risks. Moreover, another criticism might be that the existence of a drug testing system might even encourage young people to start using drugs and in fact lead to an increased drug use. This argument can be simply invalidated by comparing the prevalence figures of stimulant drug use in The Netherlands to countries that do not have an elaborate system for drug testing. Prevalence of psychostimulant drug use for the last decade in The Netherlands has rather been on the low end of the scale if compared to countries with no means of public drug testing (UNODC, 2011; EMCDDA, 2010). The same basically applies to the other countries that have a drug testing system for some time. This suggests that the existence of a drug testing system does not contribute to a higher prevalence of drug use.

Another interesting way of harm reduction is through the surveillance function of the DIMS using warning campaigns such as described in chapter 2. Substances that were identified as hazardous in those warning campaigns were always quickly removed from the market (Spruit, 2001). Also, in other countries with drug testing and monitoring systems, the chemical composition of illicit drugs seems to correspond more closely to what is expected than in countries without such systems, suggesting at least some influence of the drug testing systems on the illegal market (Kriener et al., 2001; Parrott, 2004).

4. The added value of drug monitoring as a tool to aid national and international drug health policy.
Despite some skepticism and criticism, illicit drug market monitoring is recognized more and more as a valuable tool for public health (Winstock et al., 2001; Katz et al., 2010; Ritter, 2010). Drug monitors keep track of (more) hazardous substances in illicit street drugs and this may result in national or international politics to take action. In collaboration with the Netherlands Health Care Inspectorate (IGZ) and under the authority of the Dutch Ministry of Health, Welfare and Sport (VWS), a national warning campaign (also referred to as a “Red Alert”) can be orchestrated, often through the media, in the case of dangerous adulterants or other risk situations related to the illicit drug market. In chapter 2 the different warning and prevention activities in The Netherlands were described. Furthermore, risk assessments were sometimes deemed necessary on the basis of DIMS results, that are made by the Coordination Centre for the Assessment and Monitoring of new drugs (CAM) (Van Amsterdam et al., 2004). A risk assessment is an official scientific evaluation of a certain substance and is presented to the government in order to determine whether further decisive steps should be undertaken legally to remove this substance from society. This may result in a re-evaluation of the national drug policy and registration of substances under the Dutch Opium Act, making trade and possession illegal offences.

On an international level, DIMS data are essential in alerting the European Union. The European Early Warning System (EWS), an European Union collaborative system, regularly updates information with DIMS data, and can call for an official risk assessment to be made when widespread use of new and hazardous chemicals is suspected. As was described in chapter 2, the reporting of BZP, 4-MTA, PMA and MBDB in ecstasy tablets to the EWS was followed by risk assessments and consecutive bans of these substances (EMCDDA, 2010). The DIMS was amongst the first drug monitors to report these substances (Spruit, 1999). More recently, there were DIMS reports of the partial replacement of MDMA in tablets sold as ecstasy by the previously unseen substance mephedrone (chapter 6). In the UK, there was widespread use of mephedrone reported among youth, which was partly due to the deteriorated ecstasy- and cocaine markets in the UK (Winstock et al., 2011; Measham et al., 2010; Brandt et al., 2010a).
Reports of incidents and fatalities with the substance and the general unfamiliarity with it caused it to be banned in the UK in 2010 (Morris, 2010). Based on the DIMS data and EWS reports from other states, a risk assessment has been conducted by the EMCDDA, which will possibly lead to a ban in all remaining EU member states (EMCDDA, 2011). The EMCDDA has a special interest in the continuing rise of these new psychoactive substances and adulterants, and this will undoubtedly keep monitoring systems like the DIMS at the heart of international policy making.

Limitations

Although the data presented in this thesis have some valuable applications and can provide some unique insights, there are also limitations that need to be discussed. First, there is the representativeness of the monitoring data to consider. For instance, in chapters 3 and 5, DIMS data were treated as predictive drug time series to represent the situation on the drug market. However, by definition, the DIMS is not an exact representation of the Dutch drug market situation, but it rather functions as an approximation. It is mainly focused on the national diversity of illicit drugs rather than the precise number of drugs and the precise frequency of events. Moreover, it is limited to a fraction of all drug users. Most drug users will probably never enter a testing facility of the DIMS. In its form, it is probably the best possible way to describe the diversity of the drug markets. But this still means that representative information about the market is missed and purity or adulteration figures are best possible estimates of the actual situation. However, there is an indication that the DIMS data are a good approximation of the illicit drug market since the DIMS drug market data were in good agreement with police seizures over two years (Vogels et al., 2009). Another limitation in inferring causality of the DIMS derived time series to other time dependent phenomena was the fact that only annual time series were available from health care monitoring systems in The Netherlands. With this long sampling lag period (one year) it is only possible to detect broad patterns in fluctuation, whereas important details about short-term effects are missed. In that respect, it would be
profitable to have more frequent reports from the other monitoring agencies, so more could be inferred about exact causes and effects. Another recurring limitation of the DIMS methodology in this thesis is the possible sample bias. For instance, in chapter 5 it was stressed that a convenience sample was used, i.e. drug users that had access to ecstasy tablets and had the opportunity to test them. There was no way of knowing whether the increased health concerns or changed drug use behaviour were also applicable to the total population of ecstasy users. Likewise, in the other chapters, possible bias in submitted drugs at the DIMS may have occurred because of specific concerns or discontent with the effects of the drugs in question. However, some results implied that this was not the case, such as the results in chapter 7, were many more ecstasy tablets were submitted that were associated with desirable effects than tablets which weren’t. Nevertheless, some caution has to be warranted as the DIMS might have received proportionally more suspicious (diluted) samples than were actually circulating on the streets. It is also important to bear in mind that many of the effects reported in this thesis (e.g. chapters 4, 6 and 7) were experienced under the assumption that substances contained something else or were of higher purity. Finally, it has to be stressed the DIMS is a purposely anonymous system because drug users would otherwise refrain from using the testing facilities for reasons of personal privacy and possible fear of prosecution. It therefore lacks interesting variables (e.g. gender, age, psychosomatic history, education) that would enrich some studies and give better answers in terms of causative factors for effects or outcomes. Additionally, information about the settings of use, routes of administration, dose or polydrug use was lacking in much of the individual cases. Therefore, findings are often very basic and only allow the study of a pharmaco-centric route of drug-induced effects. The lack of potentially confounding factors often makes it difficult or even impossible to reach causal inferences and interpretations. On the other hand, this is the strength of the system, because pharmaco-centric data are often missing in most psychopharmacological studies.
Future developments and future research

As is shown in this thesis, drug monitoring is a dynamic process that can be adjusted and evolved over the course of time. For all its strengths, there may be additions or further developments that await continuously, for example, the expansion and improvement of the DIMS website to generate more validated and accurate data about the illicit drug markets. But other systems of monitoring might also be considered. To sum up some possibilities:

- sewage epidemiology (broad scale for monitoring existing drugs, but also small scale for detection of new drugs)
- adding information to the current DIMS databank to allow a better control for potential confounders
- designing a specific website to collect user data on illicit drugs in order to monitor the nature of effects, separate from the DIMS data collection
- general internetsurveys to collect a vast amount of data concerning drugs
- linking DIMS with other databases

Conclusion

The findings in this thesis show that drug monitoring can be used to resolve some health issues and that it can also be applied to gain insights for the development of drug policy. Through all layers of drug politics, nationally or internationally, the DIMS is consulted for information updates. The data in this thesis show that the illicit psychostimulant markets in The Netherlands are very dynamic and continuously changing. When the purity of certain psychostimulants dropped, the probability of new psychoactive substances or new adulterants appearing on the market increased. Also, the market dynamics of illicit drugs showed remarkable similarities with that of regular consumer products. With regard to prevention activities, timely monitoring by DIMS has repeatedly resulted in timely mass media
warnings and through the DIMS network the communication was specifically directed at the groups at risk and maintained at a level of professionalism appreciated by these specific groups. The results in this thesis support the awareness of drug users about the drugs they consume and show the increasing awareness about the option of drug testing. Coupling the chemical data of the DIMS to the information that was communicated by the drug consumers yielded many new insights into the different effects of the expected, but mainly unexpected, psychostimulants and other substances in the drug samples. These examples can be seen as a basis for more refined research.

Finally, with some notes on future directions, promising new avenues for assembling drug data are underway, like drug monitoring through the analysis of public wastewater for example. Especially, combining different sources of drug data and more frequent reports would hold promise for optimal data for interpretation and creating timely drug policies. Furthermore, while warranting anonymity, enriching the DIMS database in the future with new items, like dose, route of administration, age, gender etc., would greatly increase the scientific value of the DIMS data, leaving less room for speculation or misinterpretation of effects.